FORMULATION AND EVALUATION OF SUSTAINED RELEASE MICROSPHERES OF ROSIN CONTAINING CAPTOPRIL

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By

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CERTIFICATE

This is to Certify that the dissertation entitled **"FORMULATION AND EVALUATION OF SUSTAINED RELEASE MICROSPHERES OF ROSIN CONTAINING CAPTOPRIL"** submitted by **Mr.GURUSANKAR.R [Register Number: 26102202**] for the award of the degree of **"MASTER OF PHARMACY"** is a bonafide research work done by him in the Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Tiruchirappalli under my guidance and direct supervision.

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This is to Certify that the dissertation entitled **"FORMULATION AND EVALUATION OF SUSTAINED RELEASE MICROSPHERES OF ROSIN CONTAINING CAPTOPRIL"** done by **Mr.GURUSANKAR. R [Register Number: 26102201]** for the award of the degree of **"MASTER OF PHARMACY"** under The Tamilnadu Dr. M.G.R Medical University, Chennai is a bonafide research work performed by him in the Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Tiruchirappalli. The work was performed under the guidance and direct supervision of **Prof.T.N.K.Suriyaprakash, M.Pharm., Ph.D.,** Head of the Department, Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Tiruchirappalli.

This dissertation is submitted for acceptance as project for partial fulfillment of the degree of **"MASTER OF PHARMACY"** in **Pharmaceutics**, of The Tamilnadu Dr. M.G.R Medical University, during May 2012.

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ABBREVATIONS

nm	**Nano Meter**
FT – IR	**Fourier Transform Infrared Spectroscopy**
UV	**Ultraviolet**
mm	**millimeter**
µm	**microgram**
PVA	**Poly vinyl alcohol**
SEM	**Scanning Electron Microscopy**
f	**Fraction bioavailability**
τ	**Dosing Interval**
HPMC	**Hydroxy Propyl Methyl Cellulose**
FDDS	**Floating drug delivery systems**
HTN	**Hypertension**
BP	**Blood Pressure**
TPR	**Total peripheral resistance**
DASH	**Dietary approaches to stop hypertension**
mmHg	**millimeter mercury**
kPa	**Kilo pascal**
ECG	**Electrocardiogram**
NSAID	**Non streiods anti inflammatory drug**

1. SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Sustained release dosage form is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug. Drugs are defined precisely under some acts[1] . It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment, cure of a disease[2]. Yet to a common man they are just substances which are administered to win back an individual from the states of disease or ill health to the normal health. The drugs also had mysterious origins and hence the word drug was a form of the word called 'drogues' meaning of mysterious origin. The word disease can be expressed as a combination of 'dis' and 'ease' indicating absence of easiness or well being or a feeling contrary to the feeling of health.

With many drugs the basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. The basic objective in dosage form design is to optimize the delivery of medication so as to achieve a measure of control of therapeutic effect in the face of uncertain fluctuations in the *in-vivo* environment in which drug release takes place. The appropriate dosage form and correct dose will ensure the maximum availability of the drug. The pharmaceutical industry provides a variety of dosage forms and dosage levels of particular drugs thus enabling the physician to control the onset and duration of drug therapy by altering the dose or mode of administration[3].

Scope of Sustained Drug Delivery

Sustained release delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. A sustained release dosage forms leads to better management of the acute or chronic disease condition. The basic

rationale of a sustained drug delivery system is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity do drug, administered by the most suitable route. This is usually accomplished by maximizing drug availability, i.e., by attempting to attain maximum rate and extent of drug absorption; however, control of drug action through formulation also implies controlling bioavailability to reduce drug absorption rates. Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect.

Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. The sustained plasma drug levels provided by sustained release products eliminates the need for night dosing, which benefits not only the patients but the care given as well.

The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and/or targeting the drug to desired site[4]. Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system. The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release of drugs.

Sustained release can be achieved by,

- Incorporating the drug in a carrier system
- Altering the structure of the drug at the molecular level

- Controlling the input of the drug into the bio-environment to ensure a programmed and desirable bio-distribution.

The primary objectives are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing.

Advantages of Sustained Release Dosage Form[4]

i. Frequency of drug administration is reduced.

ii. Patient compliance can be improved, and drug administration can be made more convenient.

iii. The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced, because a more even blood level is maintained.

iv. Implicit in the design of sustained release forms, is that the amount of drug administered can be reduced, thus maximizing availability with a minimum dose.

v. The safety margin of high-potency drugs can be increased, and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.

Disadvantages

i. Administration of sustained release medication does not permit the prompt termination of therapy.

ii. The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form regimen.

iii. Sustained release forms are designed for the normal basis of average drug biologic half-lives. Consequently, disease states that alter drug disposition, significant patient variation, so forth are not accommodated.

iv. Economically more costly processes and equipment are involved in manufacturing many sustained release forms.

The parameters that must be taken into account in optimizing sustained release dosage form designs are[5],

K_e ⟶ Elimination rate constant

K_a ⟶ Absorption rate constant

V_d ⟶ Apparent distribution volume

D_i ⟶ Loading or immediately available portion of the dose

D_m ⟶ Maintenance or slowly available portion of the dose

T_m ⟶ Time at which release of maintenance dose begins

K_r ⟶ The specific rate of release of the maintenance dose

Factors to Be Considered for the Formulation of Sustained Release[6, 7]

Physicochemical properties

a) Dose size:

For a ideal sustained release formulation the dose size should be not more than 500mg.

b) Aqueous solubility:

The drug should not be more water soluble or poorly soluble; moderate solubility is needed.

c) Partition co-efficient:

Both lipophillic or hydrophilic drugs are difficult to process and should possess optimum partition co-efficient.

d) Molecule size:

Large molecules show small diffusion co-efficient and may be difficult to place into a suitable sustained release system. Drugs of molecular weight 500-700 finds no difficult in processing.

e) Drug stability:

It should be significantly stable over an extended period of time in the GIT. Generally non-potent drugs are more stable when formulated as sustained release form. It should not show high degree of plasma protein binding.

Route of administration

Some routes of administration exert a negative influence on drug efficacy especially during chronic administration. Many physiological constrains improved by the particular route i.e., GI mobility, blood supply, first pass metabolism.

Biological properties

a) **Absorption**:

Drugs that are slowly absorbed or adsorbed with variable absorption rate are poor candidates for sustained release. It is assumed that the GI transit time of 10-12 hrs, to be ideal for sustained release.

b) **Metabolism**:

Rapid metabolism leads to poor formulation in extended release.

c) Distribution:

Drugs with high apparent volumes of distribution which in turn influences the rate of elimination for the drug are poor candidates for sustained release.

d) Duration of action

Drugs with short half life and high doses impose a constraint because of the dose size needed and those with a long half life are inherently sustained.

e) Therapeutic index

Drugs with narrow therapeutic range require precise control over the blood level of drug placing a constraint on sustained release.

f) Length of drug therapy

Expected length of drug therapy to achieve control or curve of ailment is an important factor, in design of control release products.

g) Disease state

Pathophysiological state of subject plays an important part in the design of suitable controlled release delivery system.

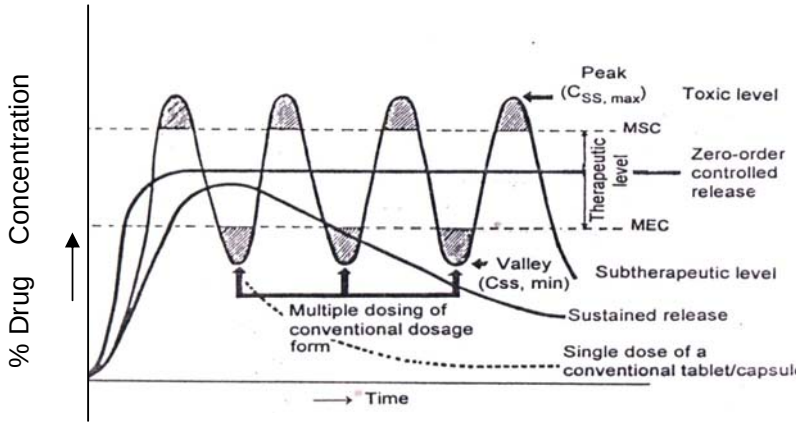
Formulation Methods of Achieving Sustained Drug Release[8]

All sustained release formulations employ a chemical or physical barrier to provide slow release of the maintenance dose. Many formulation techniques have been used to 'build' the barrier into the peroral dosage form. These techniques include the use of coatings, embedding drugs in a wax, fat or plastic matrix, microencapsulation, chemical binding to ion-exchange resins and incorporation in an osmotic pump. The initial rapidly releasing priming dose of drug may be provided by incorporating that portion of the drug in a separate rapidly releasing form in the dosage form, for instance, as uncoated, rapidly releasing granules or pellets along with coated, slowly releasing granules or pellets in a tablet or hard gelatin capsule dosage form.

Alternatively, immediate and rapid release of the priming dose has been achieved by virtue of the position of that portion of the drug being at the surface

of a porous wax or plastic matrix. The maintenance dose is provided by drug embedded deeper in the porous matrix.

