OPTIMIZATION OF DUAL CROSSLINKED CHITOSAN SUCCINATE ENCRUSTED BIODEGRADABLE POLYMERIC BEADS: APPLICATIONS TO TARGETED DRUG DELIVERY

Dissertation submitted to

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In partial fulfillment of the requirements for the award of degree of

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Submitted by

SIVAKUMAR.R.
261510012

UNDER THE GUIDANCE OF

Mrs. Priyanka Sinha, M.Pharm.,
Department of Pharmaceutics

C.L.BAID METHA COLLEGE OF PHARMACY
(AN ISO 9001-2008 CERTIFIED INSTITUTE)
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Reg .No: 261510012

Phone : 24960151, 24962592, 24960425
e-mail : clbaidmethacollege@gmail.com
Website : www.clbaidmethacollege.com

C.L. Baid Metha College of Pharmacy

An ISO 9001:2008 approved institution
Jyothi Nagar, Old Mahabalipuram Road,
Thorapakkam, Chennai - 600 097.

ISO 9001 : 2008
Reg. No : RQ91/3038

Affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai.
Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education, New Delhi

Mrs. PRIYANKA SINHA, M.Pharm.,
Assistant Professor

THE CERTIFICATE

This is to certify that the dissertation work **" Optimization Of Dual Cross-linked Chitosan Succinate Encrusted Biodegradable Polymeric Beads: Applications To Targeted Drug Delivery"** submitted to **THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree of **Master of Pharmacy in Pharmaceutics** is a bonafide research work done by **Reg. No. 261510012** under my guidance in the **Department of Pharmaceutics**, C.L.Baid Metha College of Pharmacy, Chennai-600097 during the academic year 2016-2017.

Place: Chennai-97
Date:

Mrs.Priyanka Sinha, M.Pharm.,
Assistant professor
Department of pharmaceutics
C.L.Baid Metha College of Pharmacy
Chennai- 600097

Phone : 24960151, 24962592, 24960425
e-mail : clbaidmethacollege@gmail.com
Website : www.clbaidmethacollege.com

C.L. Baid Metha College of Pharmacy

An ISO 9001:2008 approved institution

Jyothi Nagar, Old Mahabalipuram Road,
Thorapakkam, Chennai - 600 097.

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Prof. DR. Grace Rathnam, M.Pharm. Ph.D.,
HOD & Principal,

THE CERTIFICATE

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Place: Chennai-97
Date:

Dr. Grace Rathnam, M.Pharm. Ph.D.,
HOD & Principal
Department of Pharmaceutics
C.L.Baid Metha College of Pharmacy
Chennai- 600097

DECLARATION

I do here by declare that the thesis entitled, "**OPTIMIZATION OF DUAL CROSSLINKED CHITOSAN SUCCINATE ENCRUSTED BIODEGRADABLE POLYMERIC BEADS: APPLICATIONS TO TARGETED DRUG DELIVERY** " was carried out by me under the guidance and supervision of **Mrs. Priyanka Sinha, M.Pharm, Assistant professor, Department of pharmaceutics, C.L. Baid Metha college of pharmacy, Chennai-97.**The work embodied in this thesis work is original and is not submitted in any part or full by any other degree of this or any other university**.**

Place: Chennai

Date: **[R.SIVAKUMAR]**

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API	ACTIVE PHARMACEUTICAL\
USP	UNITED STATES PHARMACOPOEIA
CR	CONTROLLED RELEASE
ER	EXTENDED RELEASE
SR	SUSTAINED RELEASE
BP	BRITISH PHARMACOPOEIA
IP	INDIAN PHARMACOPOEIA
PM	PHYSICAL MIXTURE
CS	CHITOSAN
HCL	HYDRO CHLORIC ACID
FTIR	FOURIER TRANSFORM INFRARED SPECTROSCOPY
NAOH	SODIUM HYDROXIDE
UV	ULTRA VIOLET
RT	ROOM TEMPERATURE
SD	STANDARD DEVIATION
FIG	FIGURE
AVG.WT	AVERAGE WEIGHT

CDDS	CONTROLLED RELEASE DRUG DELIVERY SYSTEM
UV	ULTRA VIOLET SPECTRO PHOTOMETRY
CP	CAPECITABINE
CONC.	CONCENTRATION
%	PERCENTAGE
HR	HOUR
RPM	REVOLUTION PER MINUTE
W/W	WEIGHT/WEIGHT
µG/ML	MICROGRAM PER MILLILITER
SEC	SECONDS
G/ML	GRAM PER MILLILITER
NM	NANOMETER
MM	MILLIMETER
CM^3	CENTIMETER CUBE
CM^2	CENTIMETER SQUARE
GIT	GASTRO INTESTINAL TRACT
ER	EXTENDED RELEASE
CR	CONTROLLED RELEASE

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TARGETED DRUG DELIVERY SYSTEM

Targeted drug delivery is a kind of smart drug delivery system which is miraculous in delivering the drug to a patient. This conventional drug delivery system is done by the absorption of the drug across a biological membrane, whereas the targeted release system is that drug is released in a dosage form [1, 2].

Targeted drug delivery system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body; therefore avoiding any damage to the healthy tissue via the drug. The drug delivery system is highly integrated and requires various disciplines, such as chemists, biologist and engineers, to join forces to optimize this system. When implementing a targeted release system, the following design criteria for the system need to take into account: the drug properties, side effects of the drugs, the route taken for the delivery of the drug, the targeted site, and the disease [1, 3, 4].

Products based on such a delivery system are being prepared by considering the specific properties of target cells, nature of markers or transport carriers or vehicles which convey drug to specific receptors and ligands and physically modulated components. Ideally targeted drug delivery systems should be biochemically inert (non-toxic), should be non-immunogenic, should be physically and chemically stable in vivo and in vitro conditions, and should have restricted drug distribution to target cells or tissues or organs and should have uniform capillary distribution. It should have controllable and predictable rate of drug release and also drug release should not affect the drug action. It should have therapeutic amount of drug release and should have minimal drug leakage during transit [5, 4, 6].

Carriers used should be bio-degradable or readily eliminated from the body without any problem. The preparation of the delivery system should be easy or reasonably simple, reproductive and cost effective.A Targeted drug delivery system is preferred over conventional drug delivery systems due to three main reasons. The first being pharmaceutical reason. Conventional drugs have low solubility and more drug instability in comparison to targeted drug delivery systems. Conventional drugs also have poor absorption, shorter half-life and require large volume of distribution. These constitute its pharmacokinetic properties. The third reason constitutes the pharmacodynamic properties of drugs. The conventional drugs have low specificity and low therapeutic index as compared to targeted drug delivery system. Due to these reasons targeted drug delivery system is preferred over conventional drug delivery systems[1, 3, 4].

TYPES OF TARGETED DRUG DELIVERY

As discussed, targeting drug to a specific area is not only increases the therapeutic efficacy of drugs also it aims to decreases the toxicity associated with drug to allow lower doses of the drug to be used in therapy. For the fulfilment of such conditions, two approaches are used extensively which also has known as classification of drug is targeting [7, 8, 1].

Passive targeting

It refers to the accumulation of drug or drug carrier system at a specific site such as anti-cancerous drug whose explanation may be attributed to physicochemical or pharmacological factors of the disease. Hence, in case of cancer treatment the size and surface properties of drug delivery nano-particles must be controlled specifically to avoid uptake by theoretical-endothelial system (RES) to maximize circulation times and targeting ability. The bottom line is called passive targeting as misnomer which is simple drug delivery system via blood circulation. Drug releaseor drug actions are limited to selective sites within

the body such as a tumour but not the liver. Other examples include targeting of ant malarial drugs for treatment ofleishmiansis, brucellosis, candiadsis[7].

Active targeting

Active targeting means a specific ligand–receptor type interaction for intracellular localization which occurs only after blood circulation and extravasations. This active targeting approach can be further classified into three different levels of targeting which are:

1) First order targeting refers to restricted distribution of the drug carrier systems to the capillary bed of a predetermined target site, organ or tissue e.g. compartmental targeting in lymphatics, peritoneal cavity, plural cavity, cerebral ventricles and eyes, joints.
2) Second order targeting refers to selective delivery of drugs to specific cell types such as tumour cells and notto the normal cells e.g. selective drug delivery tokupffer cells in the liver.
3) Third order targeting refers to drug delivery specifically to the intracellular site of targeted cells e.g. receptor based ligand mediated entry of a drug complex into a cell by endocytosis [8].

COMPONENTS OF TARGETED DRUG DELIVERY

A drug delivery system primarily constitutes a target and drug carriers or markers. Target means specific organ or a cell or group of cells, which in chronic or acute condition need treatment. Route of administration involves drug carrier as a important targeting moiety and after its leakage from its carrier/markers to reach the drug to the specific or targeted site via biological metabolism with its clearance as well as not to reach at non targeted site to make this delivery system more site specific with reduced side effects of drugs and its quantity too. Carriers one of the special molecule or system essentially required for effective transportation of loaded drug up to the pre-selected sites. These are engineered vectors which

retain drug inside or onto them either via encapsulation and/ or via spacer moiety and transport or deliver it into vicinity of target cell [7, 8, 9].

DRUG DELIVERY VEHICLES

Drug delivery vehicles are also referred as drug vectors which are most important entity required for successful transportation of the loaded drug. Drug vectors transports and retains the drug to e delivered it within or in the vicinity of target. They are made capable of performing such specific functions which can be attributed by slight structural modification [10, 8, 1].

CHARACTERISTICS OF AN IDEAL VEHICLE

An ideal vehicle should be able to cross blood brain barriers and in case of tumourchemotherapy tumour vasculature. It must be recognized by the target cells specifically and selectively and must maintain the specificity of the surface ligands. The drug ligand complex should best able in plasma, interstitial and other bio-fluids. The vehicle used should be non-toxic, non-immunogenic and biodegradable.

After recognition, the carrier system should release the drug moiety inside the target organs, tissues or cells. Targeting Moieties includes antibodies, lectins and other proteins, Lipoproteins, Hormones, Charged molecules, Polysaccharides and Low molecular- weight ligands [10,12, 11, 1].

Liposomes

Liposomes are small artificially designed vesicles composed of phospholipids bilayers surrounding with the size ranging from 20 to 10 000 nm. Many liposome formulations are rapidly taken up by macrophages and this can be exploited either for macrophage-specific delivery of drugs or for passive drug targeting which allow slow release of the drug over time

from these cells into the general circulation. Cationic liposomes and lipoplexes have been extensively researched for their application in non-viral vector mediated gene therapy [13].

Monoclonal antibodies and fragments

The majority of strategies based on antigen recognition by antibodies have been developed for more specifically for cancer therapy. These strategies are mostly aimed at tumor associated antigens being presenter in more specific term expressed by tumor cells. Antibody-drug conjugates (ADC) are complex of a drug with a monoclonal antibody which provides selective targeting for tumoral cell masses or lymphomas. The drug is released by enzymatic cleavage of the linker under physiological conditions. An example of Antibody-drug conjugates (ADC) is Mylotarg (emtuzamabozogamicin) which was approved by the U.S. Food and Drug Administration (FDA), but later voluntarily withdrawn from the US market. Another ADC has been submitted for approval and at least 15antibody conjugates are currently being investigated in clinical trials [14].

Modified (plasma) proteins

Modified plasma proteins can be intelligent drug vehicle for drug transportation due to their solubility and having relatively small molecular weight. They can easily be modified by the attachment of different molecules like peptides, sugars, and other ligands to transport the drugs of interest makes them a suitable mode of drug delivery. In the case of liver cell targeting, extensive modifications of protein backbones such as albumins have been carried out effective delivery of the drug [15].

Soluble synthetic polymers have been extensively researched as versatile drug carrier systems. Polymer chemistry allows the development of tailor made conjugates in which target moieties as well as drugs can be entrapped into the carrier molecule. Forcancertherapy,

the well-established N (-2-hydroxypropyl) methacrylamide (HMPA) polymershave been extensively studied. Also it provides a solution for selective and targeted chemotherapy.

Microspheres and nanoparticles

Microspheres and nanoparticles consist of biocompatible polymers and belong either to the soluble or the particle type carriers. HPMA polymeric backbone carriers have also been prepared using dextrans, ficoll, sepharose or poly-L-lysine as the main carrier body for the drugs. Nanoparticles are smaller (0.2– 0.5 μm) than microspheres (30–200 μm) and may have a smaller drug loading capacity than the soluble polymers. Formulation of drugs into the nanoparticles can occur at the surface of the particles and in nucleus, depending on the physicochemical characteristics of the drug. The site of drug incorporation significantly affects its release rate from the particle. After systemic administration ortransportation, they quickly distribute to the target sit and subsequently become internalized by the cells ofthe phagocytic system. Besides, microspheres and nanoparticles which are mostly used for cell selective delivery of drugs, they have more recently been studied for their application in oral delivery of peptides and peptidomimetics[16,17,12,18].

Lipoproteins

Lipid particles such as LDL and HDL containing a lipid and an apo-protein moiety is termed as natural targeted liposomes and its core can be used to incorporate lipophilic drugs or lipophilic pro-drugs and it does not require covalent bonding with the drug. Modifications at the level of glycolipid incorporation can be used to introduce new targeting moieties. The majority of the research on the use of LDL and HDL particles has been done and improved at the level of targeting the drugs to the liver [19].

Quantum dots

A quantum dot is a semiconductor nanostructure that confines the motion of conduction band electrons, valence band holes or bound pairs of conduction band electrons

and valence band holes in all three spatial directions. The ability to tune the size of quantum dots is advantageous for many applications and it is one of the most promising candidates as vehicle for drug transportation with its in solid-state quantum computation used for diagnosis, drug delivery, Tissue engineering, catalysis, filtration and textiles technologies too .

Folate Targeting

Folate targeting is a method utilized in biotechnology for drug delivery purposes. It involves the attachment of the vitamin, folate (folic acid) to drug to form folate conjugate. Based on the natural high affinity of folate for the folate receptor protein (FR)which is commonly expressed on the surface of cancer cells and folate-drug conjugates also bind tightly to the foliate receptor protein(FR)which in turn, triggerellular uptake via endocytosis. The folate receptor protein (FR) is also a recognized tumor antigen/biomarker. Because of this inherent property off late receptor protein (FR), exploits its use in diagnostic and therapeutic methods especially for the treatment of cancer [20].

Delivery of drug molecule to reach its specific site is itself a difficult task in the complex cellular network of an organism. Finally, targeted drug delivery is coming forward as one of the brightest advanced techniques in the medical sciences in the diagnosis and treatment of couple of lethal diseases. It has crossed the infancy period and now touching height of growths in research and development in clinical and pharmaceutical fields. Overall, it may be concluded with the vast database of different studies, the science of site specific or targeted delivery of these drugs has become wiser and intelligent with time and the advancement of scientific technology. Manifestation of all these strategies and advanced technologies in clinical field leads to new era of therapeutic and diagnostics in future. Many problems which appeared during the development of drug targeting strategies for clinical application for different types of therapies have been identified, analyzed and solved especially in the treatment of cancer. Several such preparations have entered the phases of

clinical testing or trials have now been marketed. However, such strategies should be subjected to continuous evaluation in the light of advances in the understanding of the numerous processes occurring in response to administration of the carriers or vehicles with drugs of interest with site specificity [21].

BIODEGRADABLE POLYMERS

Biodegradable polymers are generally divided into two groups, natural and synthetic based on their origin. Synthetic origin polymers offer advantages over natural polymers by being versatile with a wide spectrum of applications, having a capability to tailor mechanical properties and altering the rate of degradation according to the need. On the other hand, natural polymers seem to be attractive due to their excellent biocompatibility, but they have not been fully investigated due to their undesirable properties like antigen city and batch-to-batch variation. [22-24]

The instability of the polymers leading to biodegradation has proven to be immensely important in many medical applications.[25] Biodegradable polymers offer tremendous potential in many exciting applications like drug delivery, tissue engineering, gene therapy, regenerative medicine, temporary implantable devices, coatings on implants, etc.[26–29] The basic criteria for selecting a polymer for use as a degradable biomaterial are to match the mechanical properties and the degradation rate to the needs of the application, non-toxic degradation products, biocompatibility, shelf life/stability, process ability and cost. [22,29] The mechanical properties should match the application so that sufficient strength remains until the surrounding tissue has been healed.[30]There are many polymers available for different application where the choice of the polymer is dependent on the requirements that a particular biomaterial demands. With respect to drug delivery, it is the time of release that governs the type of polymer, size and shape of the device.[22, 31] However, clinically approved polymers such as lactide and glycolide polymers are the polymer of choice for any application.

Polymers found a multitude of uses in the medical industry, beginning with biodegradable sutures first approved in the 1960s. [31] Polyesters which are the representative class of biodegradable synthetic polymers continue to remain attractive in many clinical

applications due to their unique properties. Other classes of polymers which made a significant contribution to the field of biomaterials include polyurethanes, polyanhydrides, polyaminoacids, etc.[23,25, 32,33] Some of the natural polymers which are found to be biocompatible are extensively investigated which lead to some breakthrough innovations like Abraxane (paclitaxel-loaded albumin particles) based on nab technology.[34]

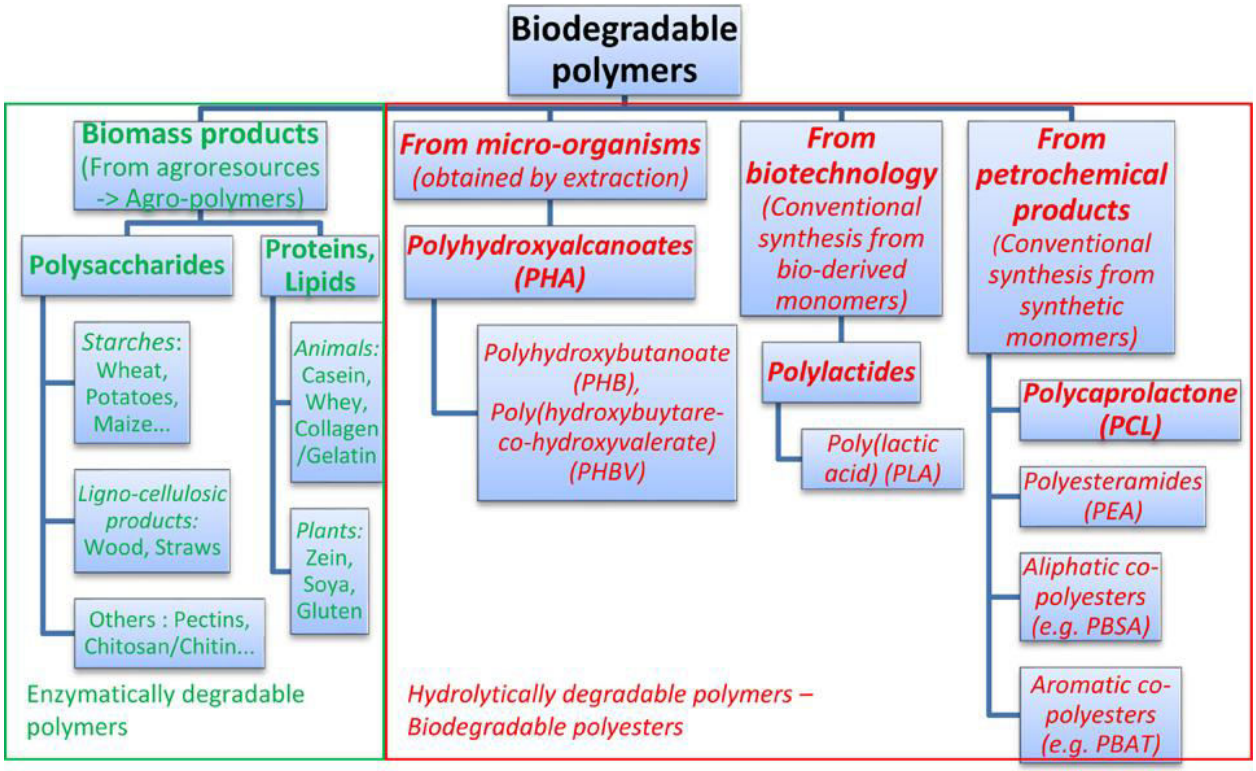


Fig NO: 1 – VARIOUS TYPES OF BIODEGRADABLE POLYMERS

There are various successful products in clinical practice, and the number of such products is ever increasing and at a faster rate from the past few decades.[22,35] Attempts have been made to develop injectable polymer compositions for use in tissue engineering applications which offer many advantages like avoiding surgery, filling cavities with complex geometries, and providing good bonding to tissue.[30] The inability of a single biodegradable polymer to meet all the requirements for biomedical scaffolds leads to the development of biodegradable polymer matrix nano composites in the field of tissue engineering. These nano composites increase and modulate mechanical, electrical and degradation properties. Polymer

matrix composites have the advantage of being very versatile, allowing fine tuning of their final properties. Biodegradable copolymers exhibiting temperature-responsive sol–gel transition have recently drawn much attention with their promising application in the fields of drug delivery, cell implantation and tissue engineering.[36] This class of copolymers exhibit amphiphilic nature due to the presence of hydrophilic (PEG)/hydrophobic segments (PLA/PLGA/PCL). These injectable hydrogels can be implanted in the human body with minimal surgical invasion. Strategies based on gene delivery or gene-activating biomaterials have a great potential in regenerative medicine, but the long-term safety of such therapies remains to be proven.[37]

SODIUM ALGINATE – A WONDER POLYMER FOR CONTROLLED DRUG DELIVERY

The design and interest in controlled release dosage forms, has been increasing steadily during the last 50 years. In most works the purpose is to make a formulation that keeps a prolonged therapeutic effect at a reduced dosing frequency. It is worthless to mention that the drugs are almost never administered in an unformulated state. Generally a dosage form consists of one or more active principles together with a varying number of other substances (excipients). These excipients enormously influence the physicochemical characteristics of the final products. It is now recognized that excipients can potentially influence the rate and/or extent of absorption of a drug (e.g. by complex formation). Therefore a well-established formulation depends on the careful selection of excipients. By reviewing the present and past scenario it is never worthless to mention, the use of polymers as a formulation aid in controlled drug delivery systems become an important area of research and development [38].

The current trend points to an increasing interest in the use of natural substances in food, drugs and cosmetics. The naturally occurring alginate polymers have a great potential in drug formulation due to their extensive application as food additives and their recognized lack of toxicity. Alginate is a nostalgic term for dietetic, biotechnology, cosmetic and pharmaceutical industries. As this group of polymers possesses a number of characteristics that makes it useful as a formulation aid, both as a conventional excipients and more specifically as a tool in polymeric-controlled drug delivery [38].

The alginates were discovered by a British Pharmacist, E.C.C. Stanford; commercial production started in 1929. The annual production of alginates in the world is about 30,000 tones; 30% of this is utilized by the food industry, the rest being used in industrial, pharmaceutical and dental applications [39, 40].

SOURCES OF ALGINATES:

Alginic acid and its salts [Ca, Mg, Na& K] are abundantly present in brown algae (pheophyta) of the genera "Macrocystis, Laminaria, Ascophyllum, Alario, Ecklonia, Eisenia, Nercocystis, Sargassum, Cystoseira, and Fucus. The most important are species of Laminaria known as kelps or sea tangles and specimens of Fucus known as Wracks [41]. However, it is two species, Macrocystis porifera and Ascophyllum nodosum, that provide the bulk of alginates production in the world [42]. In the algal thalus, Phycocolloids are the primary components of both the cell wall and the extra cellular matrix; their function as a "skeleton" increasing the mechanical strength and the flexibility of the tissue probably due to their ability to accumulate divalent metal ions and form gels of the required mechanical strength with these ions. Acetylated alginates are also isolated from some bacteria genera pseudomonas and Acetobacter[43, 44, 46,46]. Red algae belonging to the family coralenacease also contain these substances [47,48].

EXTRACTION AND PREPARATION:

Since alginates occur in the form of insoluble calcium, magnesium, sodium and potassium salts contained in the algal cell walls and the extra cellular matrix, their extraction and purification generally involve ion exchange techniques; the details of the extraction methods are usually protected by patents. Generally to prepare alginates for commercial use, the algae is mechanically harvested and dried before further processing except for M. Pyrifera which is processed in wet. Alginates are then extracted from dried and milled algal material after treatment with dilute mineral acid to remove or degrade associated neutral

homopolysaccharides such as laminarin and fucoidin. Concurrently the alkaline earth captions are exchanged for H^+. The alginate is then converted from the insoluble protonated form to the soluble sodium salt by addition of sodium carbonate at a pH below 10. After extraction, the alginate can be further purified and then converted to either a salt or acid [49]. The alginates being obtained from a natural source are likely to have a variety of impurities potentially be present. These include heavy metals, endotoxin, proteins, other carbohydrates and polyphenols. For applications in the food and beverage industry, low levels of these impurities do not pose a problem, but for pharmaceutical applications; particularly when alginates will be administered via parenteral route, these impurities should be removed [50].