Fig–1. Repeat Action versus Sustained Action Drug Therapy



A repeat action tablet may be distinguished from its sustained release counterpart by the fact that the repeat action product does not release the drug contained therein in a slow controlled manner and consequently doesn't give a plasma concentration-time curve which resembles that of sustained release product[9]. A repeat action tablet usually contains two doses of drug, the first dose being released immediately following peroral administration in order to provide a rapid onset of the therapeutic response. The release of the second dose is delayed, usually by means of an enteric coat. Consequently when the enteric coat surrounding the second dose is breached by the intestinal fluids, the second dose is released immediately.

Classification[10]

From a mathematical-modeling point of view, sustained-release systems may be classified according to the controlling physical mechanism(s) of release of the incorporated drug. We have proposed a convenient method based on the mechanism of transport for categorizing them as diffusion-controlled, swelling-controlled, osmotically controlled, and chemically controlled systems. Sustained

release of drugs, proteins, and other bioactive agents can be achieved by incorporating them either in dissolved or dispersed form in polymers.

Diffusion-Controlled drug delivery system

Diffusion is the most common mechanism for controlling the release. There are two major types of diffusion-controlled systems; reservoir devices and membrane devices. Drug release from each type of system occurs by diffusion through the macromolecular mesh or through the water-filled pores.

a) Reservoir systems

Reservoir systems consist of a polymeric membrane surrounding a core containing the drug. The rate-limiting step for drug release is diffusions through the outer membrane of the device. To maintain a constant release rate or flux of drug from the reservoir, the concentration difference must remain constant. This can be achieved by designing a device with excess solid drug in the core. Under these conditions, the internal solution in the core remains saturated. This type of device is an extremely useful device as it allows for time - independent of zero-order release. The major drawback of this type of drug delivery system is the potential for catastrophic failure of the device.

b) Matrix system

In matrix devices, the drug is dispersed throughout the three-dimensional structure of the polymer. Release occurs due to diffusion of the drug throughout the macromolecular mesh or water-filled pores. In these systems, the release rate is proportional to time to the one-half power. This is significant in that it is impossible to obtain time independent of zero-order release in this type of system with simple geometries.

Drug can be incorporated into the gels by equilibrium partitioning, where the gel is swollen to equilibrium in concentrated drug solution, or during the polymerization reaction. Equilibrium partitioning is the favorable loading method for drug-polymer systems that could be degraded during the polymerization.

C) Swelling –Controlled release systems

In swelling-controlled release systems, the drug is dispersed within a glassy polymer. Upon contact with biological fluid, the polymer begins to swell. No drug diffusion occurs through the polymer phase. As the penetrant enters the glassy polymer, the glass transition temperature of the polymer is lowered allowing for relaxations of the macromolecular chains. The drug is able to diffuse out of the swollen, rubbery area of the polymers. This type of system is characterized by two moving fronts: the front separating the swollen (rubbery) portion and the glassy regions which moves with velocity, υ, and the polymer-fluid interface. The rate of drug release is controlled by the velocity and position of the front dividing the glassy and rubbery portions of the polymer.

For true swelling-controlled release systems, the diffusion exponent, n, is 1. This type of transport is known as Case II transport and results in zero-order release kinetics. However, in some cases, drug release occurs due to a combination of macromolecular relaxations and Fickian diffusion. In this case, the diffusion exponent is between 0.5 and 1. This type of transport is known as anomalous or non-Fickian transport.

d) Chemically-Controlled release systems

There are two major types of chemically controlled release systems: erodible drug delivery systems, and pendent chain systems in erodible systems, drug release occurs due to degradation or dissolution of the polymer. In pendent chain systems, the drug is affixed to the polymer backbone through degradable linkages. As these linkages degrade, the drug is released.

e) Erodible drug delivery systems

Erodible drug delivery systems, also known as degradable or absorbable release systems, can be either matrix or reservoir delivery systems. In reservoir devices, an erodible membrane surrounds the drug core. If the membrane erodes significantly after the drug release is complete, the dominant mechanism for release would be diffusion. Predictable, zero-order release could be obtained with these systems. In some cases, the erosion of the membrane occurs simultaneously with the drug release. As the membrane thickness decreased due to erosion, the drug delivery rate would also change. Finally in some erodible reservoir devices, the drug diffusion in the outer membrane does not occur. Under these conditions, drug release does not occur until the outer membrane erodes completely. In this type of device, the entire contents are released in a single, rapid burst.

For erodible matrix devices, the drug is dispersed within the three-dimensional structure of the polymer. Drug release is controlled by drug diffusion through the gel of erosion of the polymer. In true erosion-controlled devices, the rate of drug diffusion is significantly slower than the rate of polymer erosion, and the drug is released as the polymer erodes. In erodible system, there are three major mechanisms for erosion of the polymer.

Degradation of the cross-links

This degradation can occur by hydrolysis of water-labile linkages, enzymatic degradation of the junctions, or dissolution of physical cross-links such as entanglements or crystallites in semi - crystalline polymers.

Solubilization of insoluble or hydrophobic polymers

This could occur as a result of hydrolysis, ionization, or protonation of pendent groups along the polymer chains. Degradation of backbone bonds to produce small molecular weight molecules. Typically, the degradation products

are water soluble. This type of erosion can occur by hydrolysis of water-labile backbone linkages or by enzymatic degradation of backbone linkages.

Environmentally responsive systems

Environmentally responsive materials show drastic changes in their swelling ratio due to changes in their external pH, temperature, ionic strength, nature and composition of the swelling agent, enzymatic or chemical reaction, and Electrical or magnetic stimulus In most responsive networks, a critical point exists at which this transition occurs.

Responsive materials are unique in that there are many different mechanisms for drug release and many different types of release systems based on these materials. For instance, in the most cases drug release occurs when the gel is highly swollen and is typically controlled by gel swelling, drug diffusion, or a coupling of swelling and diffusion. However, in a few instances, drug release occurs during gel syneresis by a squeezing mechanism. Also, drug release can occur due to erosion of the polymer caused by environmentally responsive swelling. Another interesting characteristic about many responsive gels is that the mechanism causing the network structural changes can be entirely reversible in nature.

The ability of these materials to exhibit rapid changes in their swelling behavior and pore structure in response to changes in environmental conditions lends these materials favorable characteristics as carriers for bioactive agents, including peptides and proteins. This type of behavior may allow these materials to serve as self regulated, pulsatile drug delivery system.

Initially, the gel is in an environment in which no swelling occurs. As a result, very little drug release occurs. However, when the environment changes and the gel swells rapid drug release occurs (either by Fickian diffusion, anomalous transport, or Case II transport). When the gel collapses as the environment changes, the release can be turned off again. This can be repeated

over numerous cycles. Such systems could be of extreme importance in the treatment of chronic diseases such as diabetes.

POLYMER FOR DRUG DELIVERY

The choice of appropriate polymer, particle size and manufacturing process will primarily depend on the bio-acceptability of the polymer.

Characteristics of Ideal Polymer System

An ideal polymer system should possess the following char

i) Inert and compatible with the environment
ii) Non-Toxic
iii) Easily administered
iv) Inexpensive to fabricate
v) Good mechanical strength.

Inert polymer matrices are most commonly employed for evaluation of sustained action dosage forms. Three classes of retardant materials demonstrating different approaches have been used for matrix formulations.

- Drugs consist of retardant material that forms insoluble or skeleton matrices.
- Drugs consist of water insoluble materials that are potentially erodable.
- Drugs consist of polymers that form hydrophilic matrices.

Classification of Polymers[11]

Polymers based on back bone

a) Polymers with carbon chain backbone:

- Polyethylene
- Polypropylene

- Poly vinyl chloride
- Poly vinyl alcohol
- Poly acrylamide
- Poly vinyl pyrrolidone

b) Polymers with heterochain backbone:

- Poly ethylene oxide
- Cellulose (poly glycoside, β-1,4)
- Amylase (polyglucose α-1,4)
- Polydimethyl silaxone
- Pectinic acid (polygalactouronoside)

Polymer classification based on source

a) Natural polymers

Protein based	:	albumin, collagen, gelatin, etc.
Polysaccharides	:	agarose, alginate, chitosan, cyclodextrin, hyaluronic acid, etc.

b) Synthetic polymers

Bio-degradable

Poly esters	**:**	poly lactic acid, polyglycolic acid, poly diaxanones, polyhydroxy butyrate, etc.
Polyanhydrides	**:**	polysabacic acid, polyadipic acid, polyterephthalic acid, etc.
Polyamides	**:**	polyimino carbonates, polyamino acids Phosphorous based: polyphosphates, polyphosphonates, polyphosphazenes, etc.

Others	**:**	Polyurethanes, polyorthoesters, polydihydropyrans, polyacetals, etc.

b) Non bio-degradable

Cellulose derivatives	:	Carboxymethyl cellulose, ethyl cellulose, HPMC, cellulose acetate, etc.
Silicones	**:**	Polydimethyl siloxane, colloidal silicate
Acrylic polymers	**:**	Polymethacrylates, polymethylmethacrylate, polyhydroethyl methacrylate, etc.
d) Others	**:**	Polyvinyl pyrrolidone, ethyl vinyl acetate, Poloxamers, poloxamines, etc.

Based on nature of physical characteristics

Insoluble inert polymers	**:**	Dibasic calcium phosphate, polyamides, Polyvinyl chloride, etc.
e) Insoluble erodable (lipid excipients)	**:**	Methyl cellulose, stearylalcohol, castor wax, PEG monostearate, carnauba wax, etc.
Methacrylate→Ethacrylate	**:**	Copolymers
Hydrophilic polymers	**:**	Methyl cellulose (400 CPS, 4000 CPS), Hydroxyl ethyl cellulose, guargum, HPMC (60 HG, 90 HG) (25 CPS, 4000 CPS, 15000 CPS), sodium carboxy methyl cellulose, etc

Hydrophilic polymer matrix system

Hydrophilic polymer matrix systems (HPMS) are widely used in oral controlled drug delivery because they make it easier to a desirable drug-release profile, as they are cost effective and have abroad US FDA acceptance. It consists of hydrophilic polymer, drug and other excipients distributed throughout the matrix. This dynamic system is dependent on polymer wetting, hydration and dissolution for controlled release of drug. At the same time, other soluble excipients (or) drug substance will also wet, dissolve and diffuse out of the matrix, whereas insoluble excipients (or) drug substances will be held in place until the surrounding polymer, excipients (or) drug complex erodes (or) dissolves away.

Matrix controlled release tablet are relatively simple system that are more forgiving of variations in ingredients, production methods and end-use conditions when compared to coated controlled release tablets of other systems. This results in more uniform release profiles with a high resistance to drug dumping. Hydrophilic matrix systems are relatively easy to formulate with existing conventional equipments and processing method. One goal of this study was to develop uncoated HPMC matrix tablet by wet granulation process, evaluating the relationship and influence of excipeints[11].

Advantages of hydrophilic matrix system

- Generally regarded as a safe excipients
- Simple concept
- Erodable – reducing ghost matrices
- Easy to manufacture by
    - Direct compression
    - Wet granulation
    - Roller compaction
- Possible to obtain different release

Disadvantages

- Need optimal rate controlling polymers
- Scale of problems

MICROENCAPSULTION[12]

Microencapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded and enclosed by an intact shell. Microencapsulation is used to modify and delayed drug release form pharmaceutical dosage forms. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a particular drug.

It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.

Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor. The intent of the paper is to highlight the potential of microencapsulation technique as a vital technique in novel drug delivery.

The Reasons for Microencapsulation

The reasons for microencapsulation are in some countless cases, the core must be isolated from its surroundings, as in vitamins from the deterioration a volatile core, improving the handling of a sticky material, or isolatin core from chemical a attack. The problem may be as simple as masking the taste or odor of the core, or as complex as increasing the selectivity of an adsorption or extraction process.

Fundamental Considerations

The realization of the potential that microencapsulation offers involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, the stability and release characteristics of the coated materials and the microencapsulation methods.

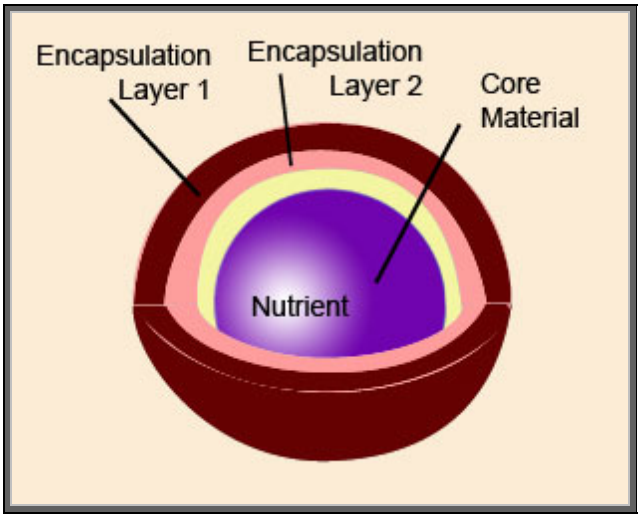
Core Material

The core material, defined as the specific material to be coated, can be liquid or solid in nature. The composition of the core material can be varied as the liquid core can include dispersed and/or dissolved material. The solid core can be mixture of active constituents, stabilizers, diluents, excipients and release-rate retardants or accelerators. The ability to vary the core materials composition provides definite flexibility and utilization of this characteristic often allows effectual design and development of the desired microcapsules properties.

Coating Material

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/microspheres.

Fig 2 - Encapsulation



While selecting a polymer the product requirements i.e. stabilization, reduced volatility, release characteristics, environmental conditions, etc. should be taken into consideration. The polymer should be capable of forming a film that is cohesive with the core material. It should be chemically compatible, non-reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability. Generally hydrophilic polymers, hydrophobic polymers (or) a combination both are used for the microencapsulation process. A number of coating materials gelatin have been used successfully; examples of these include polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate and styrene maleic anhydride. The film thickness can be varied considerably depending on the surface area of the material to be coated and other physical characteristics of the system. The microcapsules may consist of a single particle or clusters of particles.After isolation from the liquid manufacturing vehicle and drying, the material appears as a free flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions, and other dosage forms

Multiparticulate Drug Delivery Systems[14]

Multiparticulate drug delivery system applies specially to multiple particles such as pellets, beads, microspheres, microcapsules. In recent years, multiparticulate dosage forms or microparticles have gained in popularity for a variety of reasons. Considerable research efforts have been spent on oral sustained or controlled release multiparticulate drug delivery system due to its advantages over monolithic dosage forms.

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each excihibit some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm.

Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a table

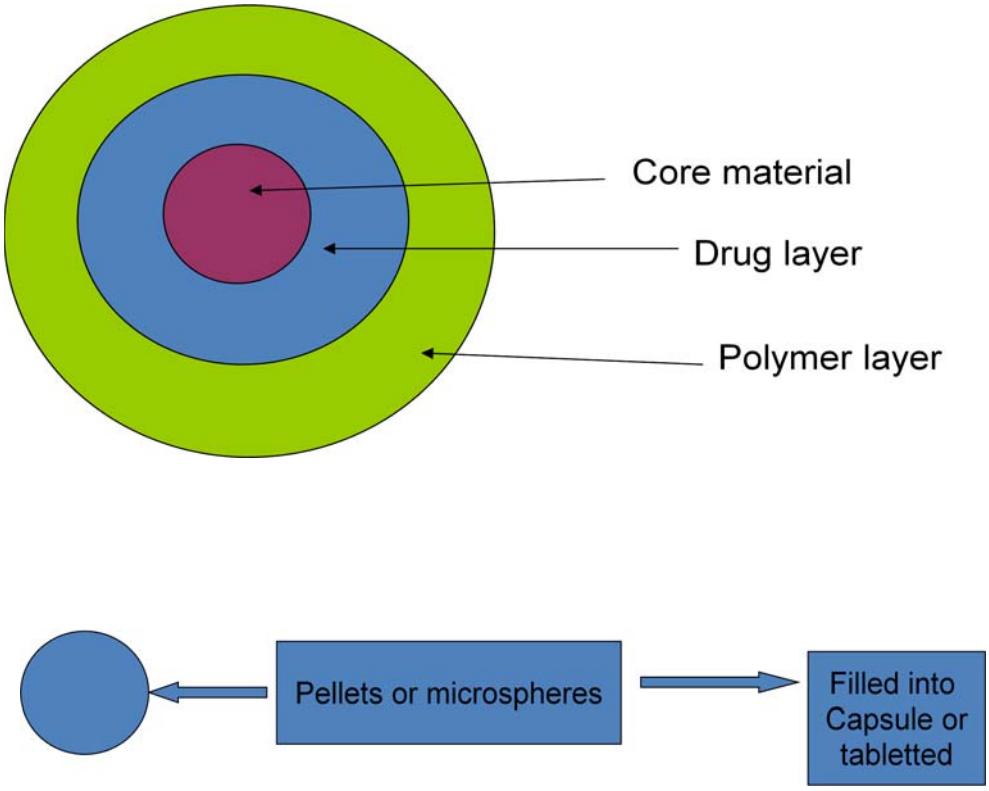


Fig – 3 MICROSPHERES CHART

The system is based on the expansion of the core (non effervescent FDDS or low density approach), which lead to floating due to low density. Also the air entrapped by the swollen polymer confers buoyancy to this dosage forms. Floating multiparticulate oral sustained release drug delivery system includes; hollow microspheres (microballoons), low density floating micropellets and Floating microbeads. Multiparticulate carriers (microspheres) are defined as homogeneous, monolithic particles in the size range of about 0.1-1000 μm and are widely used as drug carriers for controlled release. Multiparticulate carrier systems made from the naturally occurring biodegradable polymers have attracted considerable

attention for several years in sustained drug delivery. Recently dosage forms that can precisely control the release rates and target drugs to a specific body site have created enormous impact in formulation and development of novel drug delivery systems.