CHEMICAL STRUCTURE OF ALGINATES:

Chemically alginates are linear, unbranched polysaccharide composed of monomers of b-D Mannuronic acid (M) and it's C-5 epimer a –l guluronic acid(G) residues joined together by (1-4) glycoside linkages (Fig.2) The residues generally vary widely in composition and sequence and are arranged in a pattern of blocks along the chain. These homopolymeric regions of b-D mannuronic acid blocks and a-L guluronic acid blocks are inter-dispersed with regions of alternating structure (b-D-mannuronic acid –a-l-guluronic acid blocks). The composition and extent of the sequences and the molecular weight determine the physical properties of the alginates. The molecular variability is dependent on the organism and tissue from which the alginates are isolated. For example, alginates prepared from the stipes of old L. hyperborea kelp contain the highest content of a-Lguluronic acid residues while alginates from A. Nodosum and L. Japonica have low content of a-L-guluronic acid blocks. As polymunnronic acid was found to dominate tissues of young algae; in older plants it is transformed into polyguluronic acid by the enzyme C5 -epimerase [51]. In mature tissues polymannuronic acid is located mainly in the extra- cellular spaces while polyguluronic acid occurs in the cell walls. [52]

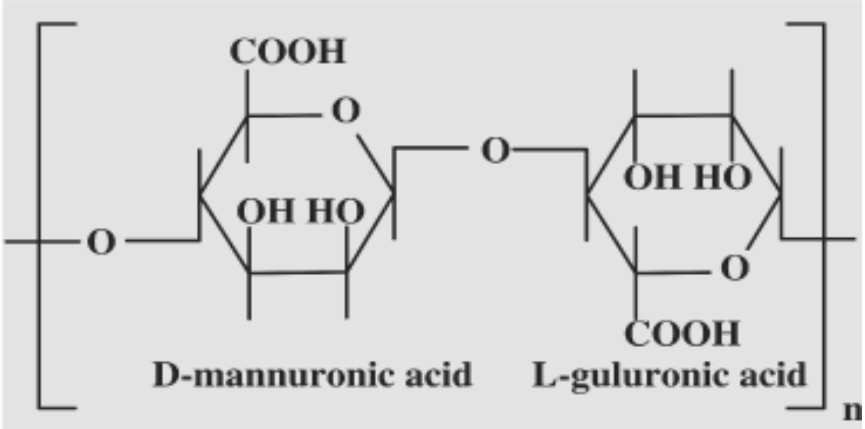


FIG NO: 2 – CHEMICAL STRUCTURES OF COMPONENTS OF THE ALGINIC ACID

PROPERTIES OF ALGINATES:

Solubility: Sodium alginates us slowly soluble in cold water, forming viscous, colloidal solution. It is insoluble in alcohol and hydro alcoholic solutions in which alcohol content is greater than 30% by weight. It is also insoluble in other organic solvents viz. Chloroform and ether, and in acids where the pH of the resulting solution falls below 3.0. A 1% solution in distilled water has a PH of approximately 7.2. Calcium alginate, is however, practically insoluble in water and organic solvents but soluble in sodium citrate [53].

Viscosity: Various grades of sodium alginates are available, yielding aqueous solutions of varying viscosity within a range of 20-400 centipoises (0.02-0.4 PaS) in 1% solution at 200C. Due to distribution of chain lengths, alginate solutions are not clearly Newtonian and behave as pseudo plastic fluid. When dissolved in pure water, their reduced viscosity is expected to increase very rapidly with dilution as observed by Focus and Straues. In the presence of supporting electrolyte rheological behavior of polyelectrolyte solution is known to depend on the ionic structure of the aqueous solvent, e.g. increasing the concentration of a strong electrolyte such as NaCl in the alginate solution up to 100mM was shown to reduce the solution viscosity due to the change in polymer conformation.

Chemical stability and degradation: Degradation of a Ca^{2+}cross-linked alginate gel can occur by removal of the Ca^{2+} ions. This can be accomplished by the use of a chelating agent such as ethylene glycol-bis (b-amino ethyl ether)-N, N, N', N'- tetra acetic acid (EGTA), lactate, citrate and phosphate or by a high concentration of ions such as Na^{+} or Mg^{2+}. As Ca^{2+} ions are removed, the cross-linking in the gel decreases and the gels are destabilized. This can lead to leakage of entrapped material and solubilization of the high molecular weight alginate polymers. Alginate gels will also degrade and precipitate in a 0.1 M phosphate buffer solution and will completely dissolve in 0.1 M sodium citrate at pH 7.8. If Ca^{2+} is used in the cross-linking solution and phosphate is used as the dissolution medium, the dissolution medium will turn turbid due to the Ca dissociating from the polymer network and forming calcium phosphate precipitate. This phenomenon is more evident when a high guluronic content alginate is used. Low a-L- guluronic acid content alginate and lower molecular weight alginate are known to release encapsulated proteins at a much faster rate .Degradation of the gel can be prevented by storing the gel beads in a medium that contains free Ca^{2+} ions and to keep the Na^{+}:Ca^{2+} ratio less than 25:1 for high a-L-guluronic acid alginates and 3:1 for low a L-guluronic acid alginates. Alginates have been reported to undergo proton catalyzed hydrolysis, which is dependent on time, pH, and temperature. A cross-linked alginate matrix delivery system when exposed to low pH can therefore undergo a reduction in alginate molecular weight, which results in faster degradation and release of a molecule when the gel is re-equilibrated in a neutral pH solution. Ability of alginate to form two types of gel depend on pH, i.e. an acid gel and an ionotropic gel, gives the polymer unique properties compared to neutral macromolecules. Alginate forms strong complexes with polycations including chitosan, polypeptides such as polylysine and synthetic polymers such as polyethylene mine.

METHOD OF PREPARATION [54, 55]

A. Air atomization - Requires an extrusion device with a small orifice through which alginate solutions containing drug are forced. Beads of 5- to 200-µm particles can be produced. The size of beads can be controlled by either adjusting gas and liquid flow and operating pressure or distance between the orifice and the surface of the cross linking solution.

B. Coaxial bead generator- Coaxial air stream pulls droplets from a needle tip into gelling bath can produce spherical beads ranging in size down to around 400 µm.

C. Dropping method-It is a Simple method Involves use of syringe with a needle or pipette. It is a most extensively utilized method for preparing the >500 µm particles. The size of beads formed is dependent on the size of needle used and viscosity of the alginate solution.

D. Electrostatic bead generator-Electrostatic force pulls droplets from needle tip into gelling bath. By this method150- to 1000-µm particles can be produced. Bead size depends on the voltage and distance between the needle tip and the gelling bath, solution viscosity, flow rate of the solution as well as on needle diameter.

E. Emulsification- Used only for stable drugs because it involves use of harsh chemical reagents to remove oil at the end of the process. Particles of size range 1- to 150-µm can be produced by this method. Size of micro beads produced depends on stirring speed and the rate of the addition of the cross-linking solution.

F. Laminar jet- A device based on laminar jet breaks up induced by applying a sinusoidal frequency break up technique with defined amplitude to the nozzle. Normally 300-to 600 mm particles can be produced.

G. Mechanical cutting- Bead formation is achieved by means of a rotating cutting tool which cuts jet into uniform cylindrical segments, which form spherical beads due to surface tension while falling down into a gelling bath. 150-µm to 3-mm particles can be produced.

H. Spinning disk atomization- Bead formation is achieved by specially designed spinning disk atomizer. It is suitable for 300- to 600-µm size particles.

I. Vibrating nozzle technique - The encapsulation technique is based on a harmonically vibrating nozzle. By this method >200-µm particles can be produced.

J. Complex Coacervation - Under specific conditions of polyion concentration, pH and ionic strength, the polyelectrolyte mixture can separate into two distinct phases; a dense coacervate phase which contains the micro beads and a dilute equilibrium phase. Oppositely charged complex poly-electrolytes have been commonly used. Optimum condition for maximum coacervate yield is pH of 3.9, an ionic strength of 1mM and a 0.15% w/v total polyion concentration.

USEFUL PROPERTIES OFALGINATE AS MATRIX FOR CONTROLLED DRUG DELIVERY:

Alginates have been widely used as tablet disintegrate, binding agent, viscosity modifying agent, as a stabilizer in disperse system in the production of suspension and emulsion and also as thickening agent in pharmaceutical industries. The most important advantage of using alginate as a matrix for Controlled release (CR) formulations is its biodegradability, because it is degraded and is absorbed by the body during and/or after drug release without any toxic effects. This allows bypass of surgical removal of the device. Hence, it can be a suitable matrix for sustained release of various drugs. Furthermore, because drug delivery can be controlled primarily through properties of polymer devices, CR is possible for conventional low molecular weight drugs as well as macromolecular drugs

including peptide hormones (e.g., insulin, growth hormone), polysaccharides (e.g., heparin), antibiotics, antigens, and enzymes. The release of drugs from alginate beads occurs mainly by diffusion through matrix and at certain pH due to erosion mechanism [51]. Release of drugs can be controlled by coating of matrix beads with sodium alginate. Sodium alginate has also been evaluated as release-controlling diluent in CR capsules. Several drugs have been incorporated into alginate matrices in a variety of forms (e.g., beads, micro spheres, films, and tablets), for CR therapies. The following properties of alginates have enabled it to be used as a most acceptable matrix for controlled drug delivery [57].

(i) It is readily available and is relatively inexpensive.

(ii) It contains ingredients that are accepted food additives.

(iii) It is non-toxic when taken orally and also has a protective effecton mucous membranes of upper gastrointestinal tract.

(iv) It is haemo-compatible and does not accumulate in any organ of the human body.

(v) It is biodegradable so there is no need for surgical removal after the drug is exhausted.

(vi) It can form hydro gels under mild conditions.

(vii) It is water soluble so it eliminates use of noxious solvents during processing and hence stability, toxicological, and environmental problems associated with solvents can be minimized.

(viii) It forms gel at room temperature and hence reduces chances of destroying activity of sensitive drugs at elevated temperatures.

(ix) Soluble sodium alginate cross-linked with a variety of cross-linking agents, forms insoluble gel, which is used to delay release of some drugs.

(x) Flow properties of drugs with needlelike crystals (e.g., Sulfadiazine) can be improved by incorporating in alginate beads. This method of agglomeration also avoids polymorphic transformations as agglomerates are formed from drug dispersions.

(xi) Beads formed are mechanically strong so they could be coated with enteric polymers to prepare enteric drug delivery systems.

(xii) Adopted by European Pharmacopoeia.

(xiii) The acceptable daily intake (ADI)for alginates are not specified which is the highest possible classification for food additives. The Food and Drug Administration has granted the generally recognized as safe (GRAS) status to alginates. The joint additive committee of the FAO and WHO experts has concluded that the daily permissible dose of sodium alginate 0-50 mg per Kg of human body weight. In 1990, the FAO and WHO removed the limitations for the daily consumption of alginates by man.

TAMARIND GUM – A NATURAL POLYMER

Gums and Mucilages are polysaccharide complexes formed from sugar and uronic acid units. They can absorb large quantity of water and swell. They find wide range of pharmaceutical applications that includes their use as binder, disintegrates in tablets, emulsifiers, suspending agents, gelling agents and also used as sustaining agents in tablets.[58]Synthetic hydrophilic polymers are used more often than natural polymers, but because of cost associated with synthetic polymers, researchers are now showing interest in natural polymers (Non-Synthetic)such as gums. Tamarind (Tamarindus Indica L.) is amongst the most common and commercially important, large evergreen tree that grows abundantly in dry tracks of central and south Indian states, also in other south East Asian countries. The pulpy portion of fruit is mainly used asacidulant in Indian receipes. [59] Tamarind seeds or kernel is a byproduct of Tamarind pulp industry.

Tamarind gum is obtained from endosperm of seeds of the tamarind tree, which is a seed gum with potential industrial application. Tamarind gum or tamarind kernel powder came into commercial production in 1943 as a replacement for starch in cotton sizing in Indian textile market. [60] It is also used in microbial production of lipids. It is also used in microbial production of lipids. It is an important sizing material for textile, a good creaming agent for concentration of rubber latex used as a soil stabilizer, a rich source of proteins and amino acids. Moreover tamarind kernel powder may also be used as afeed for cattle and pigs.6 It is also used as food ingredient. Currently purified and refined tamarind kernel powder is produced and permitted in Japan as a thickening, stabilizing and gelling agent in the food industry. Gum solutions of good adhesive strength from tamarind gum and sisal fibers were prepared which have potential industrial applications such as for false roofing and room portioning. Tamarind gum is used as a creamer for latex, in explosives, in boraxprinting

and paper manufacturing. It is also used as stabilizer in ice creams and as an emulsion textile paste. Thus tamarind gum is having applications in paper, food, textile industries. Recent year's research has been initiated on the use of tamarind gum in pharmaceutical and cosmetic applications.

Chemical composition:

The composition of tamarind kernel, the source of gum, resembles the cereals. With 15.4 % to12.7 % protein, 3-7.5 % oil, 7-8.2 % crude fiber, 61-72.2 % non-fiber carbohydrates, 2.45-3.3 %ash; all were measured on a dry basis. Chemically tamarind kernel powder is highly branched carbohydrate polymer. Its backbone consists of D-glucose units joined with (1-4) b-linkages similar to that of cellulose. It consists of a main chain of b-D- (1-4)-galactopyranosyl unit with aside chain of single xylopyranosyl unit attached to every second, third and fourth of D-glucopyranosylunit through a-D- (1-6) linkage (as shown in Fig 1). One galactopyranosyl unit is attached to one of the xylopyranosyl units through b-D- (1-2) linkage. The exact sequential distribution of branches along the main chain is uncertain.

Physical properties:

Tamarind kernel powder disperses and hydrates quickly in cold water but does not reach maximum viscosity unless it is heated for 20-30 mins. The solution exhibits typical on-Newtonian flow properties common to most other hydrocolloids. The functional property of tamarind kernel powder of protein concentrates was reported. The rheological properties of tamarind kernel powder suspension showed that suspension behaved like non-newtonian, pseudo plastic fluid with yield stresses and exhibited thyrotrophic characteristics. An increasing concentration produces increase in non-newtonian behavior as in consistency latex, yields stress and apparent viscosity.[61]

Pharmaceutical applications Tamarind seed polysaccharide

Polysaccharide present in tamarind kernel powder is called as tamarind seed polysaccharide. Tamarind seed polysaccharide is having molecular weight 52350 units and monomer of glucose, galactose and xylose in molar ratio of 3:1:2.Various methods have been reported for isolation of tamarind seed polysaccharide from tamarind kernel powder. It is insoluble in organic solvents and dispersible in hot water to form a highly viscous gel such as mucilageneous solutions with a broad pH tolerance and adhesively. [62] In addition it is nontoxic and nonirritant with haemostatic activity. Recently tamarind seed polysaccharide is widely used for pharmaceutical applications.

Pharmaceutical applications of tamarind seed polysaccharide:

1. Binder in tablet dosage form

Evaluations of tamarind seed polyose as a binder for tablet dosage forms was taken up for the weight granulation as well as direct compression methods. The results indicated that tamarind seed polyose could be used as binder for weight granulation and direct compression table ting methods. [63]

2. In Ophthalmic drug delivery

Tamarind seed polysaccharide is used for production of thickened ophthalmic solutions having apseudoplastic rheological behavior and mucoadhesive properties. Said solution is used as artificial tear and as a vehicle for sustained release ophthalmic drugs. The concentrations of tamarind seed polysaccharide preferably employed in ophthalmic preparations for use as artificial tears i.e. a products for replacing and stabilizing the natural tear fluid, particularly indicated for the treatment of eye syndrome are comprised between 0.7-1.5% by weight. The concentrations of tamarind polysaccharides preferably employed in the production of vehicles (i.e. delivery system) for ophthalmic drugs having the function of

prolonging the prevalence time of medicaments at their site of actions are comprised between 1 and 4 % by weight. [64]

3. In sustained drug delivery

It is used as potential polysaccharide having high drug holding capacity for sustained release of verapamil hydrochloride. The release pattern was found to be comparable with matrices of other polysaccharide polymers such as ethyl cellulose, hydroxyl ethyl cellulose and hydroxylpropylmethyl cellulose, as well as the commercially available sustained release tablets (isoptin SR). [65] It is also used as suitable polymer for sustained release formulations of low drug loading. Sustained release behaviors of both water soluble (acetaminophen, caffeine, theophylline and salicylic acid) and water insoluble (indomethacin) drugs on tamarind seed polysaccharide was examined. Studies showed that tamarind seed polysaccharide could be used for controlled release of both water-soluble and water insoluble drugs. Zero order release can be achieved taking sparingly soluble drugs like indomethacin from tamarind seed polysaccharide.

The rate of release can be controlled by using suitable diluents like lactose and microcrystalline cellulose. For water-soluble drugs, the release amount can also be controlled by partially crosslinking the matrix. The extent of release can be varied by controlling the degree of crosslinking. The mechanism of release due to effect of diluents was found to be anomalous and due to crosslinking was found to be super case II. [66]

4. In Ocular drug delivery

Tamarind seed polysaccharide was used for ocular delivery of 0.3 % rufloxacin in the treatment of experimental pseudomonas aeruginosa and staphylococcus aureus keratitis in rabbits. The polysaccharide significantly increases the intraocular penetration of rufloxacin in both infected and uninfected eyes. Polysaccharide allows sustained reduction of S. Aureus in

cornea to be achieved even when the time interval between drug administrations was extended. The results suggested that tamarind seed polysaccharide prolongs the precorneal residence time of antibiotic and enhances the drug accumulation in the cornea, probably by reducing the washout of topically administered drugs. [67]

5. In controlled release of spheroids

Tamarind seed polysaccharide was used as release modifier for the preparation of diclofenacsodium spheroids using extrusion spheronization technique with microcrystalline cellulose as spheronization enhancer. It was found that release was sustained over a period of 7.5 hour. A credible correlation was obtained amongst swelling index, viscosity, and surface roughness of the polysaccharide particles and in vitro dissolution profile of spheroids. In the comparative bioavailability study the developed spheroids have able to sustained drug release and also was found to improve the extent of absorption and bioavailability of drug. [67]

CHITOSAN & ITS DERIVATIVES: RECENT INNOVATIONS

Over the last few decades, the global environmental problem has attracted significant awareness of the research community and policymakers for the development of polymeric materials which are degradable in a natural environment. The production of biodegradable polymers which are decomposed by microorganisms and photodegradable polymers that are decomposed by sunlight is a priority among researchers. An ideal biodegradable polymeric material is one which after being disposed of can be recycled many times before promptly being decomposed by microorganisms or sunlight providing carbon dioxide and water. Chitosan is such a type of polymer which is degradable in natural environment.

Chitosan is a poly cationic naturally occurring bio-degradable, non-toxic, non-allergenic biopolysaccharide derived from chitin which is found in abundance in nature[68]. It contains more than 5000 glucosamine units and is obtained commercially from shrimp and crab shell containing chitin which is an *N*- acetyl glucosamine polymer. The *N*- acetyl glucosamine gets converted in to glucosamine units by alkaline de-acetylation with NaOH (with 40-50% conc.).Chitosan is considered as most promising materials for future applications on account of its excellent biodegradability, biocompatibility, non-toxicity, antimicrobial activity, and its economic advantages. The chemical structure of chitin is made up of linear monomeric units of 2- acetamido-2-deoxy- D-glucopyranose attached through β-(1-4) linkages.

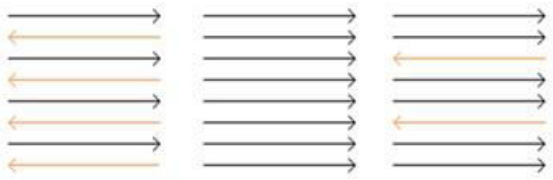
SOURCES AND EXTRACTION OF CHITOSAN FROM RAW MATERIALS:

Chitin, the main source of chitosan is widely distributed both in the animal and the plant kingdom. Henry Braconnot (1780–1855) was the first who isolated chitin from mushrooms in 1811 about two centuries ago. It was the first polysaccharide which was identified by man preceding by cellulose about 30 years. The main sources of chitin are

Fungi, Algae, Echiruda, Annelida (Segmented worms), Mollusca, Cnidaria (jellyfish), Aschelminthes (roundworm), Entoprocta, Bryozoa (Moss or lace animals, Phoronida (Horse shoe worms), Brachiopoda (Lamp shells), Arthropoda and Ponogophora. Chitin; also the major component of arthropods tendons, exoskeletons and the linings of their digestive, excretory and respiratory systems and insect's external structure as well as of some fungi.

It is also found in the iridophores (reflective material) of both eyes and epidermis of cephalopods and arthropods of phylum Mollusca and the epidermal cuticle of the vertebrates. Epidermal cuticle of Paralipophrystrigloides is also chitinous in nature.

Chitin occurs in three polymorphic solid state forms designated as α, β, and γ chitin which differ in their degree of hydration, size of unit cell, and number of chitin chains per unit cell. Chains of chitin may be arranged in a tightly compacted crystalline structure of ant parallel sheets and extensive intermolecular hydrogen bonding (α-chitin), in a more mobile allomorph of parallel sheets (β-chitin), or a combination of both (γ-chitin) (Fig. 3).α-Chitin is most abundant and is found in shellfish exoskeletons and fungal cell walls. β-Chitin is mainly found in squid pens and diatoms while γ-chitin may be predominantly found in squid and cuttlefish stomach lining.[69,70]



α-chitin β-chitin γ-chitin

FIG NO.3 SHOWING α, β AND γ-CHITIN

Chitosan is commercially interesting compounds because of its high nitrogen content (as compared to synthetically substituted cellulose) which makes chitosan a very useful chelating agent. The elemental composition of Chitosan [71] is described in Table 1.

TABLE NO. 1 ELEMENTAL COMPOSITION OF CHITOSAN

SR. NO	ELEMENTS	% IN CHITOSAN
1.	Carbon	44.11
2.	Nitrogen	7.97
3.	Hydrogen	6.84

Both chitin and chitosan have unusual multifunctional properties, including high tensile strength, bioactivity, biodegradability, biocompatibility, non-toxicity and non-antigen city which made them possible to be used in many applications.

Furthermore, the chemical modifications of the three reactive functional groups of chitosan had increased the applications of chitosan in different fields. Chitosan has three reactive groups, which is primary (C-6) and secondary (C-3) hydroxyl groups (Fig. 4) on each repeat unit and the amino (C-2) group on each deactivated unit. The presence of these reactive functional groups which may readily subject to chemical modifications to alter physico-mechanical properties of chitosan formulates it wonderful material for different purposed applications.

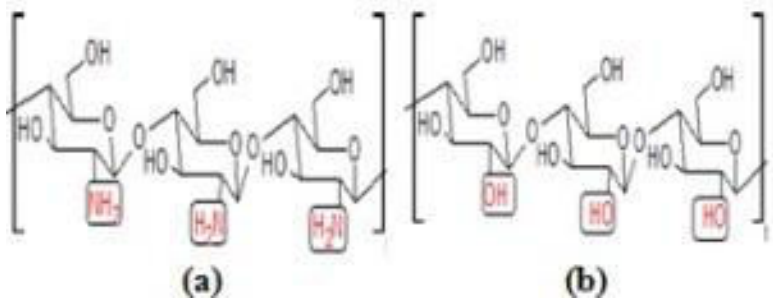


Fig NO: 4 - SHOWING STRUCTURES OF (a) CHITOSAN AND (b) CELLULOSE

PROPERTIES OF CHITOSAN:[72-74]

Chitosan has attracted increasing attention in the past decade due to its unique properties including non-toxicity, biocompatibility, and biodegradation including many others discussed in the pending text. One; among the notable and much exploited is; its antimicrobial commotion inhibiting the growth of a wide variety of fungi, yeasts and bacteria making it beneficial for use in the field of biomedicine.

It can also bind toxic metal ions, beneficial for use in air cleaning and water purification applications. These properties arise as a result of protonation of NH_2 groups on the chitosan backbone. Structurally, chitosan is a linear-chain copolymer composed of D-glucosamine and N-acetyl-D-glucosamine being obtained by the partial deacetylation of chitin.

The structure of chitosan is very much similar to that of cellulose and is the second most abundant natural polymer after cellulose. The solubility, biodegradability and reactivity of chitosan and adsorption of substrates depend on the extent of protonated amino groups in the chain of polymer. Chitosan is incapable of being dissolved in water, organic solvents and aqueous bases however get dissolved after stirring in acetic, nitric, hydrochloric, perchloric and phosphoric acids. The amino group of chitosan is not protonated in alkaline or neutral

medium and therefore it is insoluble in water; while in acidic pH it gets the resultant soluble protonated polysaccharide.

Chitosan forms water-soluble salts with inorganic and organic acids including glyoxylate, pyruvate, tartarate, malate, malonate, citrate, acetate, lactate, glycolate, and ascorbate. Inherent chitosan becomes soluble in organic acids when the pH of the solution is less than 6.5. The water-soluble salts of chitosan may well be formed by neutralization with acids such as lactic acid, hydrochloric acid, acetic acid, or formic acid.

There are various other factors which may affect the physicochemical properties of chitosan enabling the researchers to formulate different grades of chitosan which differ primarily in molecular weight, crystallinity and degree of deacetylation. During its processing from raw material, different conditions such as type and concentration of reagents, time and temperature employed can affect the physical characteristics of chitosan product. Its molecular weight also depends on solubility, viscosity, elasticity and tears strength.

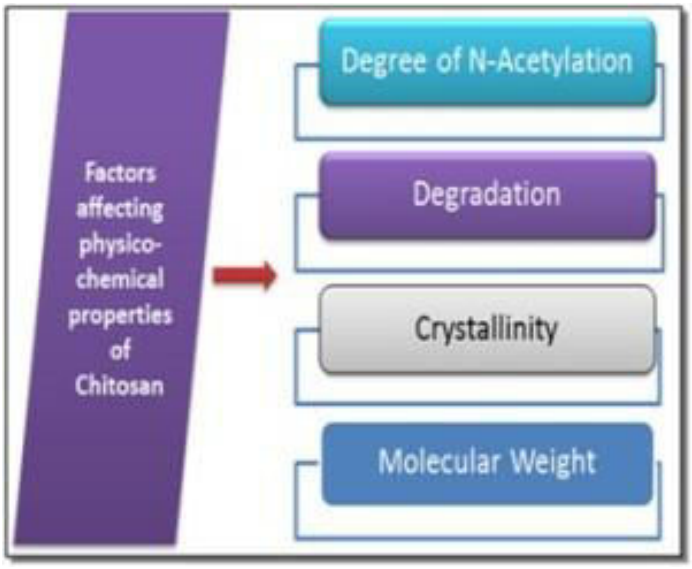


FIG. NO: 5 - FACTORS AFFECTING PHYSICO-CHEMICAL PROPERTIES OF CHITOSAN

Chitosan is a pseudo plastic material and is an excellent viscosity-enhancing agent in acidic environments. The viscosity of chitosan solution is affected by the molecular weight, degree of deacetylation, pH, ionic strength, concentration, and the temperature. Generally, there is a decrease in the viscosity of the solution on the increase in temperature and increases with an increase in chitosan concentration. The effect of the pH on the viscosity depends on particular type of acid used.