Microspheres form an important part of such novel drug delivery systems. They have varied applications and are prepared using various polymers. However, the success of these microspheres is limited due to their short residence time at the site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling gastroretentive and bioadhesion characteristics to multiparticulates and developing gastroretentive bioadhesive, multiparticulates. These multiparticulates have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site4. It is stated that, 'the multiparticulates' float on the stomach contents, and then adhere to the mucous linings as the stomach empties (Figure 2). The release of drug from the system can be controlled to coincide with the half-life emptying of the system from the stomach.

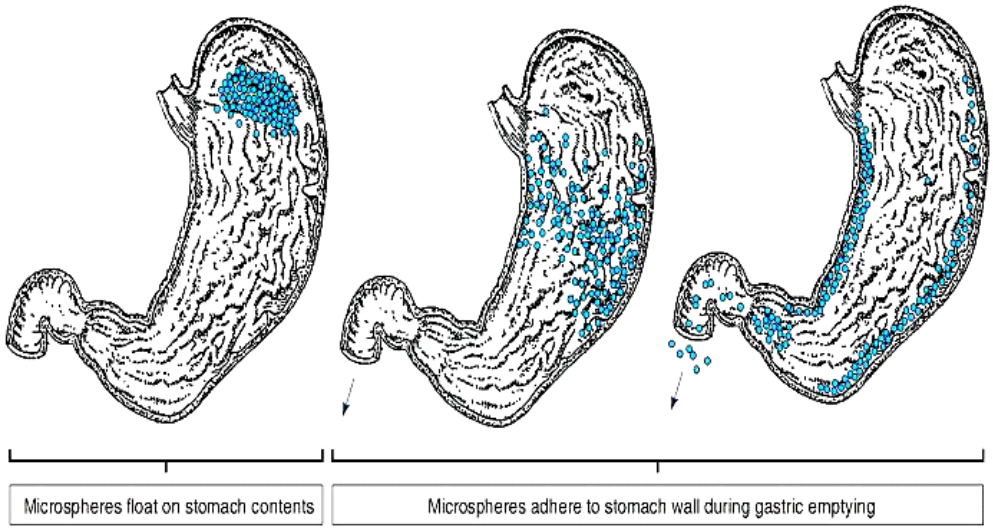


Fig – 4 Proposed mechanism for retention of microspheres in the human stomach

The floating multiparticulate oral sustained release drug delivery system have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.

Floating multiparticulates drug delivery system has following objects;

- Sustain release or prolong release medication
- Taste masking
- Improve stability
- Increase solubility or dispersability
- Increase therapeutic effciency.

HYPERTENSION[15]

Hypertension (HTN) or **high blood pressure** is a chronic medical condition in which the systemic arterial blood pressure is elevated. It is the opposite of hypotension. It is classified as either primary (essential) or secondary. About 90–95% of cases are termed "primary hypertension", which refers to high blood pressure for which no medical cause can be found. The remaining 5–10% of cases (Secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart, or endocrine system

Persistent hypertension is one of the risk factors for stroke, myocardial infarction, heart failure and arterial aneurysm, and is a leading cause of chronic kidney failure. Moderate elevation of arterial blood pressure leads to shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment may prove necessary in patients for whom lifestyle changes prove ineffective or insufficient.

Classification[16]

The variation in pressure in the left ventricle and the aorta over two cardiac cycles ("heart beats"), showing the definitions of systolic and diastolic pressure

Table-1.Classification of BP

Classification	Systolic pressure		Diastolic pressure	
	mmHg	**kPa**	**mmHg**	**kPa**
Normal	90–119	12–15.9	60–79	8.0–10.5
Prehypertension	120–139	16.0–18.5	80–89	10.7–11.9
Stage 1	140–159	18.7–21.2	90–99	12.0–13.2
Stage 2	≥160	≥21.3	≥100	≥13.3
Isolated systolic hypertension	≥140	≥18.7	<90	<12.0

Blood pressure is usually classified based on the systolic and diastolic blood pressures. Systolic blood pressure is the blood pressure in vessels during a heart beat. Diastolic blood pressure is the pressure between heartbeats. A systolic or the diastolic blood pressure measurement higher than the accepted normal values for the age of the individual is classified as prehypertension or hypertension.

Hypertension has several sub-classifications including, hypertension stage I, hypertension stage II, and isolated systolic hypertension. Isolated systolic hypertension refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly.

SIGN AND SYMPTOMS[17]

Accelerated hypertension

Accelerated hypertension is associated with headache, drowsiness, confusion, vision disorders, nausea, and vomiting symptoms which are collectively referred to as hypertensive encephalopathy. Hypertensive encephalopathy is caused by severe small blood vessel congestion and brain swelling, which is reversible if blood pressure is lowered.

Children

Some signs and symptoms are especially important in newborns and infants such as failure to thrive, seizures, irritability, lack of energy, and difficulty breathing. In children, hypertension can cause headache, fatigue, blurred vision, nosebleeds, and facial paralysis.

Even with the above clinical symptoms, the true incidence of pediatric hypertension is not known. In adults, hypertension has been defined due to the adverse effects caused by hypertension. However, in children, similar studies have not been performed thoroughly to link any adverse effects with the increase in blood pressure. Therefore, the prevalence of pediatric hypertension remains unknown due to the lack of scientific knowledge.

Secondary hypertension

Some additional signs and symptoms suggest that the hypertension is caused by disorders in hormone regulation. Hypertension combined with obesity distributed on the trunk of the body, accumulated fat on the back of the neck ('buffalo hump'), wide purple marks on the abdomen (abdominal striae), or the recent onset of diabetes suggests that an individual has a hormone disorder known as Cushing's syndrome. Hypertension caused by other hormone disorders such as hyperthyroidism, hypothyroidism, or growth hormone excess will be accompanied

by additional symptoms specific to these disorders. For example, hyperthyrodism can cause weight loss, tremors, heart rate abnormalities, reddening of the palms, and increased sweating. Signs and symptoms associated with growth hormone excess include coarsening of facial features, protrusion of the lower jaw, enlargement of the tongue, excessive hair growth, darkening of the skin color, and excessive sweating.. Other hormone disorders like hyperaldosteronism may cause less specific symptoms such as numbness, excessive urination, excessive sweating, electrolyte imbalances and dehydration, and elevated blood alkalinity. and also cause of mental pressure.

Pregnancy

Hypertension in pregnant women is one symptom of pre-eclampsia. Pre-eclampsia can progress to a life-threatening condition called eclampsia, which is the development of protein in the urine, generalized swelling, and severe seizures. Other symptoms indicating that brain function is becoming impaired may precede these seizures such as nausea, vomiting, headaches, and vision loss.

In addition, the systemic vascular resistance and blood pressure decrease during pregnancy. The body must compensate by increasing cardiac output and blood volume to provide sufficient circulation in the utero-placental arterial bed.

Causes

Essential hypertension

Essential hypertension is the most prevalent hypertension type, affecting 90–95% of hypertensive patients. Although no direct cause has been identified, there are many factors such as sedentary lifestyle, smoking, stress, visceral obesity, potassium deficiency (hypokalemia), obesity (more than 85% of cases occur in those with a body mass index greater than 25), salt (sodium) sensitivity,alcohol intake, and vitamin D deficiency that increase the risk of developing hypertension. Risk also increases with aging, some inherited genetic

mutations, and having a family history of hypertension. An elevated level of renin, a hormone secreted by the kidney, is another risk factor, as is sympathetic nervous system overactivity. Insulin resistance, which is a component of syndrome X (or the metabolic syndrome), is also thought to contribute to hypertension. Recent studies have implicated low birth weight as a risk factor for adult essential hypertension.

Secondary hypertension

Secondary hypertension by definition results from an identifiable cause. This type is important to recognize since it's treated differently to essential hypertension, by treating the underlying cause of the elevated blood pressure. Hypertension results in the compromise or imbalance of the pathophysiological mechanisms, such as the hormone-regulating endocrine system, that regulate blood plasma volume and heart function. Many conditions cause hypertension, some are common and well recognized secondary causes such as Cushing's syndrome which is a condition where the adrenal glands overproduce the hormone cortisol. In addition, hypertension is caused by other conditions that cause hormone changes such as hyperthyroidism, hypothyroidism (citation needed), and certain tumors of the adrenal medulla (e.g., pheochromocytoma). Other common causes of secondary hypertension include kidney disease, obesity/metabolic disorder, pre-eclampsia during pregnancy, the congenital defect known as coarctation of the aorta, and certain prescription and illegal drugs.

Pathophysiology

Most of the mechanisms associated with secondary hypertension are generally fully understood. However, those associated with essential (primary) hypertension are far less understood. What is known is that cardiac output is raised early in the disease course, with total peripheral resistance (TPR) normal; over time cardiac Output drops to normal levels but TPR is increased. Three theories have been proposed to explain this:

- Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as Atrial Natriuretic Factor being secreted to promote salt excretion with the side effect of raising total peripheral resistance.
- An overactive Renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume leads to hypertension.
- An overactive sympathetic nervous system, leading to increased stress responses.

It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.

Recently, work related to the association between essential hypertension and sustained endothelial damage has gained popularity among hypertension scientists. It remains unclear however whether endothelial changes precede the development of hypertension or whether such changes are mainly due to long standing elevated blood pressures.

Diagnosis

Hypertension is generally diagnosed on the basis of a persistently high blood pressure. Usually this requires three separate sphygmomanometer (see figure) measurements at least one week apart. Often, this entails three separate visits to the physician's office. Initial assessment of the hypertensive patient should include a complete history and physical examination. Exceptionally, if the elevation is extreme, or if symptoms of organ damage are present then the diagnosis may be given and treatment started immediately.

Once the diagnosis of hypertension has been made, physicians will attempt to identify the underlying cause based on risk factors and other symptoms, if present. Secondary hypertension is more common in preadolescent children, with

most cases caused by renal disease. Primary or essential hypertension is more common in adolescents and has multiple risk factors, including obesity and a family history of hypertension. Laboratory tests can also be performed to identify possible causes of secondary hypertension, and determine if hypertension has caused damage to the heart, eyes, and kidneys. Additional tests for Diabetes and high cholesterol levels are also usually performed because they are additional risk factors for the development of heart disease require treatment.

Creatinine (renal function) testing is done to determine if kidney disease is present, which can be either the cause or result of hypertension. In addition, it provides a baseline measurement of kidney function that can be used to monitor For side-effects of certain antihypertensive drugs on kidney function. Additionally, testing of urine samples for protein is used as a secondary indicator of kidney disease. Glucose testing is done to determine if diabetes mellitus is present. Electrocardiogram (EKG/ECG) testing is done to check for evidence of the heart being under strain from high blood pressure. It may also show if there is thickening of the heart muscle (left ventricular hypertrophy) or has experienced a prior minor heart distubance such as a silent heart attack. A chest X-ray may be performed to look for signs of heart enlargement or damage to heart tissue.

Prevention

The degree to which hypertension can be prevented depends on a number of features including current blood pressure level, sodium/potassium balance, detection and omission of environmental toxins, changes in end/target organs (retina, kidney, heart, among others), risk factors for cardiovascular diseases and the age at diagnosis of prehypertension or at risk for hypertension. A prolonged assessment in which repeated measurements of blood pressure are taken provides the most accurate assessment of blood pressure levels. Following this, lifestyle changes are recommended to lower blood pressure, before the initiation of prescription drug therapy. The process of managing prehypertension according the

guidelines of the British Hypertension Society suggest the following lifestyle changes:

- Weight reduction and regular aerobic exercise (e.g., walking): Regular exercise improves blood flow and helps to reduce the resting heart rate and blood pressure.
- Reducing dietary sugar.
- Reducing sodium (salt) in the body by disuse of condiment sodium and the adoption of a high potassium diet which rids the renal system of excess sodium. Many people use potassium chloride salt substitute to reduce their salt intake.
- Additional dietary changes beneficial to reducing blood pressure include the DASH diet (**d**ietary **a**pproaches to **s**top **h**ypertension) which is rich in fruits and vegetables and low-fat or fat-free dairy products. This diet has been shown to be effective based on research sponsored by the National Heart, Lung, and Blood Institute. In addition, an increase in dietary potassium, which offsets the effect of sodium has been shown to be highly effective in reducing blood pressure.
- Discontinuing tobacco use and alcohol consumption has been shown to lower blood pressure. The exact mechanisms are not fully understood, but blood pressure (especially systolic) always transiently increases following alcohol or nicotine consumption. Abstaining from cigarette smoking reduces the risk of stroke and heart attack which are associated with hypertension.

Limiting alcohol intake to less than 2 standard drinks per day can reduce systolic blood pressure by between 2-4mmHg.

- Reducing stress, for example with relaxation therapy, such as meditation and other mindbody relaxation techniques, by reducing environmental stress such as high sound levels and over-illumination can also lower blood pressure. Jacobson's Progressive Muscle Relaxation and biofeedback

are also beneficial, such as device-guided paced breathing, although meta-analysis suggests it is not effective unless combined with other relaxation techniques.

Increasing omega 3 fatty acids can help lower hypertension. Fish oil is shown to lower blood pressure in hypertensive individuals. The fish oil may increase sodium and water excretion.

Treatment[18]

Lifestyle modifications

The first line of treatment for hypertension is the same as the recommended preventative lifestyle changes such as the dietary changes, physical exercise, and weight loss, which have all been shown to significantly reduce blood pressure in people with hypertension. If hypertension is high enough to justify immediate use of medications, lifestyle changes are still recommended in conjunction with medication. Drug prescription should take into account the patient's absolute cardiovascular risk (including risk of myocardial infarction and stroke) as well as blood pressure readings, in order to gain a more accurate picture of the patient's cardiovascular profile. Different programs aimed to reduce psychological stress such as biofeedback, relaxation or meditation are advertised to reduce hypertension. However, in general claims of efficacy are not supported by scientific studies, which have been in general of low quality.

Regarding dietary changes, a low sodium diet is beneficial; A Cochrane review published in 2008 concluded that a long term (more than 4 weeks) low sodium diet in Caucasians has a useful effect to reduce blood pressure, both in people with hypertension and in people with normal blood pressure. Also, the DASH diet (Dietary Approaches to Stop Hypertension) is a diet promoted by the National Heart, Lung, and Blood Institute (part of the NIH, a United States government organization) to control hypertension. A major feature of the plan is

limiting intake of sodium, and it also generally encourages the consumption of nuts, whole grains, fish, poultry, fruits and vegetables while lowering the consumption of red meats, sweets, and sugar. It is also "rich in potassium, magnesium, and calcium, as well as protein".

Medications

Several classes of medications, collectively referred to as antihypertensive drugs, are currently available for treating hypertension. Agents within a particular class generally share a similar pharmacologic mechanism of action, and in many cases have an affinity for similar cellular receptors. An exception to this rule is the diuretics, which are grouped together for the sake of simplicity but actually exert their effects by a number of different mechanisms.

Reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. The aim of treatment should be reduce blood pressure to <140/90 mmHg for most individuals, and lower for individuals with diabetes or kidney disease (some medical professionals recommend keeping levels below 120/80 mmHg). If the blood pressure goal is not met, a change in treatment should be made as therapeutic inertia is a clear impediment to blood pressure control. Comorbidity also plays a role in determining target blood pressure, with lower BP targets applying to patients with end-organ damage or proteinuria.

Often multiple drugs are combined to achieve the goal blood pressure. Commonly used prescription drugs include:

- ACE inhibitors (e.g., captopril)
- Alpha blockers (e.g., prazosin)
- Angiotensin II receptor antagonists (e.g., losartan)
- Beta blockers (e.g., propranolol)

- Calcium channel blockers (e.g., verapamil)
- Diuretics (e.g. hydrochlorothiazide)
- Direct renin inhibitors (e.g., aliskiren)

Some examples of common combined prescription drug treatments include:

- A fixed combination of an ACE inhibitor and a calcium channel blocker. One example of this is the combination of perindopril and amlodipine, the efficacy of which has been demonstrated in individuals with glucose intolerance or metabolic syndrome.
- A fixed combination of a diuretic and an ARB.

Combinations of an ACE inhibitor or angiotensin II–receptor antagonist, a diuretic and an NSAID (including selective COX-2 inhibitors and non-prescribed drugs such as ibuprofen) should be avoided whenever possible due to a high documented risk of acute renal failure. The combination is known colloquially as a "triple whammy" in the Australian health industry.

In the elderly Treating moderate to severe high blood pressure with prescription medications decreases death rates in those under 80 years of age however there is no decrease in those over 80 years old. Even though there was no decrease in total mortality, the results showed similarities between cardiovascular mortality and morbidity.

LITERATURE REVIEW

Literature Review For Microspheres

Dr.lakshmanu prabu, shirwaikar.AR et al, (2007) Prepare the sustained release Aceclofenac microspheres by uing rosin as an encapsulating polymer. The release rate of drug from the microspheres could be properly controlled for about 24h. Appropriate variation in the proportions of drug; polymer and stabilizer can lead to a product with the desired controlled release features.

Vinay mishara et al., (2008) to Prepare and Evaluate matrix microspheres system for simultaneous and sustained release of Candesartan cilexetil and captopril for the management of nephritic syndrome, Ethyl cellulose was used as a retardant polymer decrease of side effect, increase of bioavailability and therapeutic action of both combination drugs.

KBR chowdary, Dana (2008) reported that the study is to evaluate ethylcellulose as a coat for controlled release microcapsules of diclofenac. Ethylcellulose coated microcapsules were prepared by an emulsion-solvent evaporation method employing different proportions of core and coat and the microcapsules were evaluated for size, drug content and microencapsulation efficiency.