The characteristics of chitosan required for a particular application are dependent upon the degree of acetylating (DA) and its molecular weight. The degree of deacetylation of molecular chain of chitin; however, an extrinsic property; hence increased by increasing the temperature or strength of the alkaline solution. The viscosity of chitosan also influences the biological properties such as wound-healing properties as well as biodegradation by lysozyme.

As the Chitosan is hydrophilic in nature, therefore it has the ability to form gels at acidic pH. This type of gels can be used as a slow-release drug-delivery system. The solubility of Chitosan can be decreased by cross-linking it with covalent bonds using glutraldehyde. The swelling property of the chitosan decreases with an increase in the concentration of cross-linking agent.

The various chemical and biological properties of chitosan are as follows:[75-81]

- Natural, linear polyamine with reactive amino and hydroxyl groups.
- Chelates with transitional metal ions.
- Biocompatible and biodegradable to normal body constituents.
- Non-toxic and safe to use.
- Binds to microbial and mammalian cells.
- Haemostatic, fungi static and spermicidal agent.

- Antitumor and anti-inflammatory agent.
- Accelerate bone regeneration.
- Immuno adjuvant and drug delivery agent.

DERIVATIVES OF CHITOSAN:

The use of chitosan has been postulated in numerous areas of biopharmaceutical research such as mucoadhesion, permeation enhancement, vaccine technology, gene therapy and wound healing. Recent applications of chitosan are in ophthalmic, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal drug delivery and mucosal-vaccine and gene carrier. It can also be used in the pharmaceutical industry in direct tablet compression, as tablet disintegrant, for the production of controlled release solid dosage form or for the improvement of drug dissolution Chitosan derivatives were developed to improve not only biological activities but also water-soluble property, because the water-insoluble property was a major limiting factor for industrial application in spite of its unique biological aspects.

The improvement of structural properties of chitosan for a particular application can be easily brought about by chemical modification. Fortunately, chitosan is amenable to chemical modifications due to having of hydroxyl, acetamido and amine functional groups. For that reason, chemical modifications would not change the fundamental skeleton of chitosan and would keep the original physicochemical and biochemical properties while bringing new or improved properties. The various derivatives of chitosan developed by different researchers during the recent years are briefly described as:

***Quaternarized water-soluble derivatives of chitosan*:**[82]

Chitosan and its derivatives; having solubilities in pH values of lower than 6.0 are not desired for their use in cosmetics, medicine and food relevance. In order to improve its

solubility at neutral pH, firstly it is derivatized with substituents containing quaternary amino group, caboxymethylation and then sulfonation by adding strongly hydrophilic substituent. The simplest derivative of chitosan is the trim ethyl ammonium salt. The treatment of chitosan in N-methyl-2 pyrrolidone containing sodium iodide and methyl iodide with chloride ion in presence of sodium hydroxide resulting into the trim ethyl ammonium salt of chitosan having high degree of substitution. The anionic changes of iodide with chloride ions are necessary for stabilization resulting in water soluble product at neutral pH.

Chitosan-triphosphate nanoparticles:

Ionotropic gelation methods are the most common to achieve a pharmaceutical product with desired characteristics. Super-paramagnetic iron oxide nanoparticles (SPIONPs) were encapsulated by Sanjaia, et al. at various concentrations within chitosan-triphosphate (SPIONPs-CS) using the ionotropic gelation method. Ionotropic gelation is based on the ability of polyelectrolytes counter ions to cross link to form hydrogels. Naturally occurring polysaccharides such as chitosan which have relevant use as biopolymers has been increased in the novel area such as hydrogel sustained release formulation, thus providing an eco-friendly pharmaceutical product development process.

The dispersion ability of CS nanoparticles get enhanced by encapsulation of SPIONPs in aqueous solution, with all particles being lower than 130 nm in size and having high positive surface charge. The SPIONPs-CS nanoparticles exhibited super-paramagnetic properties at room temperature. These SPIONPs-CS nanoparticles can be applied as tissue-specific MRI contrast agents. This system has advantages over other MR agents in that preparation is simple, and can be undertaken under mild conditions. Furthermore, SPIONPs CS nanoparticles showed low cytotoxicity against skin fibroblast cells at proper concentrations, and excellent stability for over prolonged periods. These SPIONPs-CS

nanoparticles have the potential to be utilized as a MR contrast agents in tissue environments in the human body.

Bentonite/Chitosan Beads [83]

Bentonite is a common group of clay minerals, which is a hydrous aluminium silicate, and it has been reported as an economical material for adsorption of fluoride from water. Chitosan has been cited as an excellent material for defluoridation from water. However, raw chitosan used in the form of flakes or powder is unstable and the adsorption capacity reported is minimum, thus, it is necessary to modify chitosan physically or chemically in order to improve its practical uses.

Recently Zhang et al. has synthesized a new adsorbent namely bentonite/chitosan beads for its defluoridation efficiency. Bentonite was activated and the beads were prepared by using the inverse suspension polymerization method. The adsorption of fluoride onto the adsorbent followed Freundlich isotherm model and pseudo-second order kinetic model. The fluoride loaded adsorbent could be regenerated using sodium hydroxide. Bentonite/chitosan beads are of low-cost, effective and reusable adsorbent for adsorption of fluoride.

Chitosan based hydrogels: [83-84]

Hydrogel (also called aquagel) is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are highly absorbent (they can contain over 99.9% water) natural or synthetic polymers. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content.

Hydrogels based on covalently cross-linked chitosan can be divided into three types with respect to their structure: chitosan cross-linked with itself (Fig. 6a), hybrid polymer networks (HPN) (Fig. 6b) and semi- or full-interpenetrating polymer networks (IPN) (Fig.

6c). The simplest structure presented here is chitosan cross-linked with it. As represented in (Fig. 6a),cross linking involves two structural units that may or may not belong to the same chitosan polymeric chain.

The final structure of such a hydrogel could be considered as a cross-linked gel network dissolved in a second entangled network formed by chitosan chains of restricted mobility. In hydrogels formed by a HPN, the cross linking reaction occurs between a structural unit of a chitosan chain and a structural unit of a polymeric chain of another type (Fig. 6b), even if cross linking of two structural units of the same type and/or belonging to the same polymeric chain cannot be excluded.

Finally, semi- or full- IPNs contain a non-reacting polymer added to the chitosan solution before cross linking. This leads to the formation of a cross-linked chitosan network in which the non-reacting polymer is entrapped (semi-IPN). It is also possible to further crosslink this additional polymer in order to have two entangled cross-linked networks forming a full-IPN, whose microstructure and properties can be quite different from its corresponding semi-IPN.

Semi and full interpenetrating polymer network (IPN) type hydrogels were prepared by free radical in situ polymerization of methacrylic acid in presence of chitosan using N, N methylene-bis-acrylamide (MBA) and glutaraldehyde (for full IPN) as cross-linker. Several semi and full IPN type hydrogels were prepared by varying initiator and cross-linker concentration and also monomer to chitosan mass ratio. These hydrogels were characterized and used for removal of methyl violet and congo red dye from water.

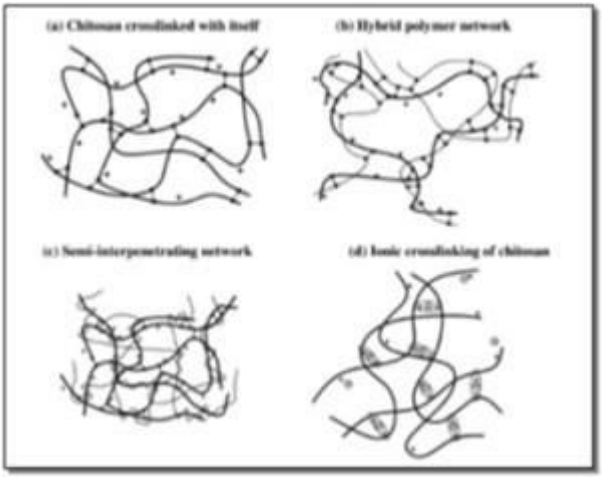


FIG. NO.6- STRUCTURE OF CHITOSAN HYDROGELS FORMED BY (A) CHITOSAN CROSS-LINKED WITH ITSELF; (B) HYBRID POLYMER NETWORK; (C) SEMI-INTERPENETRATING NETWORK; (D) IONIC CROSSLINKING

CAPECITABINE IN THE MANAGEMENT OFCOLORECTAL CANCER

5-Fluorouracil (5-FU) was initially introduced over 40 years ago and has remained a mainstay in treatment regimens for colorectal cancer (CRC) since that time, both alone and in combination with other agents. Its impact on cancer care has been substantial as CRC is the third most commonly diagnosed cancer in the United States with 142,570 new cases in 2009, and it is the third leading cause of cancer death in both men and women with a combined 51,370 fatalities in the same year. [93]Despite the importance of 5-FU to cancer care, its short half-life, requirement for a central line, and the need for continuous infusions led researchers to design an oral formulation of the drug. In June 2005, capecitabine (Xeloda®; Hoffman-LaRoche, Nutley, NJ) was approved by the Food and Drug Administration (FDA) as an oral prodrug of 5-FU for use as monotherapy in the adjuvant setting when treating Dukes' stage C CRC.

Capecitabine has a number of advantages over traditional 5-FU. After absorption across the digestive tract, it is converted to 5-FU through three sequential enzymatic reactions. The final enzyme in the pathway, thymidine phosphorylase (TP), is believed to be present at disproportionately high levels in tumor tissue, which is said to increase both the efficacy and tolerability of the agent through targeted delivery. Its oral administration simplifies care, frequently precluding the need for central venous access or infusion pumps. As a result, capecitabine is increasingly used for off-label indications in CRC, including monotherapy in the advanced or metastatic setting, combination therapy in conjunction with oxaliplatin in the advanced or metastatic setting, and with concurrent radiation for the neoadjuvant treatment of rectal cancer.[86] As off-label use of capecitabine increases, it

becomes even more important to understand the efficacy and tolerability across settings, which support its utilization in order to ensure the appropriate treatment of patients.

The purpose of this introducing is, therefore, to provide an overview of capecitabine's mechanism of action and rate of adverse events as well as an analysis of the evidence supporting its use in the settings outlined above. In addition, this article will highlight the regional differences in tolerance that affect dosing decisions and the evidence behind its use in the elderly, which remains an area of controversy. Finally, the economic literature will be discussed. The decision to prescribe capecitabine is a complex one; however, increasing evidence is emerging to guide clinicians.

1. **Kathiravan P et al., (2015),** have formulated and evaluated Colon Specific Drug Delivery System of Capecitabine Containing Polymer Coated Capsule Dosage Form; a polymer surface encompassed capsule dosage form of capecitabine was investigated and personalized for colon-targeted delivery of drugs. The sandwich replica of the system was designed by imparting the essences of time-release function and a pH-sensing function to a hard gelatin capsule. The technical traits of the system are fabricated to contain an organic acid together with an active ingredient in a capsule coated with a three-layered film consisting of an acid-soluble polymer, a water-soluble polymer, and an enteric polymer. In order to prioritize the suitable formulation, various formulation factors were investigated through a series of in vitro dissolution studies. The results are compiled as: (1) various organic acids can be used for this system invariably; (2) a predictable timed-release mechanism of a drug can be attained by tailoring the thickness of the Eudragit E 100 layer; and (3) the outer enteric coating with CMEC lends acceptable acid-resistibility. The result out comes postulate and suggests that this approach can provide a beneficial and practical means for colon-targeted delivery of drugs. This engineered structure has a proven benefit in various fronts for the end organ (colon), getting optimum concentration of drug to cause the therapeutic improvisation in the segment of malignancy and its associated risks within it.[87]

2. **Hetal K Patel, et al., (2008),** have designed the Characterization of calcium alginate beads of 5-fluorouracil for colon delivery- A multiparticulate system combining pH-sensitive property and specific biodegradability for colon targeted delivery of 5-fluorouracil (5-FU) was examined. The purpose of this study was to prepare and evaluate the colon-specific alginate beads of 5-FU for the treatment of colon cancer. Calcium alginate beads were prepared by extruding 5-FU loaded alginate solution to calcium chloride solution, and gelled spheres were formed instantaneously by ionotropic gelation reaction using different ratios of FU and alginate, alginate and calcium chloride, stirring speeds (500-1500 rpm), and reaction time. The core beads were coated with Eudragit S-100 to prevent drug release in the stomach and provide controlled dissolution of enteric coat in the small intestine and maximum drug release in the colon. Morphology and surface characteristics of the formulation were determined by scanning electron microscopy. In vitro drug release studies were performed in conditions simulating stomach to colon transit. No significant release was observed at acidic pH, however, when it reached the pH where Eudragit S-100 starts to dissolve, drug release was

observed. Also, release of drug was found to be higher in presence of rat caecal content.[88]

3. **Mohamad Anuar Kamaruddin, et al., (2014),** was formulated preparation and characterization of alginate beads by drop weight, the preparation and characterization of macro alginate beads are always associated with appropriate techniques involving precise measurement of shape, size, volume and density of the products. Depending on the type of application, encapsulation of macro alginate beads can be accomplished by various techniques including chemical, ionotropic, physical and mechanical methods. This work describes a method for preparing macro alginate beads through drop weight. The macro beads (2.85–3.85 mm) were prepared via different concentrations of alginate (0.5, 1.0, 1.5 and 2.0 g/L), dripping tip size (0.04–0.14 cm) and immersion into a predetermined concentration of calcium chloride ($CaCl_2$) bath. A custom made dripping vessel fabricated from acrylic plastic, connected to an adjustable dripping clamp was used to simulate the dripping process of the molten alginate at different tip sizes. It was observed that at different dripping tips, the correction factor for the alginate slurry was found in the range of 0.73–0.83. Meanwhile, the lost factor, KLF was observed at 0.93–2.3 and the shrinkage factors were limited to 2.00% from the overall distributed data. It was concluded that liquid properties had no effect on the liquid lost factor. The bead size prediction for different concentrations of alginate solution was compared to the experimental data. Subsequently, it was concluded that increasing the tip size caused the bead size to deviate almost 20% when compared to the experimental and predicted values, respectively. [89]

4. **Lorena Segale et al., (2016),** developed Calcium Alginate and Calcium Alginate-Chitosan Beads Containing Celecoxib Solubilized in a Self-Emulsifying Phase - In this work alginate and alginate-chitosan beads containing celecoxib Solubilized into a self-emulsifying phase were developed in order to obtain a drug delivery system for oral administration, able to delay the drug release in acidic environment and to promote it in the intestinal compartment. The rationale of this work was linked to the desire to improve celecoxib therapeutic effectiveness reducing its gastric adverse effects and to favor its use in the prophylaxis of colon cancer and as adjuvant in the therapy of familial polyposis. The systems were prepared by ionotropic gelation using needles with different diameters (400 and 600 μm). Morphology, particle size, swelling behavior, and in vitro drug release performance of the beads in aqueous media with different pH were investigated. The

experimental results demonstrated that the presence of chitosan in the formulation caused an increase of the mechanical resistance of the bead structure and, as a consequence, a limitation of the bead swelling ability and a decrease of the drug release rate at neutral pH. Alginate-chitosan beads could be a good tool to guarantee a celecoxib colon delivery.[90]

5. **Bera H et al., (2015),** designed Alginate gel-coated oil-entrapped alginate-tamarind gum-magnesium stearate buoyant beads of risperidone. A novel alginate gel-coated oil-entrapped calcium-alginate-tamarind gum (TG)-magnesium stearate (MS) composite floating beads was developed for intragastricrisperidone delivery with a view to improving its oral bioavailability. The TG-blended alginate core beads containing olive oil and MS as low-density materials were accomplished by ionotropic gelation technique. Effects of polymer-blend ratio (sodium alginate:TG) and cross linker ($CaCl_2$) concentration on drug entrapment efficiency (DEE, %) and cumulative drug release after 8 h (Q8h, %) were studied to optimize the core beads by a 3(2) factorial design. The optimized beads (F-O) exhibited DEE of 75.19±0.75% and Q8h of 78.04±0.38% with minimum errors in prediction. The alginate gel-coated optimized beads displayed superior buoyancy and sustained drug release property. The drug release profiles of the drug-loaded uncoated and coated beads were best fitted in Higuchi kinetic model with Fickian and anomalous diffusion driven mechanisms, respectively. The optimized beads yielded a notable sustained drug release profile as compared to marketed immediate release preparation. The uncoated and coated Ca-alginate-TG-MS beads were also characterized by SEM, FTIR and P-XRD analyses. Thus, the newly developed alginate-gel coated oil-entrapped alginate-TG-MS composite beads are suitable for intragastric delivery of risperidone over a prolonged period of time. [91]

6. **Ji Zhang et al., (2008),** was prepared and Characterization of Tamarind Gum/Sodium Alginate Composite Gel Beads. A two-step preparation and the characterization of composite gel beads of tamarind gum (2.0 wt%) and sodium alginate (0.6 wt%) as spherically well-shaped forms are reported. In the first step, the prepared solution containing tamarind gum and sodium alginate was extruded as small drops by means of syringe into a stirred calcium chloride ($CaCl_2$, 3.0 wt%) at 4ºC and then in the second step the beads were soaked in solidified agent solution ($Na_2B_4O_7$, 2.0 Wt%). Thus, we obtained composite gel beads with diameter range between 2 and 3 mm. We have demonstrated the properties of the composite beads, such as morphological, thermal

stability and functional groups characterized by different techniques (i.e., SEM, DSC, and FTIR). The swelling behaviour in response to pH variation as well as the mechanical strength of the composite gel beads are examined and reported. The results have demonstrated that the composite gel beads not only have the advantages of rather rough surface, three-dimensionally network structure, and high anti-acid and anti-alkali properties, they are not prone to breakage under load. The composite gel beads prepared are potentially useful as polymeric carriers or supports in biotechnology and biochemistry applications.[92]

7. **Seong-In Park et al., (2013),** formulated Glutaraldehyde-crosslinked chitosan beads for sorptive separation of Au(III) and Pd(II): Opening a way to design reduction-coupled selectivity-tunable sorbents for separation of precious metals- Glutaraldehyde (GA)-cross linked chitosan beads (GA-CS) are prepared with coagulating solution containing sodium tripolyphosphate and GA, and used for the adsorption of metals from binary-metal solution Au(III) and Pd(II). GA-CS exhibited selective sorption of Au(III) in the Au(III)–Pd(II) mixture. X-ray diffraction analyses showed that Au(III) was reduced to Au(0) following sorption, while Pd(II) was present as unreduced divalent form. Increased GA led to more selectivity toward Au(III), indicating that Au(III) selectivity is attributed to reduction-couple sorption of Au(III) with a reducing agent GA. Furthermore, a 2-step desorption process enabled selective recovery of Pd and Au using 5 M HCl and 0.5 M thiourea–1 M HCl, respectively, leading to pure Pd(II) and Au(III)-enriched solutions. This finding may open a new way to design reduction-coupled selectivity-tunable metal sorbents by combination of redox potentials of metal ions and reducing agents. [93]

8. **Abeer Bashir et al., (2016),** extracted and characterized xyloglucan (tamarind seed polysaccharide) as pharmaceutical excipient- Recent study includes extraction and characterization of the xyloglucan from tamarind (Tamarindus indica) seed polysaccharide as a pharmaceutical agent. Tamarind seed polysaccharide was obtained by water based extraction in Soxhlet apparatus. For characterization of the extracted tamarind seed polysaccharide phytochemical screening was done and micromeritic properties, flow behavior and swelling index were determined. It was also found that extracted tamarind seed polysaccharide had good flow properties and pH was 6.4, this showed that it can be used in dosage form, without any irritation. Mucoadhesive nature of extracted tamarind seed polysaccharide was also evaluated by texture analyzer in

different concentration range (0.5% and 1%, w/v) and results revealed that it shows concentration based mucoadhesive strength. It can be concluded that tamarind derived seed polysaccharide (xyloglucan) can be used as pharmaceutical agent to prepare different types of formulations. [94]

9. **Thulasi V Menon et al., (2013),**formulated and evaluated Sustained Release Sodium alginate micro beads of carvedilol. The main aim of the study is to formulate Carvedilol loaded micro beads of sodium alginate using gelatin and pectin as release modifiers by ionotropic gelation method. The micro beads were prepared by varying the concentration of sodium alginate, gelatin and pectin. The drug-polymer compatibility was studied by FTIR studies. The prepared micro beads were evaluated for swelling ratio, particle size, drug entrapment, Scanning electron microscopy (SEM), bio adhesion study and inviter release study. Particle size distribution of both placebo and drug loaded formulations were measured by an optical microscope and particle size of optimized beads was determined by SEM. No significant drug-polymer interactions were observed in FT-IR studies. *In-vitro* drug release profile of Carvedilol micro beads was examined in pH 1.2 N Hydrochloric acid for first 2 hours followed by phosphate buffer pH 7.4 for remaining time. The in vitro wash-off test indicated that the sodium alginate micro beads had good mucoadhesive properties. The formulated beads had shown higher entrapment efficiency, drug loading, low particle size and moisture content. The formulation F3 released carvedilol for longer duration (24 hours) and showed better mucoadhesion. [95]

10. **A. Kramar et al., (2002),** designed Statistical optimization of diclofenac sustained release pellets coated with polymethacrylic films - The objective of the present study was to evaluate three formulation parameters for the application of polymethacrylic films from aqueous dispersions in order to obtain multiparticulate sustained release of diclofenac sodium. Film coating of pellet cores was performed in a laboratory fluid bed apparatus. The chosen independent variables, i.e. the concentration of plasticizer (triethyl citrate), methacrylate polymers ratio (Eudragit RS:Eudragit RL) and the quantity of coating dispersion were optimized with a three-factor, three-level Box-Behnken design. The chosen dependent variables were cumulative percentage values of diclofenac dissolved in 3, 4 and 6 h. Based on the experimental design, different diclofenac release profiles were obtained. Response surface plots were used to relate the dependent and the independent variables. The optimization procedure generated an optimum of 40% release in 3 h. The levels of plasticizer concentration, quantity of coating dispersion and polymer

to polymer ratio (Eudragit RS: Eudragit RL) were 25% w/w, 400 g and 3/1, respectively. The optimized formulation prepared according to computer-determined levels provided a release profile, which was close to the predicted values. We also studied thermal and surface characteristics of the polymethacrylic films to understand the influence of plasticizer concentration on the drug release from the pellets. [96]

11. **Hong Wu et al., (2005),** Prepared and Drug Release Characteristics of Pingyangmycin-Loaded Dextran Cross-Linked Gelatin Microspheres for Embolization Therapy - Gelatin microspheres (GMs) containing Pingyangmycin hydrochloride were prepared for the interventional embolization by a double-phase emulsified thermal gelation method using oxidized dextran (ox-dex) as the cross-linking agent. The average diameter of the microspheres was 82 μm with 74% ranging from 50–200 μm. Drug content and the characteristics of drug release in vitro and in vivo were evaluated using UV-spectroscopy and HPLC, respectively. The prepared microspheres showed a rather high percentage of encapsulation ranging from 85 to 88% and drug content at 7.2%. The results of in vitro experiments showed that about 65.5% of the total amount of the encapsulated drug was released after 6 h at 37°C. Experiments conducted through artery perfusion and artery embolization in rabbits revealed that the local drug concentration was significantly higher than the systemic blood– drug concentration, with a high level of local drug concentration maintained for more than 120 min after artery embolization with the Pingyangmycin-loaded ox-dex-GMs. The results indicated that the external carotid artery embolization with Pingyangmycin-loaded ox-dex- GMs at reduced dosages prolonged the local drug concentration at a higher level, and could achieve the purpose of a localized targeting tumor therapy. Compared with other embolization materials, ox-dex-GMs are an excellent alternative interventional embolization material for the treatment of head and neck tumors. [97]

12. **TaeHee Kim et al., (2005),** Performed Drug release from xyloglucan beads coated with Eudragit for oral drug delivery Xyloglucan (XG), which exhibits thermal sol to gel transition, non-toxicity, and low gelation concentration, is of interest in the development of sustained release carriers for drug delivery. Drug-loaded XG beads were prepared by extruding drop wise a dispersion of indomethacin in aqueous XG solution (2 wt.-%) through a syringe into corn oil. Enteric coating of XG bead was performed using Eudragit L 100 to improve the stability of XG bead in gastrointestinal (GI) track and to achieve gastro resistant drug release. Release behavior of indomethacin from XG beads in vitro

was investigated as a function of loading content of drug, pH of release medium, and concentration of coating agent. Adhesive force of XG was also measured using the tensile test. Uniform-sized spherical beads with particle diameters ranging from 692 ± 30 to 819 ± 50 μm were obtained. The effect of drug content on the release of indomethacin from XG beads depended on the medium pH. Release of indomethacin from XG beads was retarded by coating with Eudragit and increased rapidly with the change in medium pH from 1.2 to 7.4. Adhesive force of XG was stronger than that of Carbopol 943 P, a well-known commercial mucoadhesive polymer, in wet state. Results indicate the enteric-coated XG beads may be suitable as a carrier for oral drug delivery of irritant drug in the stomach. [98]

13. **Praveen Kumar Gaur et al., (2013),** was developed and optimized gastro-retentive mucoadhesive microspheres of gabapentin by Box– Behnken design *Context:* Gabapentin follows saturation kinetics for absorption because of carrier-mediated transport and narrow absorption window in stomach. There is need to develop a gastro-retentive formulation to maximize the absorption without crossing the saturation threshold for absorption. *Objective:* The aim was to develop a gastro-retentive formulation of gabapentin to increase the fraction of drug absorbed in stomach. *Materials and methods:* Sodium alginate and sodium Carboxymethylcellulose were used to formulate the microsphere by ionotropic gelation with calcium chloride. The formulation was optimized using a three-factor, three-level Box – Behnken design. *Results:* The particle size varied from 559.50 to 801.10 m, entrapment efficiency from 61.29 to 81.00% and in vitro release from 69.40 to 83.70%. The optimized formulation was found using point prediction, and formulation OF-3 showed optimum results at 608.21 m size, 79.65% entrapment efficiency and 82.72% drug release and 81% mucoadhesion up to 10 h. The drug release was controlled for more than 12 h. *Discussion:* The particle size was most influenced by sodium alginate while entrapment efficiency and drug release depended upon both polymers. The release followed Higuchi model. *Conclusion:* Gastro-retentive formulation was successfully optimized by a three-factor, three level Box – Behnken design and found to be useful.[99]

14. **UbaidullaUdhumansha et al., (2008),** Optimized Chitosan Succinate and Chitosan Phthalate Microspheres for Oral Delivery of Insulin using Response Surface... In the present study, a Box-Behnken experimental design was employed to statistically optimize the formulation parameters of chitosan phthalate and chitosan succinate microspheres

preparation. These microspheres can be useful for oral insulin delivery system. The effects of three parameters namely polymer concentration, stirring speed and cross linking agent were studied. The fitted mathematical model allowed us to plot response surfaces curves and to determine optimal preparation conditions. Results clearly indicated that the crosslinking agent was the main factor influencing the insulin loading and releasing. The in vitro results indicated that chitosan succinate microspheres need high amount of crosslinking agent to control initial burst release compared to chitosan phthalate microspheres. The reason may be attributed that chitosan succinate is more hydrophilic than chitosan phthalate. The relative pharmacological efficacy for chitosan phthalate and chitosan succinate microspheres (18.66, 3.84%, 16.24, 4%) was almost three-fold higher than the efficacy of the oral insulin administration (4.68 1.52%). These findings suggest that these microspheres are promising carrier for oral insulin delivery system. [100]

15. **Jakir Ahmed Chowdhury et al., (2011),** developed and Evaluated Diclofenac Sodium Loaded Alginate Cross-Linking Beads - Sustained-release polymeric beads containing Diclofenac sodium fabricated with sodium alginate were prepared by the ionotropic gelation method. Drugs were blended with sodium alginate in 1:1, 1:2, 1:2.5, 1:3, 1:3.5 and 2:2 ratios. Here, calcium chloride and aluminium sulphate was used as a cross-linking agent. Beads of Diclofenac sodium were prepared with different concentrations of drug, polymers and electrolytes. Prepared beads were evaluated for their drug entrapment efficiency, loss on drying, swelling index and release behavior. The entrapment efficiency of drug in beads depended on the amount of drug and polymer ratio as well as electrolyte concentration. The percent entrapment was highest when beads were prepared with 5 % electrolyte solution. In case of calcium chloride solution with highest amount of polymer i.e.3.5 gram the entrapment efficiency was75.12 %. But, in aluminium sulphate solution the entrapment efficiency was highest (99.06 %) when polymer amount was 2 gram. In most cases, the swelling study revealed that, up to third hour the formulations swelled high, but swelling started to decrease after fourth hour. In case of loss on drying of beads after formation showed that, the rate of solvent loss until three hours eventually continued to increasing but then decreased. In vitro dissolution data showed that, with increasing drug, polymer and electrolyte amount the Diclofenac release percentage also decreased. Among the sixteen formulations, nine of them followed Higuchi release kinetics. Thus, by modifying the polymer amount and the selection of cross linking agent plays a vital role in efficiency and sustained-release characteristics. [101]

16. **Namratapatel et al., (2015),** designed and Developed In Vitro Characterization of Capecitabine-Loaded Alginate–Pectinate–Chitosan Beads for Colon Targeting. Colon-targeted capecitabine beads were formulated by an ionotropic gelation method. The sodium alginate to pectin ratio and chitosan concentration was optimized using a 3^2 full factorial design. Analysis of response surface plots allowed the identification of an optimized formulation with high drug entrapment and controlled release. Insignificant differences in observed and predicted values for responses validated the optimization method. Optimized beads possessed an average diameter of 1395 µm and good flow properties. Their production as spherical beads having a smooth surface was confirmed by scanning electron microscopy. Fourier transform infrared spectroscopy revealed the compatibility of drug with added excipients, while differential scanning calorimetry study confirmed complete drug entrapment in polymer matrix. Higher swelling of beads in phosphate buffer pH 7.4 was obtained in comparison to pH 6.8. An in vitro wash off test indicated 70% mucoadhesion by the beads. In vitro dissolution studies of beads loaded into enteric-coated capsules revealed negligible release in simulated gastric and intestinal fluid, followed by 49.23% release in simulated colonic fluid, in 4 h. The optimized beads were found to be stable for three months at 25 ± 2°C/60 ± 5% RH. In conclusion, the formulated beads showed colon-specific controlled release properties, and thus could prove to be effective for colon cancer treatment.[102]

17. **EhsanTaghizadehDavoudi et al., (2013),** Prepared and Characterized Gastric Floating Dosage Form of Capecitabine Gastrointestinal disturbances, such as nausea and vomiting, are considered amongst the main adverse effects associated with oral anticancer drugs due to their fast release in the gastrointestinal tract (GIT). Sustained release formulations with proper release profiles can overcome some side effects of conventional formulations. The current study was designed to prepare sustained release tablets of Capecitabine, which is approved by the Food and Drug Administration (FDA) for the treatment of advanced breast cancer, using hydroxypropyl methylcellulose (HPMC), carbomer 934P, sodium alginate, and sodium bicarbonate. Tablets were prepared using the wet granulation method and characterized such that floating lag time, total floating time, hardness, friability, drug content, weight uniformity, and in vitro drug release were investigated. The sustained release tablets showed good hardness and passed the friability test. The tablets floating lag time was determined to be 30–200 seconds, and it floated more than 24 hours and released the drug for 24 hours. Then, the stability test was done and

compared with the initial samples. In conclusion, by adjusting the right ratios of the excipients including release-retarding gel-forming polymers like HPMC K4M, Na alginate, carbomer934P, and sodium bicarbonate, sustained release Capecitabine floating tablet was formulated. [103]

18. **Sanchita Mandal et al., (2010),** The objective of this study was to develop a sustained release dosage form of Trimetazidine dihydrochloride (TMZ) using a natural polymeric carrier prepared in a completely aqueous environment. TMZ was entrapped in calcium alginate beads prepared with sodium alginate by the ionotropic gelation method using calcium chloride as a crosslinking agent. The drug was incorporated either into preformed calcium alginate gel beads (sequential method) or incorporated simultaneously during the gelation stage (simultaneous method). The beads were evaluated for particle size and surface morphology using optical microscopy and SEM, respectively. Beads produced by the sequential method had higher drug entrapment. Drug entrapment in the sequential method was higher with increased $CaCl_2$ and polymer concentration but lower with increased drug concentration. In the simultaneous method, drug entrapment was higher when polymer and drug concentration were increased and also rose to a certain extent with increase in $CaCl_2$ concentration, where further increase resulted in lower drug loading. FTIR studies revealed that there is no interaction between drug and $CaCl_2$. XRD studies showed that the crystalline drug changed to an amorphous state after formulation. Release characteristics of the TM loaded calcium alginate beads were studied in enzyme-free simulated gastric and intestinal fluid. [104]

19. **M Nagpal et al., (2012),** The present study was designed to investigate the effects of different variables on the release profile of ibuprofen microspheres formulated using modified emulsification method. Eight batches of microspheres (F1-F8) were prepared by applying 2^3 factorial design. The amount of sodium alginate, amount of calcium chloride, and amount of magnesium stearate were selected as formulation variables. All the batches were evaluated in terms of percentage yield, percentage encapsulation efficiency and *in vitro* release characteristics. The batch F7 was found to be optimum batch and was further characterized via scanning electron microscopy (SEM) and particle size analysis. Multiple linear regression was applied to confirm significant effect of each variable on release characteristics. The model developed in the present study can be effectively utilized to achieve the formulation with desired release characteristics.[105]

20. **Sevgi Takka et al., (2010),** Bovine serum albumin-loaded beads were prepared by ionotropic gelation of alginate with calcium chloride and chitosan. The effect of sodium alginate concentration and chitosan concentration on the particle size and loading efficacy was studied. The diameter of the beads formed is dependent on the size of the needle used. The optimum condition for preparation alginate–chitosan beads was alginate concentration of 3% and chitosan concentration of 0.25% at pH 5. The resulting bead formulation had a loading efficacy of 98.5% and average size of 1,501 μm, and scanning electron microscopy images showed spherical and smooth particles. Chitosan concentration significantly influenced particle size and encapsulation efficiency of chitosan–alginate beads ($p < 0.05$). Decreasing the alginate concentration resulted in an increased release of albumin in acidic media. The rapid dissolution of chitosan–alginate matrices in the higher pH resulted in burst release of protein drug.[106]

21. **VM. Sherina et al., (2012),** The objective of the current investigation is to reduce dosing frequency and improve patient compliance by designing and systematically evaluating sustained release micro beads of Nifedipine. Frequent administration and variable low bioavailability (40-50%) after oral administration are problems of conventional dosage forms of Nifedipine can be attenuated by designing it in the form of mucoadhesive micro beads which would prolong the residence time at the absorption site to facilitate intimate contact with the absorption surface and thereby improve and enhance the bioavailability. Nifedipine-loaded mucoadhesive micro beads were successfully prepared by ionotropic gelation and cross linking technique by using sodium alginate as the hydrophilic carrier in combination with HPMC and chitosan polymers as drug release modifiers. Prepared beads were evaluated for particle size, swelling ratio, drying rate, drug entrapment, bio adhesion study, inviter release, release kinetic and stability study. Particle size distribution of both placebo and drug loaded formulations were measured by an optical microscope and particle size of optimized beads was determined by SEM. No significant drug-polymer interactions were observed in FT-IR studies. In-vitro drug release profile of Nifedipine micro beads was examined in phosphate buffer pH 6.8 and exhibited zero order kinetic followed by super case II-transport. The in vitro wash-off test indicated that the sodium alginate micro beads had good mucoadhesive properties. The drug loaded batches were found to be stable when stored at room temperature for 45 days. Hence the formulated HPMC coated Sodium alginate beads can be used as an alternative and

cheaper carrier for the oral controlled delivery of Nifedipine, especially for the treatment of angina pectoris and hypertension. [107]

22. **Nokhodchi A et al., (2004),** Small matrices of calcium alginate or aluminium alginate have been investigated as possible controlled release systems for drugs. The objective of the present study was to sustain the release of theophylline from alginate matrices using different concentrations of aluminum chloride and calcium chloride in presence and absence of HPMC. Tablets containing differing concentrations of aluminum and calcium chloride were produced and the release rate of theophylline was tested using the basket dissolution apparatus over 8 h. Increasing amounts of aluminum chloride from 0.0001 to 0.00068 moles decreased the release of theophylline from 95.1 +/- 0.27 to 29.5 +/- 1.5, indicating a significant effect of aluminum ions on a reduction in the release rate of theophylline from sodium alginate matrices. In the case of matrices containing different concentrations of calcium ions, as the concentration of calcium chloride increased, the release rate increased to an optimum then declined after this. This was due to insufficient calcium ions being available to cross-link with the sodium alginate to form an insoluble gel. The effect of aluminum ions, as this is a trivalent ion compared to calcium, which is a divalent ion, aluminum ions are able to decrease the release rate with a smaller concentration compared to calcium ions. The results also showed that the presence of HPMC caused a reduction in release rate of theophylline from alginate matrices containing calcium chloride. Whereas, in the case of alginate matrices containing aluminum chloride the release rate of theophylline increased in presence of HPMC. For comparing the dissolution data, dissolution efficiency (DE) was used. The values of DE are consistent with the dissolution data. The results show that within a formulation series, DE values generally decrease when the cation concentration increases and this criterion can be used to describe the effect of calcium and aluminum ions on the release behavior of theophylline from polymeric matrices. [108]

23. **Phani Kumar G.K et al., (2011),** was Isolated and Evaluated of Tamarind Seed Polysaccharide being used as a Polymer in Pharmaceutical Dosage Forms. Tamarind seed polysaccharide (TSP) obtained from the seed kernel of Tamarindus indica, possesses properties like high viscosity mucilage, broad pH tolerance, no carcinogenicity, mucoadhesive nature, and biocompatibility. It is used as stabilizer, thickener, gelling agent, and binder in food and pharmaceutical industries. The objective of present investigation was to search for a cheap and effective natural excipient that can be used as

an effective alternative for the formulation of pharmaceutical formulations. Thus this mucilage will be a non-toxic, bio-degradable, cheap, economic and easily available option as a natural polymer.[109]

24. **Akbuğa J et al., (2013),** 5-Fluorouracil-loaded chitosan microspheres: preparation and release characteristics Cross-linked chitosan microspheres containing 5-Fluorouracil (5-FU) were prepared. Variables believed to be important for microsphere properties were examined; these included: drug and chitosan concentrations, cross-linking process, the type of oil, stirring rate and also additives. Initial 5-FU concentration, the type and concentration of chitosan, the viscosity of oil phase and glutaraldehyde concentration affected drug release from chitosan microspheres. 5-FU release from cross-linked chitosan microspheres is characterized by an initial rapid release of drug. Addition of substances such as alginic acid, chitin, agar, sodium caprylate and stearic acid changed the release properties of 5-FU microspheres. [110]

25. **Ziyaur Rahman et al., (2006)** Characterization of 5-fluorouracil microspheres for colonic delivery. The purpose of this investigation was to prepare and evaluate the colon-specific microspheres of 5-fluorouracil for the treatment of colon cancer. Core microspheres of alginate were prepared by the modified emulsification method in liquid paraffin and by cross-linking with calcium chloride. The core microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach and small intestine. The microspheres were characterized by shape, size, surface morphology, size distribution, incorporation efficiency, and in vitro drug release studies. The outer surfaces of the core and coated microspheres, which were spherical in shape, were rough and smooth, respectively. The size of the core microspheres ranged from 22 to 55 μm, and the size of the coated microspheres ranged from 103 to 185 μm. The core microspheres sustained the drug release for 10 hours. The release studies of coated microspheres were performed in a pH progression medium mimicking the conditions of the gastrointestinal tract. Release was sustained for up to 20 hours in formulations with core microspheres to a Eudragit S-100 coat ratio of 1:7, and there were no changes in the size, shape, drug content, differential scanning calorimetry thermo gram, and in vitro drug release after storage at 40°C/75% relative humidity for 6 months. [111]

26. **Arica B et al., (2002),** 5-Fluorouracil encapsulated alginate beads for the treatment of breast cancer. Alginate beads containing 5-fluorouracil (5-FU) were prepared by the gelation of alginate with calcium cations. Alginate beads loaded with 5-FU were prepared at 1.0 and 2.0% (w/v) polymers. The effect of polymer concentration and the drug loading (1.0, 5.0 and 10%) on the release profile of 5-FU was investigated. As the drug load increased, larger beads were obtained in which the resultant beads contained higher 5-FU content. The encapsulation efficiencies obtained for 5-FU loads of 1.0, 5.0 and 10% (w/v) were 3.5, 7.4 and 10%, respectively. Scanning electron microscopy (SEM) and particle size analysis revealed differences between the formulations as to their appearance and size distribution. The amount of 5-FU released from the alginate beads increased with decreasing alginate concentrations. [112]

27. **Merve Olukman et al., (2012),** Release of Anticancer Drug 5-Fluorouracil from Different Ionically cross-linked Alginate Beads. In this research, the release of 5-Fluorouracil (5-FU) from different ionically cross-linked alginate (Alg) beads was investigated by using Fe^{3+}, Al^{3+}, Zn^{2+} and Ca^{2+} ions as cross linking agent. The prepared beads were characterized by Fourier Transform Infrared Spectroscopy (FTIR) Differential Scanning Calorimetry (DSC) and Scanning Electron Microscopy (SEM). The drug release studies were carried out at three pH values 1.2, 6.8 and 7.4 respectively each for two hours. The effects of the preparation conditions as cross linker type, drug/polymer (w/w) ratio, cross linker concentration and time of exposure to cross-linked on the release of 5-FU were investigated for 6 hours at 37˚C. It was observed that 5-FU release from the beads followed the order of Fe > Zn > Al > Ca-Alg and increased with increasing drug/polymer ratio. At the end of 6 hours, the highest 5-FU release was found to be 90% (w/w) for Fe-Alg beads at the drug/polymer ratio of 1/8 (w/w), cross linker concentration of 0.05 M, exposure time of 10 minutes respectively. The swelling measurements of the beads supported the release results. Release kinetics was described by Fickian and non-Fickian approaches. [113]

28. **Verma Navneet et al., (2016),** formulated and evaluated chitosan containing mucoadhesive buccal patches of metoprolol succinate; Mucoadhesive buccal patches containing metoprolol succinate were prepared using the solvent casting method. Chitosan was used as bioadhesive polymer and different ratios of chitosan to PVP K-30 were used. The patches were evaluated for their physical characteristics like mass variation, drug content uniformity, folding endurance, ex vivo mucoadhesion strength, ex

vivo mucoadhesion time, surface pH, in vitro drug release, and in vitro buccal permeation study. Patches exhibited controlled release for a period of 8 h. The mechanism of drug release was found to be non-Fickian diffusion and followed the first-order kinetics. Incorporation of PVP K-30 generally enhanced the release rate. Swelling index was proportional to the concentration of PVP K-30. Optimized patches (F4) showed satisfactory bioadhesive strength of 9.6 ± 2.0 g, and ex vivo mucoadhesion time of 272 minutes. The surface pH of all patches was between 5.5 and 6.8 and hence patches should not cause irritation in the buccal cavity. Patches containing 10 mg of drug had higher bioadhesive strength with sustained drug release as compared to patches containing 20 mg of drug. Good correlation was observed between the in vitro drug release and in vitro drug permeation with a correlation coefficient of 0.9364. Stability study of optimized patches was done in human saliva and it was found that both drug and buccal patches were stable. [114]

29. **Meulenaar J et al., (2014), developed** an extended-release formulation of capecitabine making use of in vitro-in vivo correlation modeling. An oral extended-release (ER) formulation of capecitabine was developed for twice daily dosing, theoretically providing a continuous exposure to capecitabine, thus avoiding the undesirable in-between dosing gap inherent to the dosing schedule of the marketed capecitabine immediate-release formulation (Xeloda(®)). The target 12-hour in vivo release profile was correlated to an in vitro dissolution profile using an in vitro-in vivo correlation model based on the pharmacokinetic (PK) and dissolution characteristics of Xeloda(®). Making use of the slow dissolution characteristics of amorphous capecitabine as reported previously and screening of a panel of ER excipients, an ER formulation was designed. Kollidon(®) SR induced the most prominent ER. Moreover, it was shown that tablets prepared from CoSD capecitabine and Kollidon(®) SR have an additional threefold delay in dissolution compared with tablets prepared from the same but only physically mixed components. Therefore, a prototype tablet formulation composed of co-spray-dried capecitabine and Kollidon(®) SR (98/2%, w/w) mixed with colloidal silicon dioxide (0.5%, w/w) and magnesium stearate (2.5%, w/w) was defined. This prototype shows similar dissolution characteristics as the modelled dissolution profile. Currently, the in vivo PK of our designed ER capecitabine formulations is investigated in a clinical study. [115]

30. **G. Pavani et al., (2013),** Formulated and Evaluated Of Capecitabine Sustained Release Tablets. The objective of the present investigation was to formulate and devaluate sustained release of Capecitabine tablets. Capecitabine sustained release tablets were developed different polymers HPMC K 100, Carbopol 974 and Xanthan Gum with different ratios. Totally 9 formulations were prepared. Sustained release tablets of Capecitabine were prepared by wet granulation technique. The prepared granules evaluated in terms of their Pre-compression studies like Tapped Density, Bulk Density, Angle of repose, Carr's Index and Hausner's ratio. The tablets were evaluated by Post-compression studies like hardness, thickness, friability and in vitro studies. The results of in vitro drug release studies showed that formulation-2 (API and HPMC and Xantham gum) has better drug release (98.44%) for 24hrs. [116]

AIM AND OBJECTIVE

Colorectal cancer is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths in the world. The global burden of colorectal cancer is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030. Rapid increases in both CRC incidence and mortality are now observed in many countries particularly in Europe, Asia and South America. Capecitabine drug has been widely used for treating colon cancer but it's very short plasma half- life (0.85 hours) leads to its rapid elimination from the body necessitating its frequent administration.

The oral colon targeting system refers to the system, in which the release of orally administered therapeutic agents is controlled, until they reach cecum or colon. Hence the local action can be exerted into the diseased region devoiding destructing the normal cells of upper GIT. This approach facilitates the therapeutic efficacy of the drug by minimizing the toxic or adverse effect at the same time. Most of the conventional drug delivery systems targeting colon fails, as the therapeutic agent don't reach up to the colon in appropriate concentration. This effective and safe therapy aspiring colon specific delivery is of almost challenging task.

During past few decades, employing natural polymers for the development of various drug delivery systems has been time lighted. Natural polymers have ample of advantages like easy availability, cost effectiveness, biodegradability and biocompatibility. Alginates are generally regarded as safe (GRAS) by the FDA. Na-Alg is a Na salt of alginic acid, which is a co-polymer of β-D-alginic acid, which is a co-polymer of β-D-mannuronic acid (m) and α-L-gluuronic acid (G) having 1,4-glycosidic linkage between them. Many authors were reported that calcium alginate beads have been used for oral control drug delivery system but it has a main drawback of pH dependent solubility which could lead to fast dissolution rate and rapid drug release in gastro intestinal fluid and it also shows poor entrapment efficiency due to its poor viscosity.

In recent year's blended polymeric system are exploited in the region of targeted drug delivery systems. Biodegradable polymers obtained from Tamarindus indica L. seeds received the consideration of several researches because of its economic and easy availability. TSP is composed of chemically highly branched carbohydrate polymer. Its backbone consists of D-glucose units joined with (1-4) b-linkages similar to that of cellulose. It consists of a main chain of b-D- (1-4)-galactopyranosyl unit with a side chain of single

xylopyranosyl unit attached to every second, third and fourth of D glucopyranosyl unit through a-D- (1-6) linkage. Earlier report was shown while increasing the ratio of the TSP the drug loading was found to be maximum might be due to increase in viscosity of the polymer-blend solutions and could prevent the drug leakage from the beads.

The objective of the study was to develop colon specific drug delivery system (CDDS) which is capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine but only released and absorbed once the system reaches the colon. Cross-linked Chitosan succinate was reported as pH dependent polymer which was most suitable polymer for colon specific delivery system and protected acid degradation of capecitabine in acidic pH. To our best knowledge still no reports were available for the study of chitosan succinate cross-linked CP loaded AG-TG beads as a novel colon targeted drug delivery system.

PLAN OF THE WORK

1. **LITERATURE SURVEY**
2. **PREFORMULATION STUDIES**
   a) Organoleptic properties
   b) Incompatibility studies
   c) Calibration curve of Capecitabine
3. **TAMARIND GUM**
   a) Isolation of Tamarind gum
   b) Characterization of Tamarind gum
4. **CHITOSAN SUCCINATE**
   a) Preparation of Chitosan succinate
   b) Characterization of Chitosan succinate
5. **OPTIMIZATION OF BEADS**
   a) Preparation of Sodium alginate and Tamarind gum beads
   b) Preparation of Capecitabine loaded Sodium alginate and Tamarind gum beads
   c) Chitosan succinate decorated Capecitabine loaded Sodium alginate and Tamarind gum beads
6. **EVALUATION OF BEADS**
   a) Particle size and surface morphology
   b) Tapped density
   c) Compressibility index
   d) Angle of repose
   e) Hausner's ratio

f) Moisture content

g) Drug entrapment efficiency

h) Drug loading

i) Swelling studies

7. INVITRO RELEASE STUDIES

8. INVITRO RELEASE KINETICS

9. STABILITY STUDIES

DRUG PROFILE

CAPECITABINE [117-119]

IUPAC Name:

Pentyl [1-(3, 4-dihydroxy-5-methyltetrahydrofuran-2-yl)-5-fluoro-2-oxo-1H pyrimidin-4-yl] carbonate

Structure:

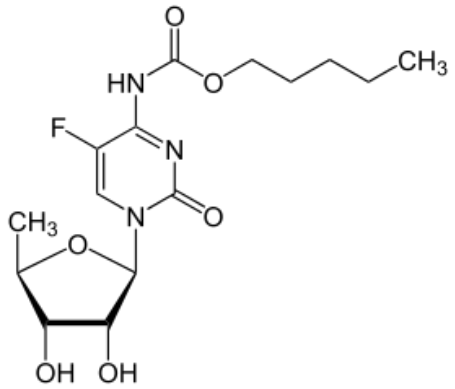


FIG NO: 7 STRUCTURE OF CAPECITABINE

Molecular Formula	**:**	$C_{15}H_{22}FN_3O_6$
Molecular weight	**:**	359.35
Melting point	**:**	110-121˚C
LogP	**:**	0.4
Solubility	**:**	It is soluble in water (2ymg/ml)
Category	**:**	Antineoplastic
$T_{1/2}$	**:**	Approximately 38-45 minutes
Dose	**:**	The usual starting dose is 2,500mg/m2/day in two divided doses, 12 hours apart. One cycle includes two weeks of treatment followed by one week without treatment. Cycles can be repeated every three weeks.
BCS	**:**	Class type III (High solubility, Low permeability)

Pharmacokinetics:

Absorption:

Readily absorbed through GI tract (approximately 70%).Time to reach peak plasma concentration for Capectabine is approximately 1.5 hours and for 5-fluorouracil is 2 hours. Food decreased peak plasma concentration is 60% and area under curve is 35% for Capecitabine and decreased peak plasma concentration (Cmax) 4.3% and area under curve 21% for 5-fluorouracil. Food delayed Tmax is 1.5 hours.

Protein binding:

Less than 60% protein binding (mainly albumin).

Metabolism:

Metabolized by thymidine phosphorylase to fluorouracil .