Rajashree hirlekar et al., (2008) to develop bucoadhesive drug delivery system of Metoprolol tartarate using various polymer like sodium carboxy methyl cellulose and natural polymers like gum karaya, xanthum gum and locust bean gum. The formulation containing xanthum gum and locust bean gum in 2:1 ratio exhibited complete drug release in 45 minutes.

Vadhana singh et al., (2009) Develop the hollow microspheres as a new dosage form of floating drug delivery system with prolonged stomach retention time. Hollow microspheres containing ranitidine hydrochloride were prepared by solvent evaporation method using Eudragit RLPO dissolved in a mixture

of dichloromethane and ethanol. Hollow microspheres could prolong drug release time (approximately 24 hrs) and float over stimulate gastric fluid for more than 12hrs

Kem et al., (2009) to Production of uniform microspheres and double-wall microspheres capable of efficiently encapsulating model drugs. Of primary importance was the ability of monodisperse microsphere formulations. Monodisperse PPF microspheres and core-shell microparticles offer advantages in reproducibility, control, and consistency that may provide valuable assistance in designing advanced drug delivery systems. to achieve precise control of the particle size and reproducibly fabricate nanocapsules the technology

Om praksh et al., (2009) Evaluate rosin polymer , Rosin application agent, microencapsulating,agent. It had been found anti-inflammatory and antitumor activity. Its semisolid preparation such as skin cream shows good homogeneity and spreadibility. It has prominent property for the sustained release drug system with most of the drug and dosage form.

Alaghusundram., et al., (2009) reported microspheres not only for prolonged release, but also for targeting of anticancer drugs to the Tumour. In future by combining various other strategies, Microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in-vivo.*

Amal H. et al., (2009) To formulate and evaluate captopril Sustained release microparticles.using acetate propionate and employing the solvent evaporation technique .it decreases the side effects.microparticles containing different dug and polymer ratio.

Shashank tiwari. et al., (2010) To formulate micoencapsulation by solvent evaporation method (study of effect process variables) the properties of poly (lacticacid) (poly lactic co glycolic acid) the effect of this microencapsulation is successful .and to get a desire release rate and highest drug loading.

Anand,Chirag. et al., (2010) formulation and evaluation of floating micropsheres of captopril for prolong gastric residence time. Floating microspheres was formulated using biocompatible polymers like Eudragit S100 and Ethyl cellulose in different proportions by solvent evaporation technique. The prepared microspheres were evaluated for percentage yield, micromeritic properties, particle size, morphology, drug entrapment, buoyancy studies, In vitro drug release studies. Practical yield of the microspheres.

Umamaheshwari. et al., (2010) was the fabricate modified release tablets of Floating microsphere bearing acetohydroxamic acid for the treatment of H.pylori.using different portion of drug and polymer.

Durgacharan .et al.,(2011) Formulation and evaluation of Controlled Release Microspheres of Isosorbide dinitrate . Microspheres of Isosorbide dinitrate were prepared using the non-aqueous emulsification solvent evaporation method. The impacts of different factors such as stirring rate, concentration of acrycoat S 100 as matrix polymer on the characteristics of the microspheres were investigated.

Durgacharan,Mangesh R. et al., (2011) Formulation and evaluation of Controlled Release Microspheres of Isosorbide dinitrate Microspheres of Isosorbide dinitrate were prepared using the non-aqueous emulsification solvent evaporation method. The impacts of different factors such as stirring rate, concentration of acrycoat S 100 as matrix polymer on the characteristics of the microspheres were investigated and study.

Sudhamani . et al., (2011) Preparation and evaluation of ethyl cellulose micropsheres of ibuprofen for sustained drug delivery These ethylcellulose microspheres were prepared by the solvent evaporation method. The prepared microspheres were subjected to various evaluation and ***invitro*** release studies. Highest percentage of loading was obtained by increasing the amount of ibuprofen with respect to polymer. The particle sizes of the prepared microspheres were determined

Kumar,Ankit .et al.,(2011) Evaluate Microencapsulation This approach facilitates accurate delivery of small quantities of potent drugs, reduced drug concentrations at sites other than the target organ or tissue and protection of labile compounds before and after administration and prior to appearance at the site of action. Microencapsulation system offers potential advantages over conventional drug delivery systems. Microspheres and microparticales are a unique carrier system for various pharmaceuticals dosage form.

Hermen nack.et al., (1969) Microencapsulation Techniques, application and problems. Evaluation of microcapsules of acetyl salicylic acid prepared with cellulose acetate phthalate, ethyl cellulose or their mixtures by an emulsion non-solvent addition technique.

3. AIM AND OBJECTIVE

AIM

The aim of the present study was to prepare sustained release captopril microspheres using biodegradable polymer.

OBJECTIVE

- Developing sustained release microspheres matrix system containing captopril using rosin as the natural polymer
- The drug release will be sustained for a longer period of time
- The dose will be reduced that improve the patient compliance.

Microencapsulation is the process in which small droplets or particles of liquid or solid material are surrounded or coated by a continuous film of polymeric materials. The controlled drug delivery system has used to reduce the problems associated with conventional therapy and to improve the therapeutic efficacy of a given drug. The maximum therapeutic efficacy can be achieved by delivering of the active agent in the optimal rate to the target tissue, then causing little toxicity and minimum side effects. To deliver a therapeutic substance to the target site in a sustained controlled release fashion, various approaches are used. One is by using microspheres as carriers for drugs. Microspheres are considered as free flowing powders consisting of polymers which are biodegradable in nature and they have the particle size below 200µm.

Microencapsulation process helps for controlling the release characteristics of different coated materials. Microencapsulation the small coated particles are used to make to a wide variety of dosage forms and have not been feasible. Novel drug delivery systems which were initiate with the course of optimizing the bioavailability by the modification of the bioavailability of the drug concentration in blood. With the sustained and controlled release products, drug therapy can be improved that is the common goal achieved over with their non sustained and

controlled release with the same drug. Microencapsulated products (micro particles) are the small entities that have an active agent know as the core material surrounded by a shell known as the coating material or embedded into a matrix structure. Most microparticle shells are of organic polymers, but waxes and lipids are also used. Generally the size of the microencapsulated products is considered as larger than micrometer and up to 1000 micrometers in diameter. Commercially available microparticles contained 10-90% w/w core. The more recent result of pharmaceutical research is that the absorption rate of a drug can be controlled by controlling its rate of release from the dosage form .The controlled released dosage forms are so designed and formulated as having the sustained action, sustained release, prolonged action, delayed action and timed release medication. This has been done by developing the new drug entities, discovering of new polymeric materials that are suitable for prolonging the drug release, safety, improvement in therapeutic efficacy.

The main reason for microencapsulation is for sustained or prolonged release of the drug. Microencapsulation technique also helpful to prevent the incompatibility between drugs.Microencapsulation has also been employed to change the site of absorption. This application has been useful for those drugs which have the toxicity at lower pH.

Captopril, an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure. It has been reported, however, that the duration of antihypertensive action after a single oral dose of captopril is only 6–8 h, so clinical use requires a daily dose of 37.5–75 mg to be taken three times. It is most stable at pH 1.2 and as the pH increases; it becomes unstable and undergoes a degradation reaction. Thus a sustained and controlled release dosage form of captopril is desirable. Hence an attempt has been made to design a microsphere system of captopril using rosin polymer for prolonged improve the Release profile of drug.

4. PLAN OF WORK

- Collection of drug and Polymer
- Preformulation study:
    - ✓ Description
    - ✓ Solubility
    - ✓ Melting point
    - ✓ Identification of the drug
        - UV absorption maxima
        - FT-IR Studies
    - ✓ Compatibility studies
- Formulation of Microspheres
- Evaluation parameters
    - Particle size analysis
    - Shape and Surface morphology by Scanning Electron Microscopy
    - Percentage Yield
    - Drug Content Analysis
    - Percentage Drug Entrapment
    - *In- vitro* dissolution study
- Stability studies
- Release kinetics
- Results and discussion
- Conclusion

5.DRUG PROFILE

5.1CAPTOPRIL[15,16,17]

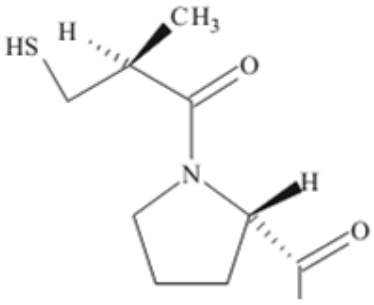


Fig. 5 Structural formula of captopril

Category

It inhibits the activity of anginotensin converting enzyme

Molecular formula

C9H15NO3S

Molecular weight

217.285

Chemical name

(2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid

Description

Nature

White to off white crystalline powder

Solubility

Soluble in water, chloroform and alcohol

Physical data

Melting point

160^0C

Pharmacokinetic data

Protein binding 25-30% bound to plasma proteins, primarily albumin

Volume of distribution Not Available

Bioavailability

70%

Metabolism

Hepatic

Half Life

2hours

Excretion

Renal

Mechanism of action

There are two isoforms of ACE: the somatic isoform, which exists as a glycoprotein comprised of a single polypeptide chain of 1277; and the testicular isoform, which has a lower molecular mass and is thought to play a role in sperm maturation and binding of sperm to the oviduct epithelium. Somatic ACE has two functionally active domains, N and C, which arise from tandem gene duplication. Although the two domains have high sequence similarity, they play distinct physiological roles. The C-domain is predominantly involved in blood pressure regulation while the N-domain plays a role in hematopoietic stem cell differentiation and proliferation. ACE inhibitors bind to and inhibit the activity of both domains, but have much greater affinity for and inhibitory activity against the C-domain. Captopril, one of the few ACE inhibitors that is not a prodrug, competes with ATI for binding to ACE and inhibits and enzymatic proteolysis of

ATI to ATII. Decreasing ATII levels in the body decreases blood pressure by inhibiting the pressor effects of ATII as described in the Pharmacology section above. Captopril also causes an increase in plasma renin activity likely due to a loss of feedback inhibition mediated by ATII on the release of renin and/or stimulation of reflex mechanisms via baroreceptors. Captopril's affinity for ACE is approximately 30,000 times greater than that of ATI.