Elimination:

Capecitabine and its metabolites are predominantly excreted in urine. About 95.5% of administered Capecitabine dose is recovered in urine. Focal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

Mechanism of Action:

Capecitabine is a prodrug that is selectively tumor-activated to its cytotoxic moiety, fluorouracil, by thymidine phosphorylase, an enzyme found in higher concentrations in many tumors compared to normal tissues or plasma. Fluorouracil is further metabolized to two active metabolites, 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP), within normal and tumor cells. These metabolites cause cell injury by two different mechanisms. First FDUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS)to form a covalently bound ternary complex. This binding inhabits the formation of thymidylate from 2'-deaxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, therefore a deficiency of this compound can inhabit cell division. Secondly, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis through the production of fraudulent RNA.

Indications and usage:

Capecitabine is a nucleoside metabolic inhibitor with anti-neoplastic activity. It is used in the treatment of adjuvant colon cancer Stage III Duke's C-used as first-line monotherapy.

Metastatic colon rectal cancer

First line as monotherapyalone is preferred.

Metastatics breast cancer

Asmonotherapy, if the patient has failed paclitaxel based treatment, and if anthracycline based treatment, and if anthracycline based treatment has either failed or cannot be continued the other reasons.

Used in combination with docetaxel, after failure of anthracycline based treatment.

Adverse reactions:

Most common adverse reactions are:

Cardiovascular	:	EKG changes, myocardial infarction, angina.
Dermatological	:	Hand and foot syndrome.
Gastrointestinal	:	Diarrhea, Nausea, Stomatitis.
Heamatological	:	Neutropenia, anemia and thrombocytopenia.
Hepatic	:	Hyperbilirubinemia.

Drug interaction:

Anticolagulants	:	May interact with warfarin and increase bleeding risk.
Phenytoin	:	May inhibit cytochrome CYP2C9 enzyme, and therefore increaselevels of substrates such as Phenytoin and other substrates of CYP2C9
Leucovorin	:	The concomitant use of Leucovorin increased the toxicity of Capecitabine without any apparent advantage in response rate.

Pharmacodynamics:

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity indicated for the treatment of metastatic breast cancer and colon cancer. It is an orally administered systemic prodrug that has little pharmacologic activity until it is converted to fluorouracil by enzymes that are expressed in higher concentrations in many tumors. Fluorouracil it then metabolized both normal and tumor cells to 5-fluoro-2'-deoxyuridine 5-'monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP).

POLYMER PROFILE

SODIUM ALGINATE [120]

Non-proprietary Names	:	BP	: Sodium Alginate
		PhEur	: Sodium Alginate
		USP-NF	: Sodium Alginate
Synonym	:	Alginatosodico, Algin, Alginic acid, Sodium salt, E40, Kelcosol, Keltone, Natriialginas, Protanal,Sodium polymannuronate.	
Chemical Name	:	Sodium alginate	
Functional category	:	Stabilizing agent, suspending agent, tablet and capsule disintegrate, tablet binder, viscosity increasing agent	
Structural Formula	:		

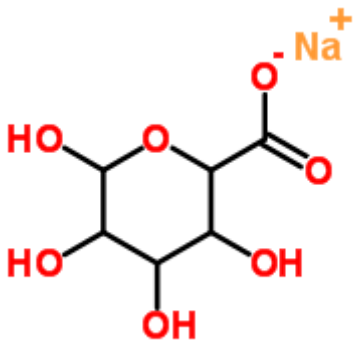


FIG NO: 8 STRUCTURE OF SODIUM ALGINATE

Molecular Weight	:	216.121gm/mol.
Description	:	Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Solubility:

Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than slowly solublein water, forming a viscous colloidal solution.

Viscosity:

Typically, a 1% w/v aqueous solution, at 20ºC, will have a viscosity of 20– 400 mPas (20–400 cP). Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions. Above pH 10, viscosity decreases.

Incompatibilities:

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenyl mercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4% of sodium chloride is present.

Stability and storage condition:

Stable, the bulk material should be stored in an airtight container in a cool, dry place.

Safety:

It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.

Application in pharmaceutical formulation or technology:

Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrate, it has been used as a diluent in capsule formulations. Sodium alginate has also been used in the preparation of sustained-release oral formulations. In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions. Recently, sodium alginate has been used for the aqueous microencapsulation of drugs.

ZINC SULPHATE [120]

Description : Zinc sulphate is the inorganic compound with the formula ZnSO4 as well as any of three hydrates. It was historically known as "white vitriol". All of the various forms are colorless solids. The heptahydrate is commonly encountered. It is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system.

Structure :

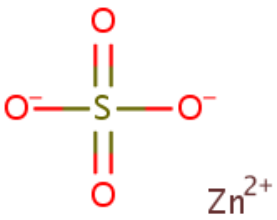


FIG NO: 9 STRUCTURE OF ZINC SULPHATE

Categories : Acids, Non-carboxylic acids, Alimentary Tract and Metabolism, Anions, Astringents, Dermatologic Agents, Electrolytes, Ions, Mineral Supplements, Sulfates, Sulfur Acids, Sulfur Compounds, Sulfuric Acids, Zinc Compounds.

Chemical Formula : $ZnSO_4$

IUPAC Name : Zinc(2+) ion sulphate

Indication : This medication is a mineral used to treat or prevent low levels of zinc. In medicine it is used together with oral rehydration therapy (ORT) and an astringent. Zinc Sulfate Injection, USP is indicated for use as a supplement to intravenous solutions given for TPN.

Pharmacodynamics : Zinc has been identified as a cofactor for over 70 different enzymes, including alkaline phosphatase, lactic dehydrogenase and both RNA and DNA polymerase. Zinc facilitates wound healing, helps maintain normal growth rates, normal skin hydration and the senses of taste and smell.

Mechanism of action : Zinc inhibits cAMP-induced, chloride-dependent fluid secretion by inhibiting basolateral potassium (K) channels, in in-vitro studies with rat ileum. This study has also shown the specificity of Zn to cAMP-activated K channels, because zinc did not block the calcium (Ca)-mediated K channels. As this study was not performed in Zn-deficient animals, it provides evidence that Zn is probably effective in the absence of Zn deficiency. Zinc also improves the absorption of water and electrolytes, improves regeneration of the intestinal epithelium, increases the levels of brush border enzymes, and enhances the immune response, allowing for a better clearance of the pathogens.

Absorption : Approximately 20 to 30% of dietary zinc is absorbed, primarily from the duodenum and ileum. The amount absorbed is dependent on the bioavailability from food. Zinc is the most bioavailable from red meat and oysters. Phytates may impair absorption by chelation and formation of insoluble complexes at an alkaline pH. After absorption, zinc is bound in the intestine to the protein metallothionein. Endogenous zinc can be reabsorbed in the ileum and colon, creating an enter pancreatic circulation of zinc.

Volume of distribution	:	After absorption zinc is bound to protein metallothionein in the intestines. Zinc is widely distributed throughout the body. It is primarily stored in RBCs, WBCs, muscles, bones, Skin, Kidneys, Liver, Pancreas, retina, and prostate.
Protein binding	:	Zinc is 60% bound to albumin; 30 to 40% bound to alpha-2 macroglobulin or transferring; and 1% bound to amino acids, primarily histidine and cysteine.
Route of elimination	:	Primarily fecal (approximately 90%); to a lesser extent in the urine and in perspiration.
Half-life	:	3 hours
Toxicity	:	Human:TDL Oral) 45mg/kg/7D-C : Normocytic anemia, pulse rate increase without fall inBP Human: TDL. (oral) 106mg/kg : Hypermotylity, diarrhea Mouse ; LD50 Oral : 245mg/kg Mouse : LD50 : subcutaneous : 781mg/kg.
Substituents	:	Transition metal sulphate, Inorganic oxide, Inorganic

CHITOSAN SUCCINATE [120]

Structure :

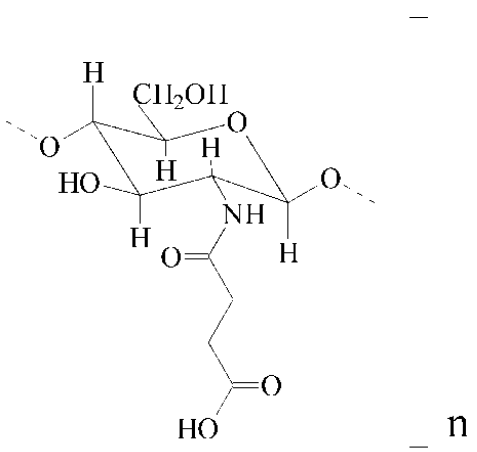


FIG NO: 10 STRUCTURE OF CHITOSAN SUCCINATE

Chitosan succinate Synthesis: Synthesis of chitosan succinate: DAC (1.0g) was dissolved in dimethyl sulfoxide (20ml). Prescribed succinc anhydride (1.0g) was added to the diluted solution and stirred at 60 C. After standing for 24h, the pH of the mixture was adjusted to with 5% w/v aq. NaOH to give a precipitate. The precipitate was collection by filtration and dispersed in 50ml of H_2O. the pH of the dispersion was adjusted to 10-12 with w/v aq. NaOH to give a pale yellow solution.. The solution was dialysed using dialysis membrane (molecular weight of, 12000-14000) at room temperature for 2-3 days and lyophilized. The lyophilized samples were recovered. The synthesis route was shown in fig 11.

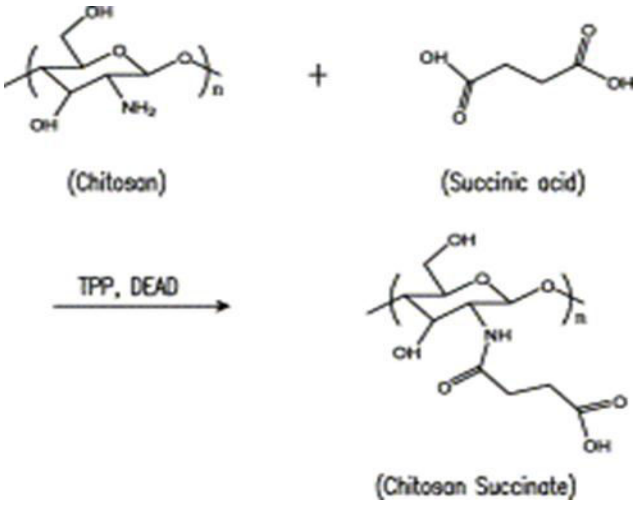


FIG NO: 11 SYNTHESIS OF CHITOSAN SUCCINATE

Isoelectric point : Chitosan succinates has both amino and carboxy group. The isoelectric point which exists equimolar of NH3* and -COOH' are calculated and was found to be 526.

Solubility : Solubility of chitosan succinate was studied in water of various pH. It showed good solubility in the basic region above pH 7.8 and this is may be due to protonation of amino group.

Those with a family history I two or more first degree relatives have a two to threefold greater risk of disease and this group accounts for about 20% of a; cases. A number of genetic syndromes are also associated with higher rates of colorectal cancer.

List of materials and suppliers

Table 2: List of materials used

S.NO	RAW MATERIALS	MANFACTURER
1.	Capecitabine	Sigma aldrich private limited
2.	Chitosan	Mahtani private limited
3.	Pyridine	Rolex laboratory reagent
4.	Ethyl alcohol	Merck life science private limited
5.	Sodium alginate	S.D Fine Chemicals, Mumbai India
6.	Zinc Sulphate	S.D Fine Chemicals, Mumbai India
7.	Glutraldehyde	Lobachemie laboratory and fine chemicals
8.	Ethanol	Lobachemie laboratory and fine chemicals

List of equipment's and manufacturer

Table 3: List of instruments used

S.NO	INSTRUMENTS	MANFACTURER
1.	Electronic balance	Wensar
2.	Digital pH meter	Elico
3.	Sonicator	Vibro cell
4.	Dissolution apparatus	Electrolab
5.	Magnetic stirrer	Remi motors
6.	Mechanical shaker	Technical lab

7.	UV spectrometer	Shimadzu, Japan
8.	Fourier transit infra-red spectroscopy	Thermo scientific Nicolet ISF
9.	Scanning electron microscopy	JEOL
10.	Electronic microscope	LW electronic microscopes
11.	Hot air oven	Techno lab

CHARACTERIZATION OF DRUG [115]

Organoleptic properties:

The organoleptic characters of the drug like colour, odour, taste and appearance play an important role in the identification of the sample and hence they should be recorded in descriptive terminology.

Solubility studies:

An excess of drug is suspended in 100ml of dissolution medium containing various concentrations of carriers in stopper flask and equilibrated by intermittent shaking for 72 hrs maintained at 37±20c.The solution is filtered through whattman filter paper. A portion of filtrate is diluted suitably and analyzed by UV spectroscopy.

ESTIMATION OF CAPECTABINE

STANDARD GRAPH OF CAPECITABINE [116]

CONSTRUCTION OF STANDARD GRAPH OF CAPECITABINE (0.1 N HCL)

PREPARATION OF STOCK SOLUTION

Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. Few ml of water was added to dissolve the drug and volume was made up to 100 ml with 0.1 N HCl. The resulted solution had the concentration of 1mg/ml which was labeled as “stock”.

PREPARATION OF WORKING STANDARD SOLUTION

From this stock solution 10ml was taken and diluted to 100 ml with 0.1 N HCl which has given the solution having the concentration of 100mcg/ml.

PREPARATION OF SERIAL DILUTIONS FOR STANDARD CALIBRATION CURVE

Necessary dilutions were made by using the standard solution to give the different concentrations of Capecitabine (0-60mcg/ml) solutions. The absorbance of above solutions were recorded at max (303nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

CONSTRUCTION OF STANDARD GRAPH OF CAPECITABINE (PH5.8 BUFFER)

PREPARATION OF STOCK SOLUTION

Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. Few ml of water was added to dissolve the drug and volume was made up to 100 ml with pH 5.8 buffer. The resulted solution had the concentration of 1mg/ml which was labeled as "stock".

PREPARATION OF WORKING STANDARD SOLUTION

From this stock solution 10ml was taken and diluted to 100 ml with pH 5.8 buffer which has given the solution having the concentration of 100mcg/ml.

PREPARATION OF SERIAL DILUTIONS FOR STANDARD CALIBRATION CURVE

Necessary dilutions were made by using this second solution to give the different concentrations of capecitabine (0-20mcg/ml) solutions. Theabsorbance of above solutions was recorded at max (303nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

CALIBRATION CURVE OF CAPECITABINE (pH 7.4)

An accurately weighed quantity of 100mg Capecitabine was transferred into a 100ml standard flask and volume was made up to the mark using Phosphate buffer of pH 7.4. From the primary stock solution 2ml was transferred to 100 ml volumetric flask and diluted upto the mark using Phosphate buffer of pH 7.4. The concentration of the solution will be 20µg/ml. Various concentrations 4µg, 8µg, 12µg, 16µg, 20µg, 24µg, 28µg 32µg, were prepared by diluting 1ml, 2ml, 3ml, 4ml, 5ml, 6ml, 7ml, 8ml, 9ml and 10ml of the stock solution to 10ml using buffer of pH 7.4 respectively. The absorbance was noted at 303nm using UV/Vis Spectrophotometer.

EXTRACTION PROCEDURE

Tamarind seeds were purchased from the seeds shop situated in the chennai, India. Seeds were boiled and mucilage was taken out. Mucilage was dried, powdered and further passed from sieve # 20 and stored in air tight container until used.

Extraction of tamarind polysaccharide includes two steps:

Step 1: Extraction of tamarind polysaccharide

Tamarind gum extracted by tamarind seeds were done as following

Crude tamarind seeds were washed neat and clean then kept for 3 hrs boiling. After completion of boiling, boiled seeds were kept for cooling for 24 hrs so that mucilage is being expelled out from the seeds. Completing 24 hrs of expulsion of mucilage from seeds, heat them for few minutes then set for cooling. Pour seeds with mucilage in the muslin cloth and press till all the mucilage is squeezed from the seeds. Temperature of extraction media was maintained at 70˚C and duration of extraction was adjusted about 6 hrs.[121,122]

Step 2: Isolation of tamarind seed polysaccharide

In hot water boiled tamarind seeds were kept for 24 hrs so that the mucilage can come out from the seeds. After 24 hrs, boiled the seeds containing tamarind gum for 1 hr. Water extracted juice were squeezed with muslin cloth bag and the concentrated juice was cooled to 4˚C. Tamarind seed polysaccharide tamarind gum was precipitated by alcohol-juice treatment 2:1(v/v) followed by continuous stirring for 15 min and mixture was further allowed to stand for 2 hrs for better tamarind seed polysaccharide precipitation. This allows filtering of polysaccharide substances because tamarind seed polysaccharide remains float on the surface of alcohol-water mixture. Floating tamarind polysaccharide coagulate was filtered through muslin cloth, washed with alcohol (95%) and squeezed. Squeezed tamarind seed polysaccharide was further dried to constant weight at 35-45°C in hot air oven. Hard tamarind seed polysaccharide cake was ground and sieved through sieve # 20, stored in desiccators for further use.

PHYSICOCHEMICAL CHARACTERIZATION OF TAMARIND SEED

pH of Tamarind Seed Polysaccharide:

Firstly, extracted tamarind gum was weighed and then dissolved in water separately to get a 1% w/v solution. The pH of solution was determined using pH meter.[123]

Powder properties

The flow properties of the sample were investigated by the angle of repose, bulk density and tapped density measurements. The angle of repose was determined on 50 g of sample using Borosilicate glass funnel (with orifice diameter and a base diameter of 6.5 mm and 8 cm respectively). Bulk and tapped densities were measured in 100 ml of graduated cylinder. The sample contained in the cylinder was tapped mechanically by means of Auto-Tap Shaker .The tapped volume was noted down when it showed no change in its value. The data generated from bulk densities and tapped densities were used in figured the Carr's index and Hausner's ratio for the tamarind seed powder. True density was obtained by helium pycnometer. The data generated from bulk density and true densities were utilized for calculating the porosity of powder mass. Moisture content was determined by official method of USP32-NF27 in a mechanical convection oven at 105˚ C to the weight constants.

Solubility behavior

One part of dry tamarind seed polysaccharide powder was shaken with different solvents and their solubility was determined. Solubility of tamarind seed polysaccharide was determined in basic solvents i.e Acetone, Chloroform, Hexane, Butanol and Water. It has been observed that polysaccharide is soluble in every solvent.[123]

SYNTHESIS OF CHITOSAN SUCCINATE

The reaction was carried out according to the previously reported method. Briefly, chitosan (1.00 g, corresponding to approximately 6.20mmols glucosamine) was dissolved in HCl aqueous solution (0.37%,50 ml) at ambient temperature, and a solution of the anhydride (6.25mmol; succinic 0.63 g) in pyridine (5 ml) was added dropwise withvigorous stirring. The reaction pH was maintained at 7.0 by the drop wiseaddition of NaOH solution (1.0 M). NaOH addition was continued till thepH was stabilized. After 40 min the reaction was terminated by the additionof NaCl aqueous solution (20%, 200 ml). The resulting precipitate wasfiltered, washed with acetone and diethyl ether, and desiccated to givechitosan succinate conjugates.

CHARACTERIZATION OF CHITOSAN SUCCINATE

Determination of Degrees of Substitution on Chitosan and UV Analysis

The degrees of phthalate or succinate substitution on chitosan were determined as follows: Chitosan conjugates (0.10 g) were completely hydrolyzed in a NaOH aqueous solution (3.0 M) and over 48 h. The concentrations ofsuccinic acids in the hydrolysis solutions were determined byUV measurement, at l = 228 nm for succinicacid. Non-conjugated chitosan was treated in the same way, and the resulting solution was used as a blank. The degree of substitution (expressed as g %)is defined as the ratio of the measured amount of succinic acid(in grams) in the hydrolysis solution, to the amount of the hydrolyzedchitosan conjugates (in grams)[114].

Solubility of polymer

Chitosan and CS polymer were placed in a 100 ml screw-capped bottle containing different pH solution (pH 1.2, 4.5 and 7.4). The polymeric suspension was then shaken using amechanical shaker (Techno Lab, Chennai) at room temperature for 48 h. The suspensionwas then filtered and left overnight to dry under vacuum. The dissolved amount was then calculated by weight difference.

OPTIMIZATION OF BEADS [100]

Two optimization processes was carried out to optimize: 1. Preparation of sodium alginate tamarind gum beads using $ZnSO_4$as a cross linker 2. Preparation of Chitosan succinate coated alginate tamarind beads using Glutraldehyde as a cross linker.

Optimization of A three-factor, one response design is suitable for exploring quadratic response surfaces and for constructing second order polynomial models with Design Expert ® (version10) Stat-Ease Inc., Minneapolis, Minnesota). The independent and dependent variables are listed in Table 4 and 5 along with their low, medium and high levels. The polynomial equation generated by this experimental design is given as:

$$Y_0 = b_0+b_1A+b_2B+b_3C+b_{12}AB+b_{13}AC+b_{23}BC+b_{23}BC+b_{11}A^2+b_{22}B^2+b_{33}C^2$$

Where dependent variable Y_1drug release for the both optimization process, and A, B and C are the independent variables representing sodium alginate, tamarind gum and calcium chloride concentrations for optimization of process one and alginate tamarind gum ratio, Chitosan succinate and glutraldehyde concentrations for optimization process two,

respectively. b_0 is a constant; b_1,b_2 and b_3 are the coefficients translating the linear weight of A, B and C, respectively; b_{12} , b_{13} and b_{23} are the coefficients translating the interactions between the variables; and b_{11} , b_{22} and b_{33} of the coefficients translating the quadratic influence of A, B and C for the both optimizations. Linear and second-order polynomials were fitted to the experimental data to obtain the regression equations, and their observed and predicted responses are given in Table 13 and 14.

Table: 4Design of experiment-levels of various process parameters

	LEVEL USED		
FACTORS	LOW(-1)	MEDIUM(0)	HIGH(+1)
A – Sodium alginate concentration (%w/v)	2	4	6
B– Tamarind gum concentration (%w/v)	2	4	6
C– Zinc sulphate concentration (%w/v)	10	15	20

Table: 5 Design of experiment-levels of various process parameters

	LEVEL USED		
FACTORS	LOW(-1)	MEDIUM(0)	HIGH(+1)
A – Sodium alginate and TG ratio (%w/v)	2:6	4:4	6:2
B– Chitosan succinate concentration (%w/v)	2	4	6
C– Glutraldehyde concentration (%w/v)	7.5	10	12.5

PREPARATION OF CHITOSAN SUCCINATE DECORATED SODIUM ALGINATE TAMARIND GUM BEADS

The concentrations of sodium alginate and zinc sulphate were optimized by preliminary experimentation in which blank beads were prepared using varying concentrations. The concentrations which yielded spherical beads having sufficient integrity were selected for preparing drug loaded beads. The composition of the various batches along with the observation is shown in Table 13 and 14. Drug loaded chitosan succinate – sodium alginate tamarind gum beads were prepared by ionotropic gelation method. The following solutions were made separately: Solution A-Accurately weighed quantities of sodium alginate (6%w/v) tamarind gum (4%w/v) andcapecitabine (200mg) were dissolved in 15 ml de-ionized water by continuous stirring for 30 minutes using a magnetic stirrer. Solution B: Accurately weighed quantity of zinc sulphate (10%w/v) was dissolved in 35 ml de-ionized water. To this solution, 10ml of solution containing Chitosan succinate (dissolved in 2% NaOH) with pH adjusted to 7±1 was added. Solution A was then extruded drop wise into solution B through hypodermic syringe with needle (20G) and stirred for 15 minutes at 50rpm using magnetic stirrer. This led to ionotropic gelation of sodium alginate in the form of beads. Stirring was continued for 30 minutes for completion of the gelation. The beads were then filtered using a man filter paper and air dried overnight. The prepared bead was cross-linked by glutraldehyde. The beads were spread uniformly in a petridish and kept in a desiccators containing glutraldehyde at the bottom. The beads were exposed to the Glutraldehyde solution for 4 hours.

CHARACTERIZATION OF CHITOSAN SUCCINATE DECORATED SODIUM ALGINATE TAMARIND GUM BEADS

%Yield

The prepared beads were weighed using a calibrated weighing balance and the % yield was calculated using the following equation:[124]

% yield= W/T

Where, W= weight of the beads

T= Total weight of sodium alginate and capecitabine taken

Drug loading and entrapment efficiency [124]

Accurately weighed beads (10 mg) were transferred to a beaker containing 10 ml Phosphate buffer pH 6.8 and the mixture was allowed to stand for 24 hours. The contents of the beaker were stirred for 1-2 hours using a magnetic stirrer for complete breakage of the beads, followed by filtration using what man filter paper. The amount of capecitabine(x) in 10 mg beads was then estimated in the filtrate by measuring the absorbance at 303 nm using U.V.-visible spectrophotometer. Drug loading and Entrapment efficiency was then calculated by following formulae:

Drug loading (%w/w) = 10x

% Entrapment efficiency=(x /T)*100

Where, x = Actual quantity of drug present in beads

T = Theoretical quantity of drug added during preparation

Micromeritic properties [124]

The size of beads was determined using optical microscopy technique. The beads were spread uniformly on a glass slide and observed under microscope. The size of 50 beads from each batch was determined using a calibrated eye piece micrometer and average was calculated. Angle of repose was measured by fixed base cone method. Bulk and tapped densities as measures of pack-ability of beads were measured using a 5 ml graduated cylinder. 1 gm of sample was added in the cylinder and volume occupied by sample was noted and bulk density was calculated. The cylinder was tapped 100 times and volume occupied was again measured to calculate tapped density.

Bulk density = (weight of sample / volume occupied by sample before tapping)

Tapped density= (weight of sample/ sample occupied by sample after tapping)

Carr's index and Hausner's ratio were also calculated as measures of powder flow properties using the following equations:

$$Carr'sIndex = \frac{Tapped\ Density - BulkDensity}{Tapped\ Density}\ X\ 100$$

Hausner's ratio= (Tapped density / Bulk density)

SIZE, SHAPE AND SURFACE MORPHOLOGY [124]

The beads were analyzed microscopically under digital microscope (Nikon digital sight, DS-Fi20) to study their size and shape. The size of the beads was determined by using a calibrated eye piece micrometer. The surface morphology of beads was studied using scanning electron microscopy (JSM-5610LV, JEOL, Japan). For this, samples were attached to sample stubs; silver coating was done and then viewed using an accelerating voltage at the magnification of 15000X.

SWELLING INDEX [124]

Accurately weighed 50mg of beads were taken in a beaker containing 10 ml of phosphate buffer 0.1 N HCL, 5.8 and 7.4 then allowed to stand at room temperature for 6 hr. The excess liquid adhered to the surface of the beads was removed by blotting with filter paper and the swollen beads were weighed. Each experiment was carried out in triplicate. The swelling index of the beads was calculated by using the formula:

$$\frac{Wt_1 - Wt_2}{Wt_2}$$

FTIR Studies[124]

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2mg ofCapecitabine, polymer and physical mixturesofsamples were weighed and mixed properly withPotassium bromide to auniform mixture. A small quantity of the powder was compressed into athin semitransparent pellet by applying pressure. The IR spectrum of the beads from 450-4000cm^{-1} was recorded taking air as the reference and compared to study any interference.

Thermal Analysis[124]

Differential scanning calorimetry of microspheres was performed with a Pyris 6 DSC (Perkin ElmerCorp., Waltham, MA). Samples (5 mg) were scanned in aluminum pans over a temperature range between 50 and 400˚C at a scanning rate of 10˚C/min. Nitrogen was used for purging the sample holder at a flow rate of 20 Ml/min. Thermogravimetricanalysis (TGA) of chitosan succinate beads powder was done on a Mettler Toledo (Greifensee, Switzerland) and sample was heated between 25and 250˚C at 10˚C/min.

IN-VITRO RELEASE STUDIES [125]

In-vitro release studies of prepared beads were carried outto900 ml of 0.1 N HCl (pH 1.2). The test was carried out in 0.1 N HCl for 2 h, and then using phosphate buffer (pH 7.4) using USP- XXII apparatus at 100 rpm, maintained at a temperature of 37±10˚C for a period up to 12 hrs. Each time interval 5 ml of sample was withdrawn, at the same time 5 ml of fresh dissolution media was added to maintain sink condition. The withdrawn samples were suitably diluted and measure the absorbance at 247 nm spectrophotometrically. Depend upon the absorbance values; we got the concentration values from the standard calibration curve. Then the cumulative percentage drug release was calculated at regular time intervals.

Dissolution Kinetics of Drug Release [125]

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: Zero order (cumulative amount of drug released vs. time), First order (log cumulative percentage of drug remaining vs. time), Higuchi's model (cumulative percentage of drug released vs. square root of time), Hixon-Crowell (cube root of amount remained to be absorbed vs. time) and Korsmeyer's (log cumulative percentage of drug released Vs log time).

CHARACTERIZATION OF TAMARIND GUM [121, 122]

It has been observed that isolated tamarind gum was whitish brown in color. It consist of no odor and taste along with irregular shape as well as hard and rough in sensation and texture. The pH of 1% solution of TG was found 6.4, which indicated that it should be non-irritating for mucus membrane. Solubility study showed that it was sparingly soluble in cold water, freely soluble and form viscous colloidal solution in warm water. The isolated sample of TG was subjected to identification.

Percentage Yield

The % yield of the polysaccharide was found to be 70.0% for tamarind. During the processing of tamarind gum isolation washing is required many times which may result in loss of dissolved polysaccharides. However extraction process of tamarind is easy and hence gives better yield.

Solubility in various solvents

The solubility was checked in common solvents depending on their polarity such as water, phosphate buffers pH7.4, 0.1N HCl, acetone, ethanol, methanol. The polysaccharide was found to be soluble in organic solvents and is also soluble in the aqueous solvents and swells to make a viscous solution. Hence the polysaccharides are hydrophilic in nature.

Particle size and size distribution

The mean particle size of 1%, w/v TG solution was 28.527 μm.

Powder Properties

The polysaccharides were subjected to the analysis of powder flow properties such as bulk density, tap density, Carr's index (CI) and Hausner ratio (HR). Direct compression of powders requires when materials show good flow ability, comapactibility and compressibility. These constraints become more decisive when the formulation contains large amount of active substances with poor compression properties. The % CI range in between 24-31 stands for poor flow. Again HR ranges in between 1.30-1.45 also possess poor flow. From the investigation the values were found to be in this range for all three polysaccharides. Hence they are of poor flow properties. The probable reason may be due to the high intermolecular force of attraction among the particles. It may be due to inadequate freeze

drying of the sample resulting fluffy powder which are tough to be sieved. The results are shown in Table 6.

Rheological Behavior

The viscosities of the different concentration (0.5%, 0.75% and 1%, w/v) of TG solutions were determined by Brookfield viscometer at different shear. All the solutions showed sufficient viscosity at different shear rate and shows pseudoplastic flow. This was observed that viscosity decreases correspondingly with increasing shear. TG shows consistent change behavior upon application of pressure.

Table: 6 Powder characteristics and flow properties of tamarind gum powder

Description	Values
Angle of repose(degree)	27.35±0.12
Compressibility index(%CI)	4.25±0.150
Hausner's ratio(H)	1.03±0.06
Bulk density(ρo)	0.63±0.03
Tapped density(ρ)	0.749±0.016
Mean particle size (μm)	81.63±42.16
True density	0.83± 0.04
% porosity	41.67±2.34
% moisture content	4.31±0.78
Ash value (%)	6.23±0.251

SYNTHESIS AND CHARACTERIZATION OF CHITOSAN SUCCINATE POLYMER

Chitosan Succinate (CS) was prepared and yield was found 90%. The conjugation reactions were carried out using succinate anhydrides in the presence of pyridine. Both anhydrides are strong electrophiles and react readily with the nucleophilic amine groups of

chitosan. Pyridine was added as an acylation catalyst. Probably, the amino groups were selectively acylated due to their superior nucleophilic character in comparison to the surrounding hydroxyl groups. The average degree of chitosan substitution by succinate moieties was found to be 12.3%. The solubility of CS was carried out in acidic and alkaline solution. In contrast to chitosan, semi-synthetic polymers exhibit the highest solubility in alkaline media; this is probably due to ionization of the carboxylic acid moieties under alkaline conditions yielding the sodium carboxylate anions. The hydrophilic ionic species facilitate efficient polymeric hydration and dissolution in aqueous media.

CHARACTERIZATION OF THE PURE DRUG

Standard Graph of Capecitabine in 0.1 N HCl

The standard graph of capecitabine has shown good linearity with R^2 values 0.9991 in 0.1 N HCl and which suggests that it obeys the "Beer-Lambert's law".

Table No: 7 Standard values of Capecitabine in 0.1N HCL

S.NO	CONCENTRATION	ABSORBANCE AT 303nm
1.	0	0
2.	10	0.19
3.	20	0.335
4.	30	0.50
5.	40	0.68
6.	50	0.82
7.	60	0.998

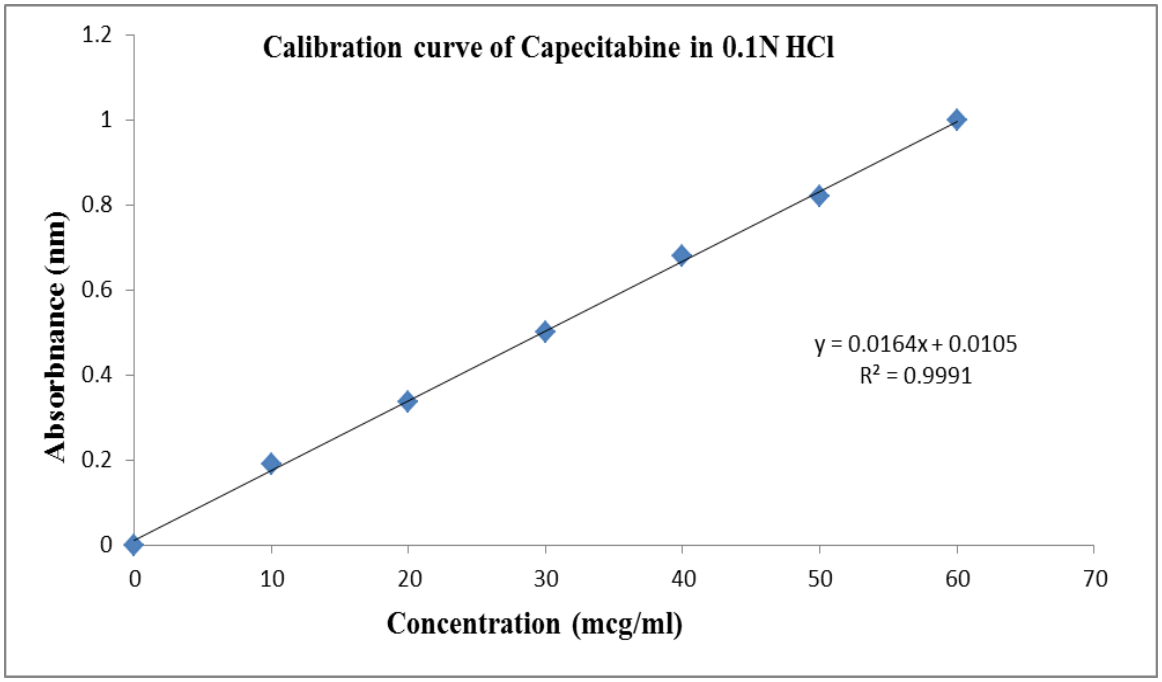


Fig No: 12 Calibration curve of Capecitabine in 0.1N HCl

STANDARD GRAPH OF CAPECITABINE IN 5.8 pH PHOSPHATE BUFFER

The standard graph of Capecitabine has shown good linearity with R^2 values 0.9947 and which suggests that it obeys the "Beer-Lambert's law".

Table No: 8 Standard values of capecitabine in 5.8 pH phosphate buffer

S.NO	CONCENTRATION	ABSORBANCE AT 303nm
1.	0	0
2.	5	0.178
3.	10	0.355
4.	15	0.554
5.	20	0.704
6.	25	0.825

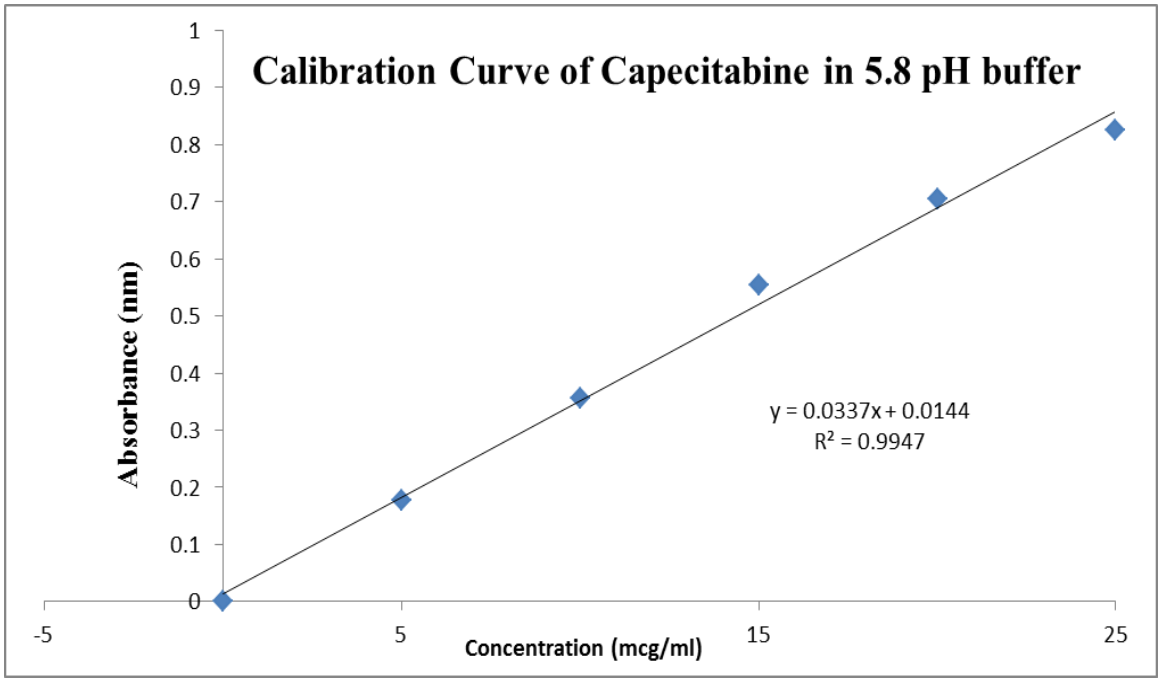


Fig No: 13 Calibration curve of Capecitabine in 5.8 pH buffer

STANDARD GRAPH OF CAPECITABINE IN 7.4 pH PHOSPHATE BUFFER

The standard graph of Capecitabine has shown good linearity with R^2 values 0.9993 and which suggests that it obeys the "Beer-Lambert's law".

Table No: 9 Standard values of capecitabine in 7.4 pH phosphate buffer

S.NO	CONCENTRATION	ABSORBANCE AT 303nm
1.	0	0
2.	4	0.545
3.	8	1.051
4.	12	1.509
5.	16	2.01
6.	18	2.254

7.	**20**	**2.492**
8.	**24**	**2.962**
9.	**28**	**3.4**

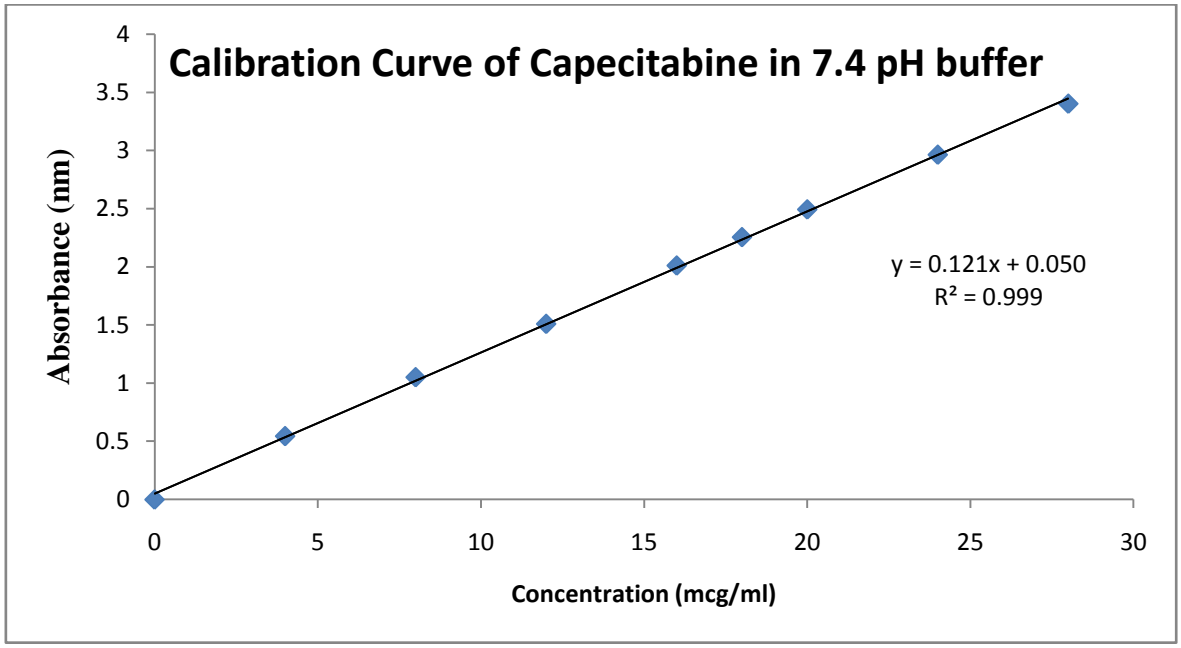


Fig No: 14 Calibration curve of Capecitabine in 7.4 pH buffer

PHYSICAL PROPERTIES OF CAPECITABINE BLEND

The pure drug was observed as White to light yellow in colour, odourless, appearance as powder in nature. Melting point of the drug was found to be 116 -117ºC and soluble in water, Ethanol, acetonitrile, dimethyl formamide, marginally soluble in methanol.

OPTIMIZATION OF BEADS [100]

Response Y_1: Effect on in vitro drug release:

Seventeen formulations were prepared and evaluated for experimental design of three-factor, one response set-up. The evaluated responses were drug release for the both the optimizations. Beads prepared with low concentration of polymers (- level) were rough and irregular in shape due to poor molecular packing and cross-linking in comparison with beads

prepared with medium and high concentration of polymers (+level) which were larger and more spherical. The variation in size and morphology of the beads with different polymeric concentrations was due to variations in availability of reacting/binding sites for cross-linking cations. As the cross-linking agent content was increased, smooth, spherical and smaller beads were obtained which were well packed and discrete (Figure – 16 and 20).

Further, we analyzed the effect of polymer concentration on drug release which was more intricate. The drug release was being affected by both of the polymers but in a reciprocal mode. Drug release was directly proportional to the amount of polymer concentration, while it was inversely proportional to the amount of cross linking agents in both the optimizations.

The mathematical relationship in the form of a polynomial equation for the measured response, % of drug release (Y_1) released from sodium alginate tamarind gum beads (Equation 4) and chitosan succinate decorated glutraldehyde sodium alginate tamarind gum (Equation 5), are given below:

$$Y_{1=} +65.00+15.37A-0.38B-8.50C+9.75A^2+6.25B^2-1.00C^2+0.000AB+1.25AC-0.25BC \quad (4)$$

$$Y_2= +2.00+0.000A-3.00B-8.25C-0.25A^2-4.25B^2-7.75C^2-0.50AB+0.000AC+3.50\ BC \quad (5)$$

where A, B and C represents the sodium alginate, tamarind gum and amount of calcium chloride concentrations for optimization 1 and sodium alginate tamarind gum ratio, chitosan succinate and amount of glutraldehyde concentrations for optimization 2 respectively. A positive value represents an effect that favours the optimization, while a negative value indicates an antagonistic effect. The values of A, B, and C were substituted in the equation to obtain the theoretical values of Y_1. The predicted values and the observed values were found to be in good agreement. The effect of pair wise interaction of the parameters is depicted in the three dimensional graphs (Figures 15-20) when the third parameter is kept constant. The optimum condition for the preparation of chitosan succinate decorated sodium alginate tamarind gum capecitabine beads as evident from Table No: 13 and Figure No: 18 .

Table: 10 Regression analysis for response Y_1 and Y_2

Model	R-squared	Adjusted R-squared	Predicted R-squared	SD	Remarks
Response (Y_1)					
• Linear	0.6026	0.5109	0.3248	5.59	-
• Second order	0.6515	0.4424	-0.1395	5.97	-
• Quadratic	0.9917	0.9810	0.8671	1.10	Suggested
• Cubic	1.0000	1.0000	N/A	0.000	-
Response (Y_2)					
• Linear	0.7987	0.7522	0.6563	6.92	-
• Second order	0.8008	0.6812	0.2993	7.85	-
• Quadratic	0.9926	0.9832	0.8823	1.80	Suggested
• Cubic	1.0000	1.0000	N/A	0.000	-

Table: 11 Analysis of variance of calculated model

Result of the ANOVA	Drug Release 2 h (%)	Drug release 12h (%)
Regression		
Sum of squares	1014.56	3070.19
Degree of freedom (df)	9	9
Mean squares	112.73	341.13
F-value	92.84	104.96
P	<0.0001	<0.0001
Residual		
Sum of squares	8.50	22.75
Degree of freedom (df)	7	7
Mean squares	1.21	3.25
Lack of Fit test		
Sum of squares	8.50	22.75
Degree of freedom (df)	3	3
Mean squares	2.83	7.58
F-value	-	-
P	-	-
Correlation coefficient (R^2)	0.9917	0.9926
Correlation of variation (%CV)	14.19	2.50

Optimization 1

Drug release study was simulated in stomach pH and colon pH since the drug has an absorption window in colon. Minimum drug release was observed in formulation containing highest concentration of polymers (+1 level). The formulations containing similar amount of sodium alginate but with lower levels of tamarind gum showed higher drug release at acidic pH. Whereas, maximum drug release was observed in alkaline pH. Formulation containing sodium alginate and tamarind gum concentration at 0 and - 1 level, respectively, and tamarind

gum at + 1 level was found decreased drug release in acidic pH and prolonged the drug release upto 12 Hrs in alkaline pH. Similarly high amount of drug release was obtained in F11 containing -1 and 0 level of sodium alginate and tamarind gum concentration, and higher level of cross-linking agent. It could be inferred that both of the polymers were affecting drug release and were more or less compensating for each other as far as drug release was concerned. The regression analysis and ANOVA was represented in table 10 and 11.

Table: 12 Experimental runs and observed values of responses for Box-Behnken design

		INDEPENDENT VARIABLES			DEPENDENT VARIABLES	
RUNS	BATCH	A	B	C	ACTUAL Y_1	PREDICTED Y_1
1.	F1	0	0	0	64.74	65.12
2.	F2	-1	1	0	65.01	64.76
3.	F3	1	-1	0	98.43	98.79
4.	F4	1	0	1	79.65	80.01
5.	F5	-1	0	1	51.24	50.63
6.	F6	1	1	0	97.82	98.26
7.	F7	0	1	-1	77.68	78.17
8.	F8	-1	0	-1	70.35	70.72
9.	F9	1	0	-1	94.87	95.38
10.	F10	-1	-1	0	65.25	64.71
11.	F11	0	1	1	61.04	61.59
12.	F12	0	-1	1	62.85	63.25
13.	F13	0	-1	-1	80.13	79.49

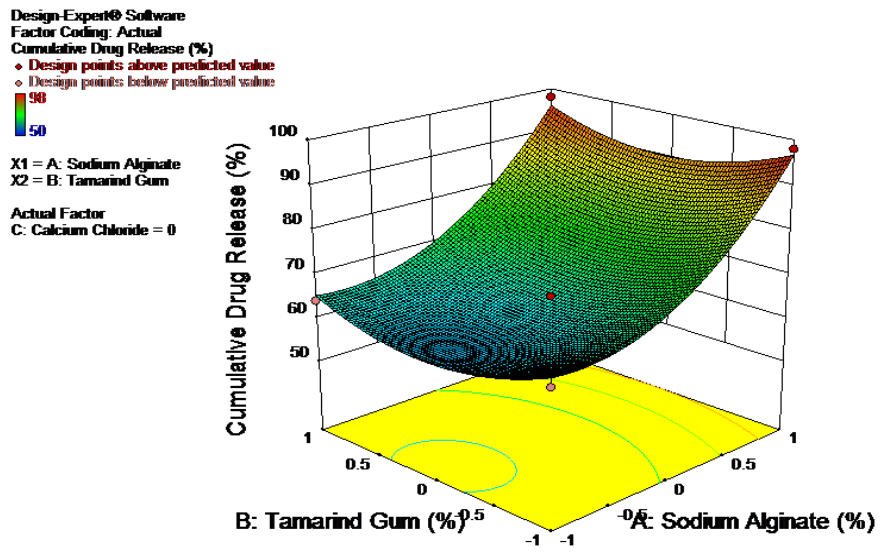


Figure No: 15 RSM of SA and TG on cumulative drug release at 12hrs at cross linking agent (10%)

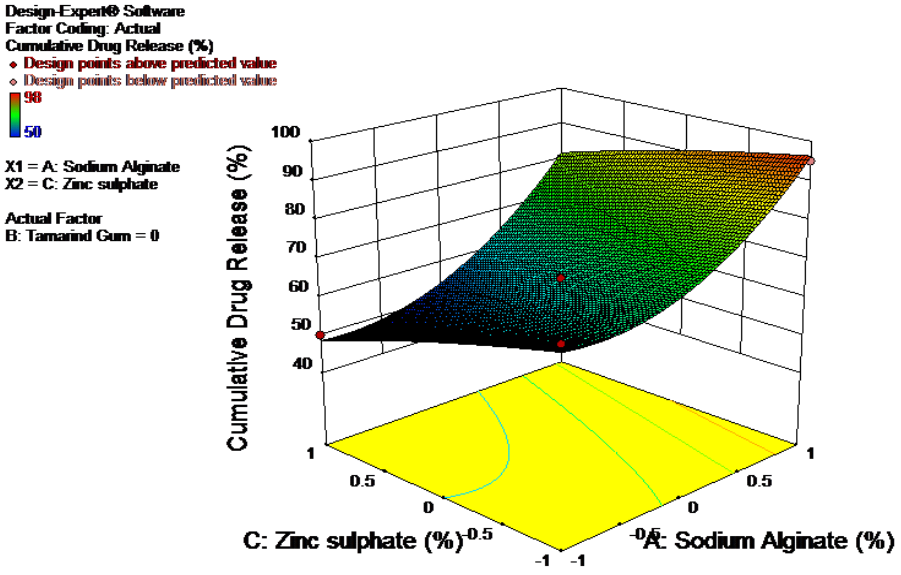


Figure No: 16 RSM of SA and Zinc sulphate on cumulative drug release at 12hrs at TG (4%)

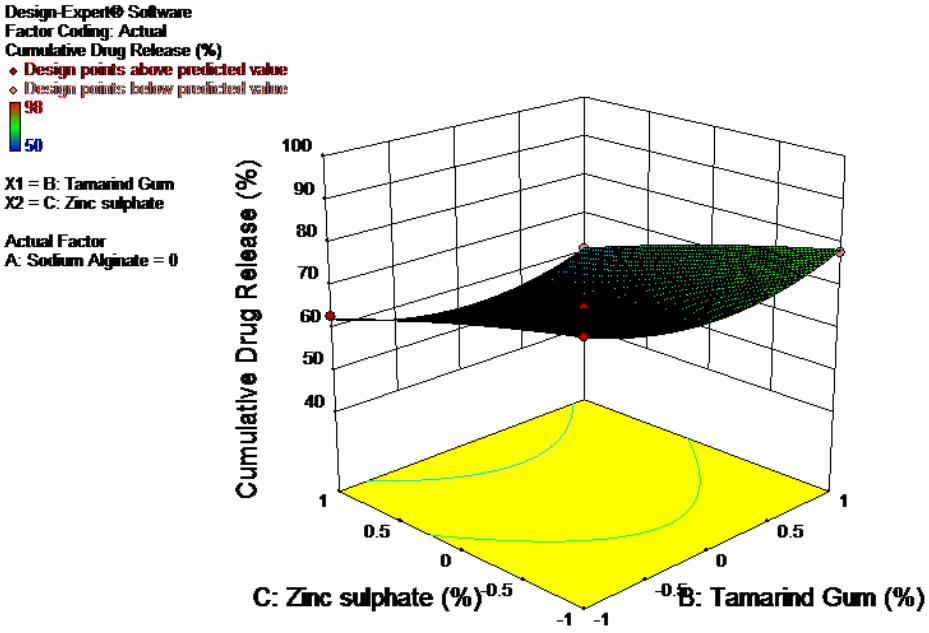


Figure: 17 RSM of TG and Zinc sulphate on cumulative drug release at 12hrs at SA (6%)

Optimization 2

Drug release of chitosan succinate decorated alginate tamarind beads was carried out in acidic medium upto 2Hrs. Minimum drug release was observed in formulation containing highest concentration of polymers (+1 level) and also cross linking agents (0 level). The results indicates that it can be observed that polymer crosslinking with glutraldehyde was successful, which led to uniform formation of beads. The mechanism of crosslinking of chitosan succinate with glutraldehyde is demonstrated that the free amino group of chitosan succinate is cross linked with aldehyde group of glutraldehyde to form schiff base (imine group).Whereas while increasing the concentration of glutraldehyde (+1 level) there is no much effect on control in drug release due to no free primary amino group present in chitosan backbone chain.