Indications

For the treatment of essential or renovascular hypertension (usually administered with other drugs, particularly thiazide diuretics). May be used to treat congestive heart failure in combination with other drugs (e.g. cardiac glycosides, diuretics, ß-adrenergic blockers). May improve survival in patients with left ventricular dysfunction following myocardial infarction. May be used to treat nephropathy, including diabetic nephropathy.

Side effects

- feeling light-headed, fainting;
- urinating more or less than usual, or not at all;
- fever, chills, body aches, flu symptoms;
- pale skin, feeling light-headed or short of breath, rapid heart rate, trouble concentrating;
- Easy bruising, unusual bleeding (nose, mouth, vagina, or rectum), purple or red pinpoint spots under your skin;
- fast, pounding, or uneven heartbeats;
- chest pain; or
- swelling, rapid weight gain.

Less serious captopril side effects may include:

- cough;
- loss of taste sensation, loss of appetite;

- dizziness, drowsiness, headache;
- sleep problems (insomnia);
- dry mouth, sores inside your mouth or on your lips;
- nausea, diarrhea, constipation; or
- mild skin itching or rash.

Dosage

Usual Adult Captopril Dose for Hypertension:

Initial dose: 25 mg orally 2 to 3 times a day one hour before meals. Maintenance dose: 25 to 150 mg orally 2 to 3 times a day one hour before meals.

Usual Adult Captopril Dose for Congestive Heart Failure:

Initial dose: 25 mg orally 3 times a day (6.25 to 12.5 mg orally 3 times a day if volume .

Maintenance dose: After a dose of 50 mg three times a day is reached, further increases in dosage should be delayed, where possible, for at least 2 weeks to determine if a satisfactory response occurs. Most patients studied have had a satisfactory clinical improvement at 50 to 100 mg three times a day. Captopril should generally be used in conjunction with a diuretic and digitalis.

Usual Adult Captopril Dose for Left Ventricular Dysfunction:

Initial dose:

6.25 mg orally for one dose, then 12.5 mg orally 3 times a day. Increasing dose: The dose is increased to 25 mg orally 3 times a day during the next several, days.

Maintenance dose:

The dose is increased to a target dose of 50 mg orally 3 times a day Therapy may be initiated as early as three days following a myocardial infarction. Captopril may be used in patients treated with other post-myocardial infarction therapies, e.g., thrombolytics, aspirin, beta blockers.

Usual Adult Captopril Dose for Diabetic Nephropathy:

The recommended dose for long-term use is 25 mg orally 3 times a day.

Usual Adult Captopril Dose for Hypertensive Emergency:

When prompt titration of blood pressure is indicated, continue diuretic therapy and halt current medication therapy and initiate 25 mg two or three times daily under close supervision. Increase the dose every 24 hours or less until a satisfactory response is obtained or the maximum dose is reached.

Usual Adult Captopril Dose for Cystinuria:

Initial dose:

25 mg orally 2 to 3 times a day one hour before meals. Initial doses may be titrated as tolerated approximately every 1 to 2 weeks to reduce the degree of cystinuria.

Limited data have shown significant reductions in the urinary excretion of cystine after daily doses of captopril of 150 mg.

Dosage forms

Form	Route	Strength
Tablet	Oral	100 mg
Tablet	Oral	12.5 mg
Tablet	Oral	25 mg
Tablet	Oral	50 mg

5.2 EXCIPIENT PROFILE[,21.32.44]

Polyvinyl Alcohol

Nonproprietary Names

PhEur : Poly(vinylis acetas)

USP : Polyvinyl alcohol

Synonyms

Airvol; *Alcotex*; *Elvanol*; *Gelvatol*; *Gohsenol*; *Lemol*; *Mowiol*; *Polyvinol*; PVA; vinyl alcohol ,polymer.

Chemical Name and CAS Registry Number

Ethenol, homopolymer [9002-89-5]

Empirical Formula and Molecular Weight

$(C_2H_4O)_n$ 20 000–200 000

Polyvinyl alcohol is a water-soluble synthetic polymer represented by the formula $(C_2H_4O)_n$. The value of *n* for commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately 20 000–200 000.

Grade Molecular weight

High viscosity	-	200 000
Medium viscosity	-	130 000
Low viscosity	-	20 000

Structural Formula

Functional Category

Coating agent; lubricant; stabilizing agent; viscosity-increasing agent.

Pharmaceutical Excipients

Applications in Pharmaceutical Formulation or Technology

Polyvinyl alcohol is used primarily in topical pharmaceutical and ophthalmic formulations.

Use Concentration (%)

Emulsions 0.5

Ophthalmic formulations 0.25–3.00

Topical lotions 2.5 .1–3 It is used as a stabilizing agent for emulsions (0.25–3.0% w/v). Polyvinyl alcohol is also used as a viscosity-increasing agent for viscous formulations such as ophthalmic products. It is used in artificial tears and contact lens solutions for lubrication purposes, in sustained release formulations for oral administration,4 and in transdermal patches.5 Polyvinyl alcohol may be made into microspheres when mixed with a glutaraldehyde solution.

Description

Polyvinyl alcohol occurs as an odorless, white to cream-colored granular powder.

Pharmacopeial Specifications

Pharmacopeial specifications for polyvinyl alcohol.

Test PhEur 2005 USP 28

Viscosity	=	+
pH 4.5	=	6.5 5.0–8.0
Loss on drying	=	_5.0% =_5.0%
Residue on ignition	=	í1.0% =í2.0%
Water-soluble substances	=	Ê0.1%
Degree of hydrolysis	=	H0.1%
Organic volatile impurities	=	+
Pharmaceutical Excipients	=	2215

Test PhEur 2005 USP 28

Assay - 85.0–115.0%

Typical Properties

Melting point:

- 228°C for fully hydrolyzed grades;
- 180–190°C for partially hydrolyzed grades.

Refractive index:

*n*25

D = 1.49–1.53

Solubility:

Soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents. Dissolution requires dispersion (wetting) of the solid in water at room temperature followed by heating the mixture to about 90°C for approximately 5 minutes. Mixing should be continued while the heated solution is cooled to room temperature.

Specific gravity:

- 1.19–1.31 for solid at 25°C;
- 1.02 for 10% w/v aqueous solution at 25°C.

Specific heat:

1.67 J/g (0.4 cal/g)

Viscosity (dynamic):

Viscosity of commercial grades of polyvinyl alcohol.

Grade Dynamic viscosity of 4%w/v aqueous solution at 20°C (mPa s)

Pharmaceutical Excipients 2215

Grade Dynamic viscosity of 4%w/v aqueous solution at 20°C (mPa s)

High viscosity 40.0	=	65.0
Medium viscosity 21.0	=	33.0
Low viscosity 4.0	=	7.0

11. Stability and Storage Conditions

- Polyvinyl alcohol is stable when stored in a tightly sealed container in a cool, dry place.
- Aqueous solutions are stable in corrosion-resistant sealed containers. Preservatives may be added to the solution if extended storage is required. Polyvinyl alcohol undergoes slow degradation at 100°C and rapid degradation at 200°C; it is stable on exposure to light.

12. Incompatibilities

Polyvinyl alcohol undergoes reactions typical of a compound with secondary hydroxyl groups, such as esterification. It decomposes in strong acids, and softens or dissolves in weak acids and alkalis. It is incompatible at high concentration with inorganic salts, especially sulfates and phosphates; precipitation of polyvinyl alcohol 5% w/v can be caused by phosphates. Gelling of polyvinyl alcohol solution may occur if borax is present.

13. Method of Manufacture

Polyvinyl alcohol is produced through the hydrolysis of polyvinyl acetate. The repeating unit of vinyl alcohol is not used as the starting material because it cannot be obtained in the quantities and purity required for polymerization purposes. The hydrolysis proceeds rapidly in methanol, ethanol, or a mixture of alcohol and methyl acetate, using alkalis or mineral acids as catalysts.