The values of *R*- squared, Adj- squared, Pred *R*- squared, SD and % CV are shown in Table III along with the regression equation. Since the cubic model was aliased due to insufficient design points to estimate the coefficients, the quadratic model was chosen for its larger adjusted *R*- squared value. The ANOVA values for different responses are represented in Table IV, and all statistically significant ($p < 0.05$) coefficients are included in the equations.

As per the optimization design, a positive value shows favorable optimization, whereas a negative value shows an inverse relationship between the factor and the response. It is evident that all the three independent variables, namely the concentration of sodium alginate concentration (A), tamarind gum (B), zinc sulphate (C), have interactive effects on the estimated response, for example, drug release (Y_1).

Table: 13 Experimental runs and observed values of responses for Box-Behnken design

		INDEPENDENT VARIABLES			DEPENDENT VARIABLES	
					ACTUAL	PREDICTED
RUNS	BATCH	A	B	C	Y_1	Y_1
1.	F14	0	0	0	2.36	2.17
2.	F15	-1	1	0	5.17	5.42
3.	F16	1	-1	0	9.31	9.73
4.	F17	1	0	1	2.63	2.37
5.	F18	-1	0	1	2.18	2.41
6.	F19	1	1	0	4.25	4.60
7.	F20	0	1	-1	15.43	15.92
8.	F21	-1	0	-1	18.82	18.59
9.	F22	1	0	-1	17.91	18.38
10.	F23	-1	-1	0	8.58	8.22
11.	F24	0	1	1	5.41	5.18
12.	F25	0	-1	1	6.23	6.53
13.	F26	0	-1	-1	31.09	30.44

The model was significantly indicated by Model F-value of 7.89 (P = 0.0003). There is only 0.01% chance that this “Model F-Value” could occur due to noise. Model terms A, B, C, AC, BC and A^2 were significantly indicated by values of “ Prob> F ” <0.001. The amount of both polymer and cross-linking agent showed profound effect on in vitro drug release. The lack of fit was not significantly indicated by the “Lack of Fit F-value” of 0.26. There is a 92.94% chance that a “Lack of Fit F-value” (quite high) could occur due to noise. The “ Pred R - squared ” of 0.9599 is in reasonable agreement with the “ Adj R - squared ” of 0.9083. “ Adeq Precision” at 13.522 indicates an adequate signal to use the model to navigate the design space. The regression analysis and ANOVA was represented in table 10 and 11.

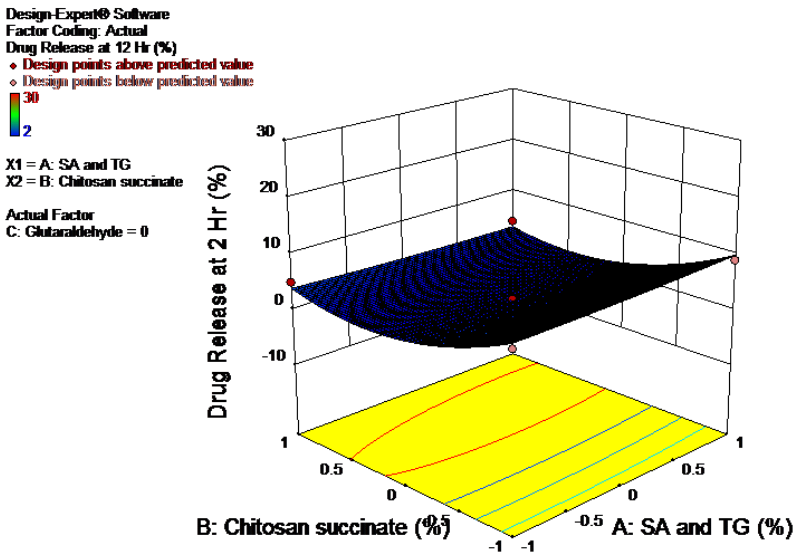


Fig No: 18 Effect of SA - TG ratio and Chitosan succinate on drug release at 2hr from beads

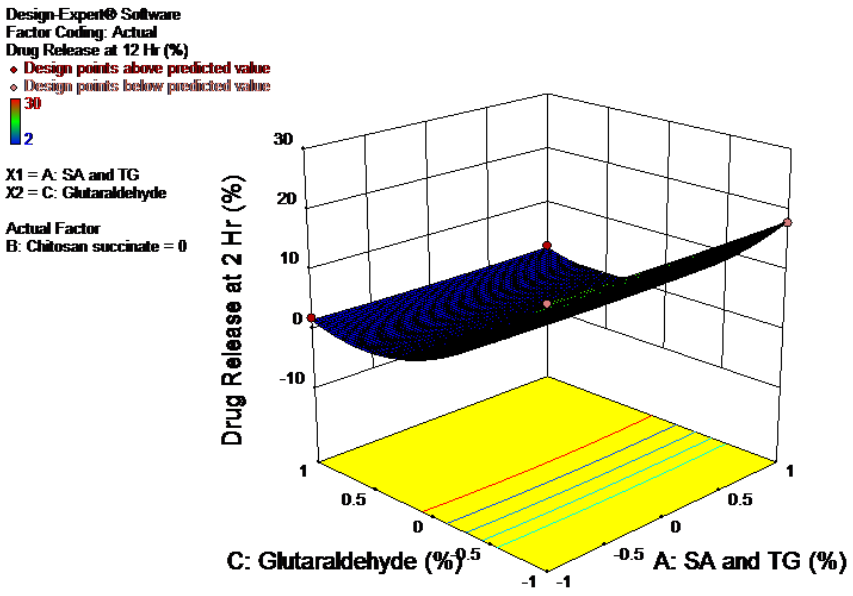


Fig No: 19 Effect of SA - TG ratio and Glutaraldehyde on drug release at 2hr from beads

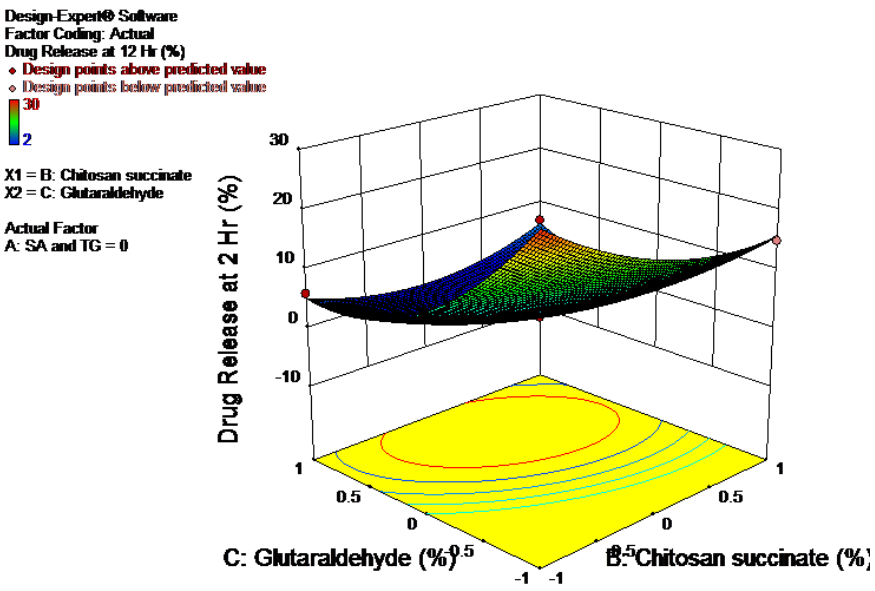


Fig No: 20 RSM of Chitosan succinate and Glutaraldehyde on drug release at 2hr from beads

CHARACTERIZATION OF CHITOSAN SUCCINATE DECORATED SODIUM ALGINATE TAMARIND GUM BEADS

% Yield, DL and DEE

For all the formulations the percentage yield, drug loading and drug entrapment efficiency were carried out for the optimized formulation the results are tabulated in the table No: 15. It is evident from the results use of chitosan succinate in chitosan succinate encrusted-alginate tamarind beads has already been recognized as stabilizing the “egg-box” structure and thereby reducing the problem of drug leaching during bead preparation. Thus, varying concentrations of chitosan succinate were added to the glutraldehyde solution in order to increase the entrapment efficiency. on increasing the chitosan succinate concentration, the drug loading and %EE increased significantly. This may be due to the fact that higher chitosan succinate concentration results in the formation of a denser matrix structure that probably decreases the loss of drug to the curing medium. In addition, electrostatic attraction between the negatively charged capecitabine and the positively charged chitosan succinate also becomes stronger, promoting the drug entrapment.[124]

Table No: 14% yield, DL and DEE for optimized formulation

Formulation	% yield	DL	DEE
Optimized formulation	45.92	72.26	58.34

MICROMERITIC PROPERTIES

The results of the micromeritic studies are shown in table 15. The values of the different micromeritic parameters indicate the poor flow properties of pure drug while all the bead formulations showed acceptable flow properties and compression characteristics. The improved flow properties might be due to the spherical shape and smooth surface of the beads which show minimum resistance to flow. An increase in tamarind gum and chitosan succinate concentration led to an increase in particle size. This result is expected since capecitabine carried negative charge and electro statically interacted with tamarind gum and chitosan succinate, which would promote formation of beads through ionic cross-linking. Thus, as the tamarind gum and chitosan succinate concentration was increased; the particle size was also increased. The optimized batch had a mean size of around 1.017 mm.

Table No: 15 Micrometric properties of pure drug and optimized formulation

Batch	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)	Average particle size (mm)
Pure drug	49.68	0.389	0.591	1.52	34.08	-
Optimized formulation	27.57	0.656	0.785	1.20	16.47	1.017

SIZE, SHAPE AND SURFACE MORPHOLOGY

In all formulations the alginate tamarind beads were more or less spherical in shape and the exterior surfaces were rough and covered with a network of small cracks and fissures, was shown in the figure 21-23.The drug was uniformly dispersed at the molecular level in the alginate beads. The spherical shape of the beads in wet state was usually lost after drying

especially for beads prepared with low concentration of SA and cross -linking agent. With the increase of SA concentration the shape of the beads retained considerably. It can be observed that polymer crosslinking with glutraldehyde was successful, which lead to uniform formation of spheres.[124]

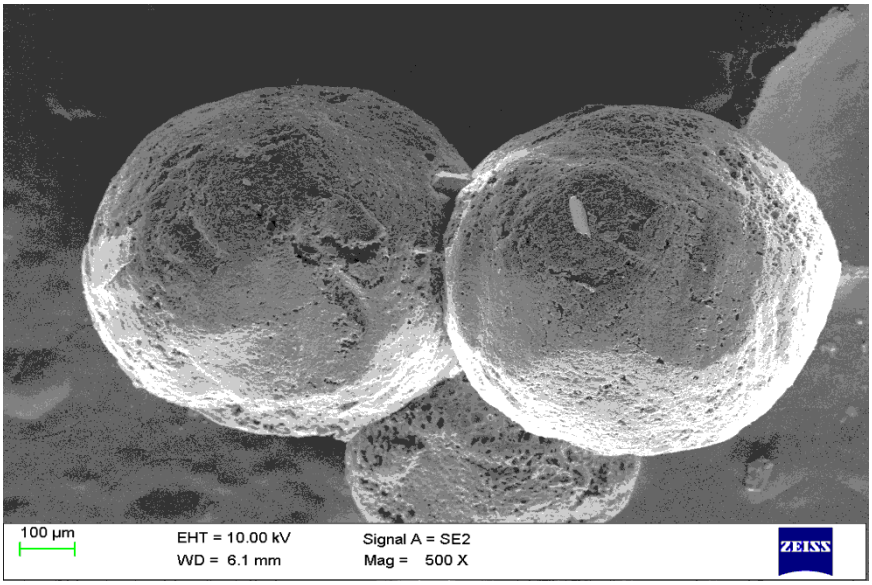


Fig No: 21 Scanning Electron Microscope (SEM) of the formulation (F_8) Sodium alginate tamarind gum beads

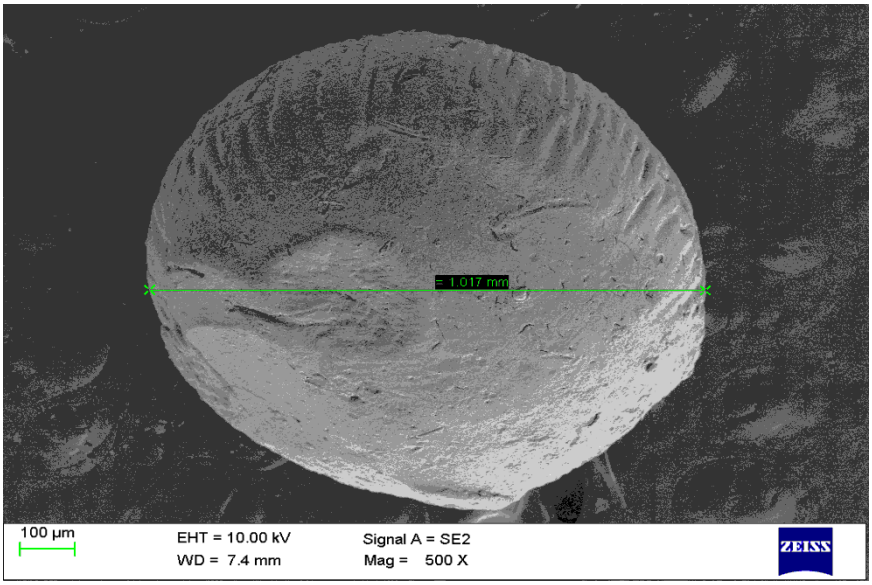


Fig No: 22 Scanning Electron Microscope image of the formulation (F_{27}) shows spherical in shape and the exterior surfaces were rough and covered with a network of small cracks and fissures

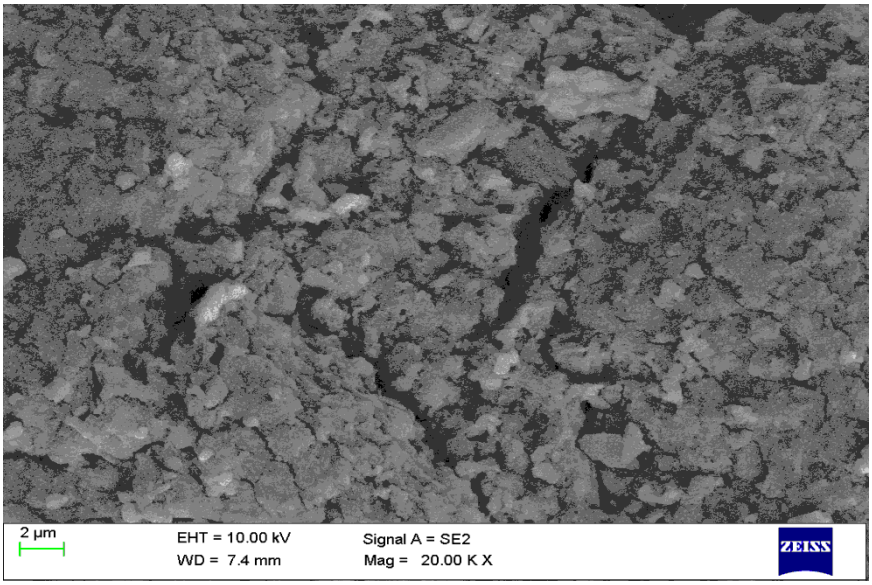


Fig No: 23 The surface morphology of CS encrusted CP-loaded alginate-TG blend beads visualized by SEM.

SWELLING INDEX

Comparison of swelling behavior for alginate, Alginate and TG beads and CS encrusted beads was performed in two different pH (1.2and 7.4) simulating transition of beads in GIT. Swelling studies results shows the maximum swelling for all the batches of beads meant for simulated intestinal fluid (pH 7.4) as shown in Fig No. 24.

The effect of pH on degree of swelling of beads is presented in Figure 8. The degree of swelling CS encrusted beads was found to be 100% and 0% soaked in 0.1N HCl (pH 1.2) and PBS (pH7.4) respectively. Whereas plain alginate beads was shown highest swelling, under acidic pH, which could probably due to formation of alginic acid regions through proton-zinc ion exchange and followed by solvent penetration into the gel-network.

Alginate and tamarind gum blended beads, which is highly acid resistant is not sensitive to external acidic environment due to its higher viscosity, the polymer chains are bulkier, leading to less flexibility and hence more time for the polymer and solvent to interact. Although the swelling ability of beads was found to be poorer in alkaline medium , the results reveals that zinc hydroxide was formed gradually as a result of the chelate complexing due to the disintegration of the alginate chains, which resulted in simultaneous increase in the degree of swelling.

The swelling of CS encrusted beads was completely controlled in acidic. This may be due to the fact that under acidic conditions, carboxylic groups present in the system exist in non-ionized form and are poorly hydrophilic, whereas in basic condition CS encrusted beads observed a maximum a degree of swelling rate (100%) due to the carboxylic groups exist in ionized form and are considerably hydrophilic. Thus, it may be concluded that CS encrusted beads, could be protected the drug from the harsh acidic environment of the stomach.

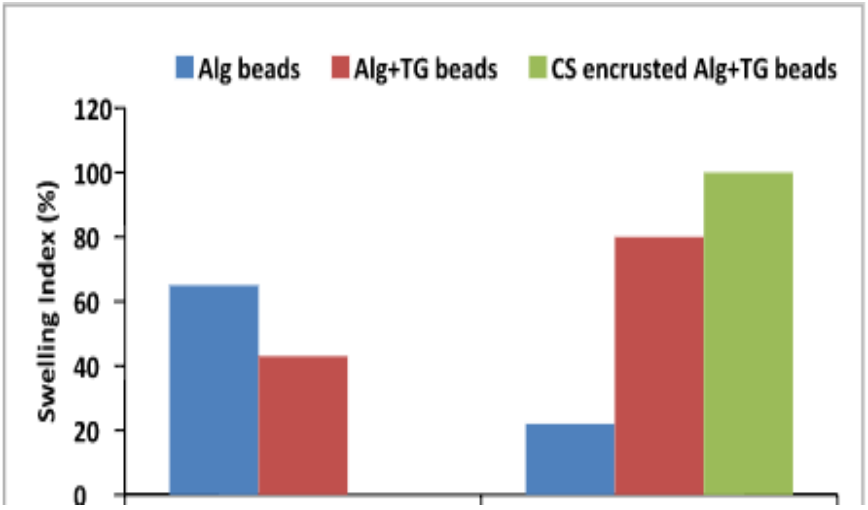


Figure: 24 Swelling Index of beads

FTIR spectroscopy analyses

FTIR spectroscopy is a useful tool in identification as well as purity of a compound. The principal absorption peaks of tamarind seed polysaccharide(fig 26) were found at 1034 cm^{-1} (C-O-C, ether group absorbance), 1657 and 1742 cm^{-1} (C=O, aldehyde absorption), 2924 cm-1 (C-H stretching), 3399cm^{-1} (primary OH) which indicate that isolated product was polysaccharide.

FTIR spectrum of SA shows the characteristic peaks were appeared 1416 cm^{-1} and 1616 cm^{-1}, for symmetric and asymmetric –C=O stretching vibrations of -COO−anions, respectively. In addition, a wideband at 3441 $cm^{-1}$was appeared due to the -OH stretching vibrations (Fig. 25).

The FTIR spectra of prepared chitosan succinate (Fig. 28), showed amide carbonyl stretching in the range of 1640 – 1670 cm^{-1} and carboxylic carbonyl stretching in the range of 1710 – 1720 cm^{-1}. The selective acylation of the amino groups is probably due to their superior nucleophilic character compared to the surrounding hydroxyl groups. The new

absorption band at 1716 cm^{-1} was attributed to carbonyl group of ester group [C=O of O (COR)] and the peak at 1650.2cm^{-1} was assigned to the carbonyl group of acyl amino group. These result indicated that succinic group was introduced into the amino group and hydroxyl group.

The Fig.27 shows the characteristics peaks of pure drug capecitabine at the wave number of 3520 cm^{-1} shows O-H stretching where the free hydroxyl group was present, the characteristic peak at 3215 cm^{-1} indicates the N-H stretching vibrations, at 2958cm^{-1} shows the C-H stretching, at wave number 2861 cm^{-1}shows the presence of aldehyde group (CH=O), at 1716 and 1611 cm^{-1} indicates the presence of C=O carbonyl group of stretching vibrations, at 1502cm^{-1}shows the N=O bending vibrations and further at 1245cm^{-1} shows the C-N bending vibrations.

FT-IR spectrum of the CS encrusted beads was shown in Fig.29. The capecitabine characteristic peak was observed in the IR spectrum. The result reveals that there is no interaction between the drug and polymer.

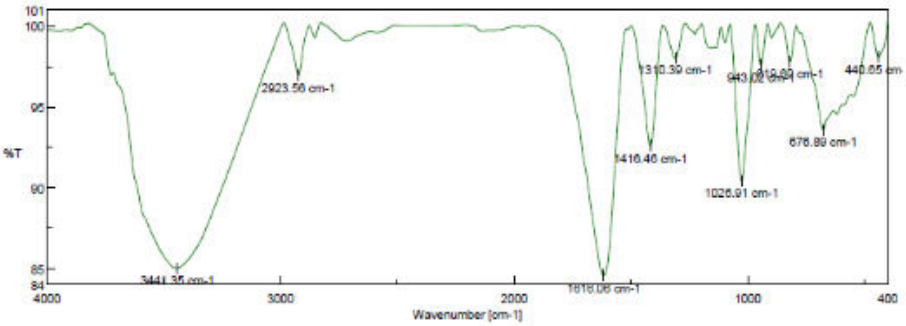


Fig No: 25 FT-IR Spectra of Sodium alginate

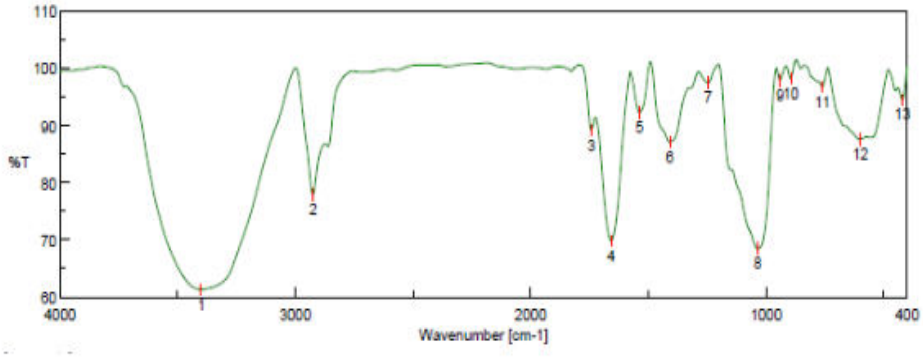


Fig No: 26 FT-IR Spectra of isolated Tamarind gum

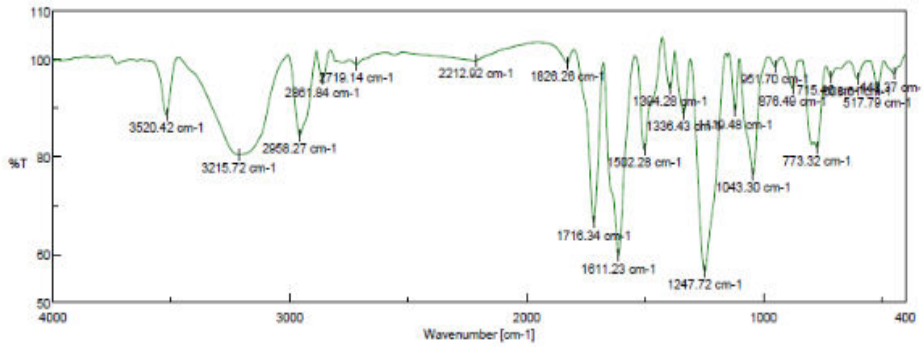


Fig No: 27 FT-IR Spectra of Pure drug Capecitabine

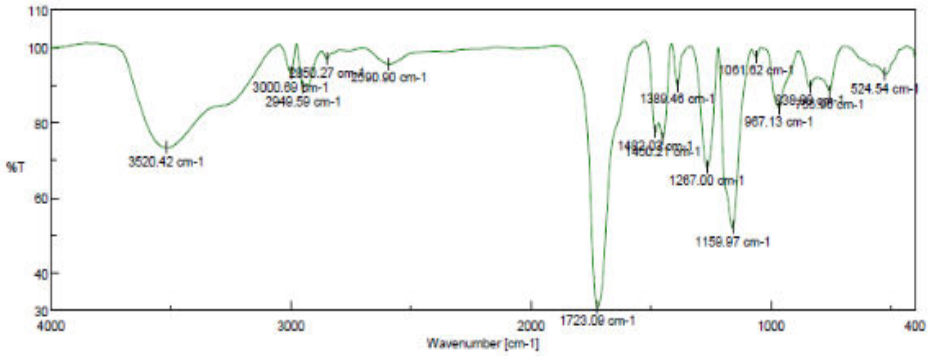


Fig No: 28 FT-IR Spectra of synthesized Chitosan succinate

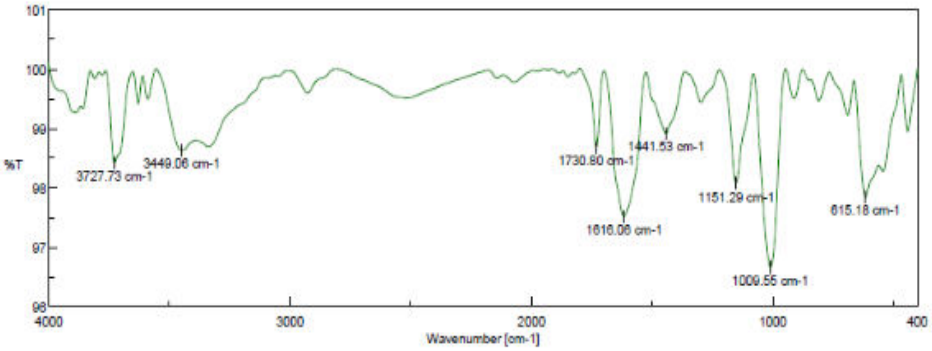


Fig No: 29 FT-IR Spectra of the CS encrusted CP loaded alginate tamarind gum beads

Thermal Analysis

The thermo gram of capecitabine showed a sharp endothermic peak at 121.9°C, which nearly corresponded to the melting point of capecitabine (116–118°C). This peak was absent in the thermo grams of drug loaded beads formulation, confirming complete entrapment of the drug in polymer matrix.

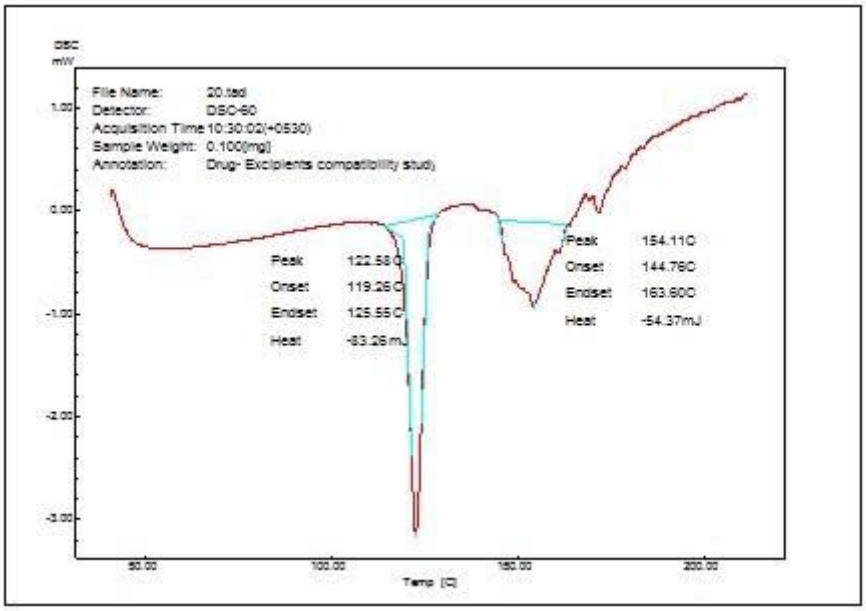


Fig No: 30 DSC thermogram of Pure Drug

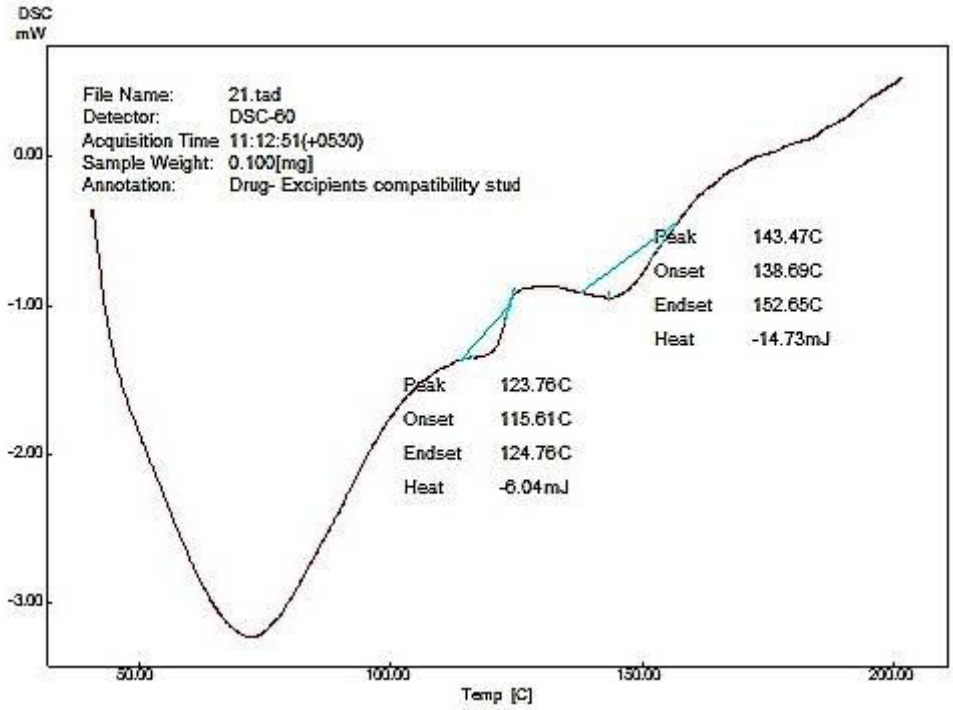


Fig No: 31 DSC thermogram of Optimized formulation

IN VITRO DRUG RELEASE STUDY

In-vitro drug release was carried out for the capecitabine loaded alginate tamarind gum beads in both acidic and alkaline pH. The result shows that drug release was observed in the acidic pH. With regard to alginate, in acidic medium, such as pH 1.0, as the chelate complexing of chains was destroyed as a result of the high concentration of H^+, hydrogels swelled rapidly and even partially dissolved. But, as the pH varied from 3.0 to 7.0, the destruction due to H^+ was not evident. With the continuous increase in the degree of alkalinity, zinc hydroxide was formed gradually as a result of the chelate complexing due to the disintegration of the alginate chains, which resulted in simultaneous increase in the drug release in acidic pH. Therefore to control the drug release in acidic beads the prepared CP loaded alginate tamarind gum beads were coated with chitosan succinate and cross-linked with glutraldehyde to provide the drug release in colon.

The in vitro capecitabine release from ionotropically gelled CS encrusted beads showed prolonged release of drug over 12 h (Fig. 9). CP release from these CS encrusted beads in the acidic dissolution medium (0.1 N HCl; pH 1.2) was slow (less than 30.21% after 2 h) and after that, faster CP release was observed in alkaline dissolution medium (phosphate buffer; pH7.4), comparatively. This may be due to the fact that these beads swelled quickly in alkaline dissolution medium than in acidic medium, and this led to comparative increased drug release in alkaline dissolution medium. In alkaline dissolution medium, probably a large swelling force was created by electrostatic repulsion between the ionized carboxylic acid groups of chitosan succinate-backbone. The cumulative drug release of CS encrusted CP loaded Tamarind- alginate blended beads after 10 h (R12h %) was within the range Fig of 50.26 ± 1.47–98.37 ± 3.20. It was expected that in alkaline medium, the CS beads could swell upon liquid uptake during the initial period and a hydrated viscous layer around beads was formed. The drug subsequently diffuses through the hydrated viscous layer. It was observed from the dissolution profiles that the chitosan succinate beads showed an initial slower drug release and a subsequent faster drug release. The overall results suggest that the dried beads swell slightly in the stomach. When they are subsequently transferred to colon region, the bead s are begun to swell and they behave as matrices for sustained release of the drug.

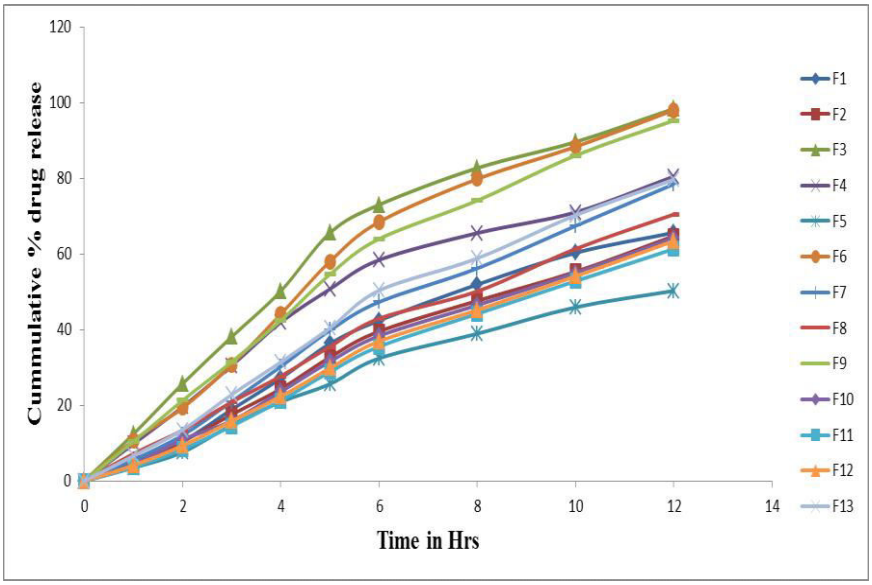


Fig No: 32 Invitro drug release profile for Capecitabine loaded alginate/tamarind gum beads

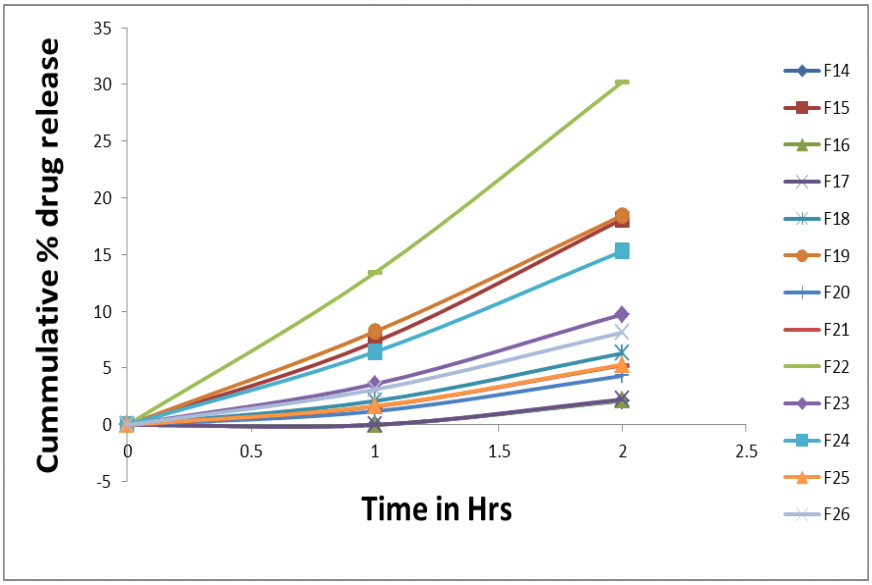


Fig No: 33Invitro drug release (2 HRS) for Chitosan succinate encrusted Capecitabine loaded alginate/tamarind gum beads

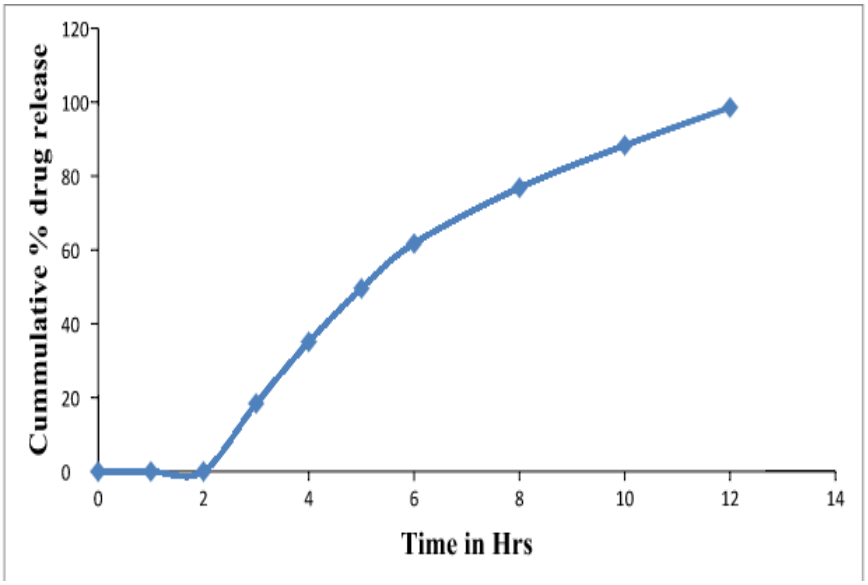


Fig No: 34 Invitro drug release for optimized formulation

KINETIC EVALUATION OF IN VITRO RELEASE DATA

Data obtained from in vitro release studies of optimized formulation was explored various kinetic models used are zero-order, first-order, and Higuchi equations. The data obtained from the in vitro release were fitted to various kinetic equations to determine the mechanism of drug release and release rate. As indicated by the higher correlation coefficient (r^2 = 0.993), the drug release from CS beads followed the Higuchi model rather than the first-order and zero order equations. These findings indicated that the drug release from the formulated CS beads was diffusion controlled. In sustained release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms followed. The drug release from the polymeric system is mostly by diffusion and is best described by Fickian diffusion. But in case of formulations containing swelling polymers, other processes in addition to diffusion play an important role in exploring the drug release mechanisms.

These processes include relaxation of polymer chains, imbibition of water causing polymers to swell and changing them from initial glassy to rubbery state. Due to swelling, considerable volume expansion take place leading to moving diffusion boundaries complicating the solution of Fick's second law of diffusion. So the release data were further treated by equation given by Ritger and Peppas or also called as the Power law . This equation is a generalization of the observation that superposes two apparently independent mechanism of drug transport, Fickian diffusion and a case-II transport describes drug release

from a swelling polymer. When n takes the value 0.5 it indicates diffusion-controlled drug release and for the value 1.0 indicates swelling-controlled drug release. Values of n between 0.5 and 1.0 can be regarded as an indicator for the both phenomena (anomalous transport). These extreme values for the exponent n, 0.5 and 1.0, are only valid for slab geometry and for spheres and cylinders different values have been derived. For beads, a spherical geometry is considered and as per Ritger and Peppas n takes values in the range of 0.45–0.89 for anomalous transport. The value of n with regression coefficient for optimized formulation was found to be 0.9799 indicating the anomalous transport. The anomalous diffusion mechanism of drug release demonstrated both diffusion-controlled and swelling-controlled drug release from chitosan succinate beads containing Capecitabine.

Table No: 16 Model fitting of in-vitro release studies

Formulation code	First order	Zero order	Higuchi	Hixon-Crowel	Korsmeyer-Peppas
	r^2				n
Optimized formulation	0.8992	0.9489	0.993	0.864	0.9799

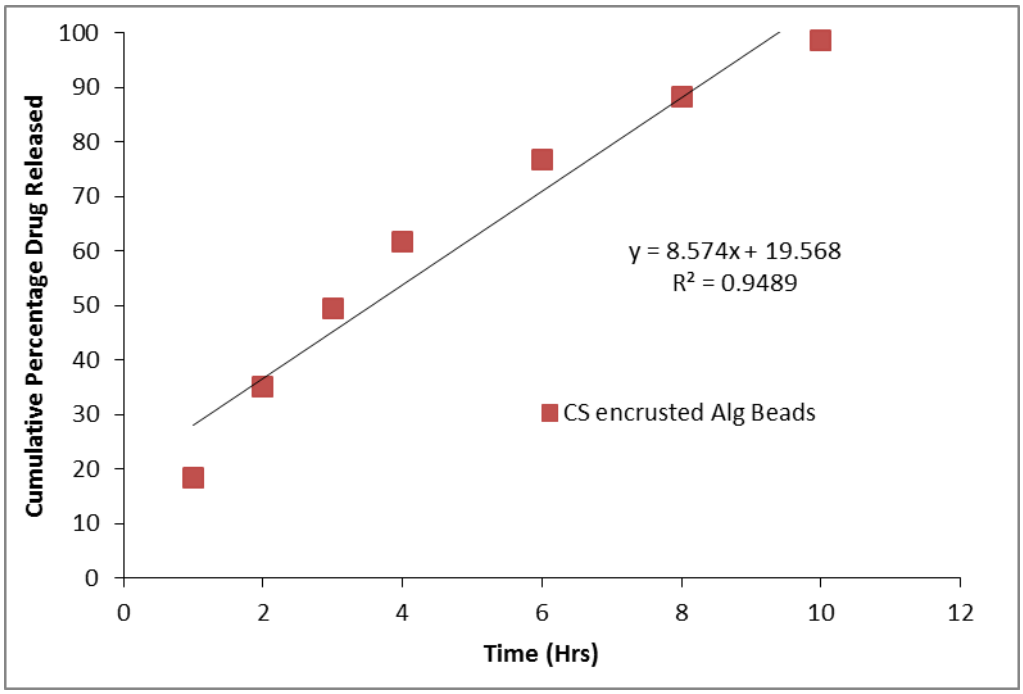


Fig No: 35 Zero order kinetics of CS encrusted alginate tamarind gum beads

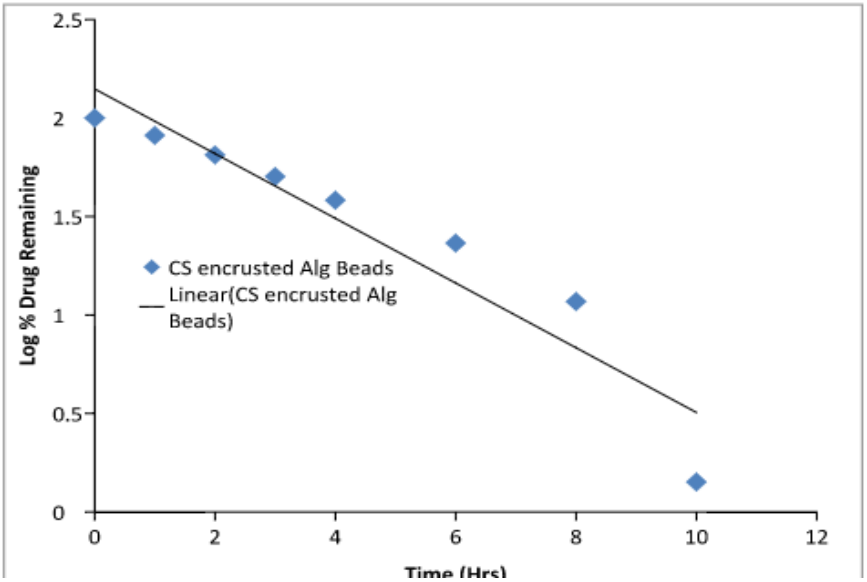


Fig No: 36 First order kinetics of CS encrusted alginate tamarind gum beads

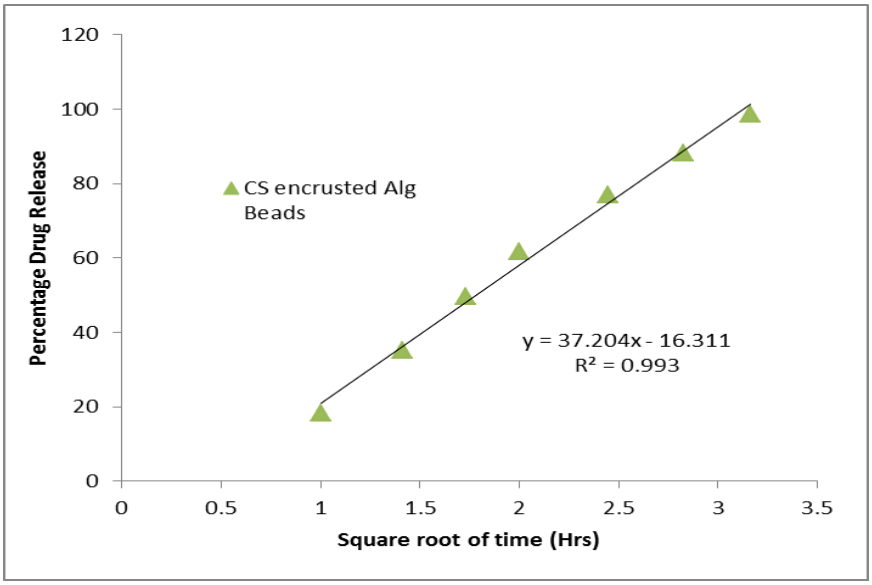


Fig No: 37 Higuchi order kinetics of CS encrusted alginate tamarind gum beads

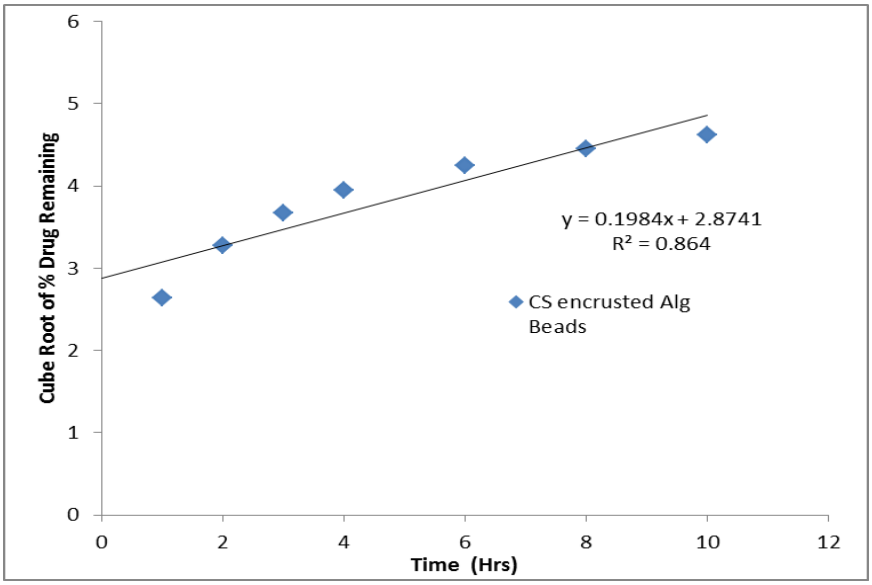


Fig No: 38 Hixon- Crowel kinetics of CS encrusted alginate tamarind gum beads

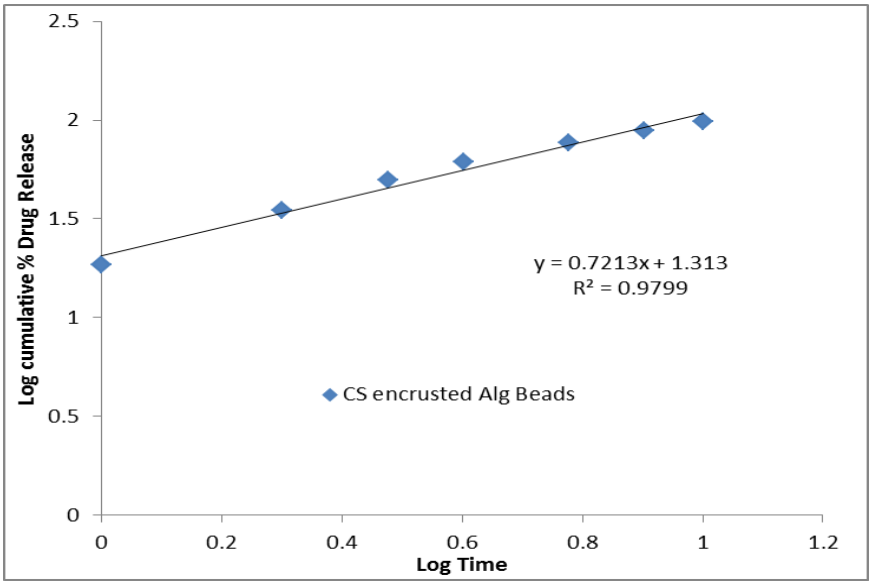


Fig No: 39 Korsmeyer-Peppas model of CS encrusted alginate tamarind gum beads

CONCLUSION

The micro beads of capecitabine were formulated and optimized using Box – Behnken model. The quantitative responses of in vitro drug release for different combinations of independent variables, sodium alginate as release retarding polymer, Tamarind gum as acid resistant polymer and calcium chloride as cross-linking agent were obtained experimentally, and the results were found to fit the design model.

The drug entrapment efficiency of the beads was increased while increasing concentration of tamarind gum. The quantitative effect of these factors at different levels on the responses could be predicted using polynomial equations, and high linearity was observed between predicted and actual values of response variables. The results of release studies indicate that chitosan succinate coated tamarind beads offer a high degree of protection from premature drug release in simulated upper GIT conditions.

Chitosan Succinate coated tamarind beads deliver most of the drug load in the colon, an environment rich in bacterial enzymes that degrade the chitosan succinate and allow drug release to occur at the desired site. Thus, dual cross-linked CS decorated alg/tamarind beads may potential system for colon delivery of capecitabine for chemotherapy of cancer.

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