14. Safety

Polyvinyl alcohol is generally considered a nontoxic material. It is nonirritant to the skin and eyes at concentrations up to 10%; concentrations up to 7% are used in cosmetics.

Studies in rats have shown that polyvinyl alcohol 5% w/v aqueous solution injected subcutaneously can cause anemia and infiltrate various organs and tissues.

LD50 (mouse, oral)	:	14.7 g/kg
LD50 (rat, oral)	:	>20 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Polyvinyl alcohol dust may be an irritant on inhalation. Handle in a well-ventilated environment. Pharmaceutical Excipients

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic preparations and oral tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

6.MATERIALS AND METHODS

LIST OF MATERIALS

Table- 2. List of Materials Used

S.NO	Materials	Manufacturer
1.	Captopril	Gift sample obtained from Madras pharmaceuticals, Chennai.
2.	Rosin	Gift sample obtained from madras pharmaceuticals, Chennai.
3.	Dicholoromethane	Nice Chemicals Private Limited, Chennai.
4.	Sodium chloride	Nice Chemicals Private Limited, Chennai.
5.	Methanol	Nice Chemicals Private Limited, Chennai.
6.	Poly vinyl alcohol	Nice Chemicals Private Limited, Chennai.

6.2 LIST OF EQUIPMENTS

Table-3 List of Equipments Used

S.No	Equipments	Manufacturer	Use
1	UV-Visible double beam spectrophotometer	Shimadzu UV 1700, Japan.	To measure the absorbance of the sample
2	Electronic Balance	Sortorius Single Pan	For weighing purpose
3	Programmable Dissolution test apaarataus	ElectroLab (Tablet Dissolution tester USP 24)	For *in-vitro* dissolution studies
4.	pH meter	Elico L 1120	To measure the pH of the solution
5.	Environmental stability testing chamber	Heco Environment Chamber	For stability studies
6.	FT-IR	Perkin Elmer	For compatibility analysis

7.PREFORMULATION

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bio available dosage forms that can be man produced.

The following preformulation studies are carried out:

- Description
- Solubility
- Melting point
- Finding the absorption maxima
- Standard curve
- Infra red spectroscopy studies (compatibility studies)

Description

About 1g of sample is taken in a dry Petidish and the sample is observed for compliance against the specification.

Melting Point

Capillary tube, which is sealed at one end is charged with sufficient amount of dry powder to form a column in the bottom of the tube 2.5mm to 3.5mm when packed down as closely as possible by moderate tapping on a solid surface. The apparatus is operated according to the standard operating procedure. The block is heated until the temperature is about 30°c below the expected melting point.

The capillary tube is inserted into the heating block, and the heating is continued at a rate of temperature increased of about 1°c to 2°c per minute until melting is complete. The temperature at which the detector signal first leaves its initial value is defined as the beginning of melting, and the temperature at which the detector signal reaches its final value is defined as the end of melting, or the melting point. The two temperature fall within the limits of melting range.

Solubility Studies

The spontaneous interaction of two or more substance to form a homogeneous molecular dispersion is called as solubility. A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system vigorously shaken and examined visually for any undisclosed solute particles. The solubility was expressed in turns of ratio of solute and solvent.

The approximate solubility's of substances are indicated by the descriptive terms in the accompanying table. The results are shown in table.

Table 4 - Solubility profile I.P.1996

Descriptive term	**Parts of solvent required for 1 part of solute.**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10, 000
Practically insoluble of Insoluble	Greater than or equal to 10,000

Identification of the drug:

Finding the absorption maxima (λ max)

The absorption maxima were found for drug identification. Ultraviolet Visible spectrophotometry has been used to obtain specific information on the chromophoric part of the molecules. Organic molecules in solutions when exposed to light in the visible/Ultraviolet region of the spectrum absorb light of particular wavelength depending on the type of electronic transition associated with the absorption.

The various batches of the microspheres were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of phosphate buffer PH 7.2 then filter. The UV absorbance of the filtrate was measured using a UV spectrometer at 203nm.

Fourier transform infrared (FTIR) spectral analysis

FT-IR is used to identify the functional groups in the molecule. The drug is mixed with KBr and pellet is formed. Each KBr disk was scanned at 4 mm/s at a resolution of 2 cm over a wave number region of 400 to 4,500 cm−1. The characteristic peaks were recorded. The results are shown in the following figure. and table.

Drug-Excipient Compatibility studies by FT-IR

Fourier infrared spectroscopy (FT-IR) analysis was performed for the pure drug and physical admixtures (Polymers, excipients) individually and then the drug and physical admixtures are mixed together and FT-IR is taken to find out that there is no interaction between drug, polymers and the excipients.The results are shown in the following figure.and table.

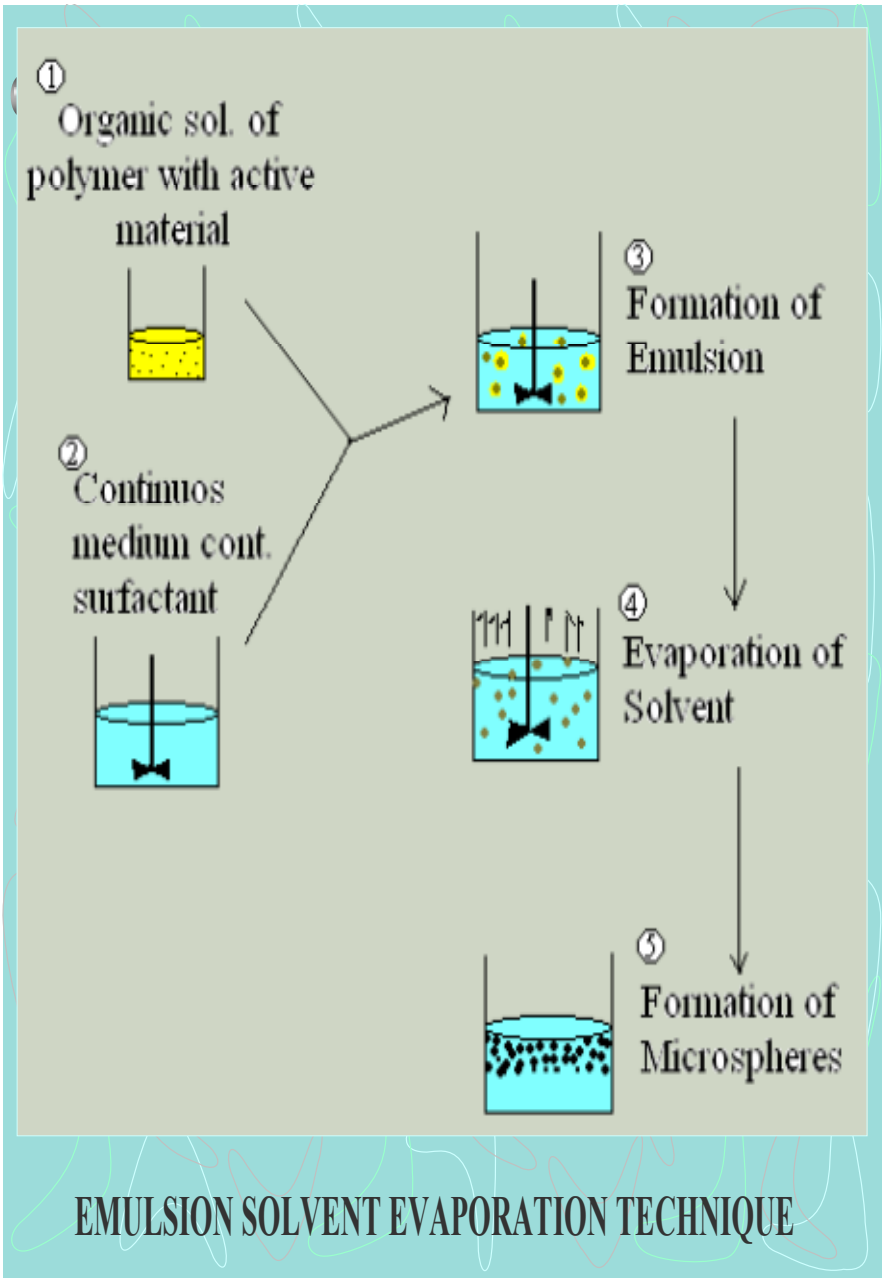
Standard Curve

The drug solutions (10,20,30,40 and 50µg/ml) were taken in a standard cuvette and scanned in the range of 200-400nm by using UV-Spectrophotometer. The absorbance of each sample was measured at 202.4nm. The standard curve is plotted against absorbance and concentration of the sample. Similarly, the procedure can be repeated for phosphate buffer pH 7.2. The values are given in the following Table and figure.

8.FORMULATION OF MICROSPHERES [20,27,30,40]

Captopril micropsheres prepare by using rosin as a polymer by solvent evaporation method.

Fig -6 Emulsion solvent techniques



FORMULATION OF MICROSPHERES[21,30,34]

- Microspheres were prepared by the solvent evaporation method using 500 mg of captopril and with different proportion of polymer were dissolved in the dichloromethane 5ml This flowable mass was introduced in to 50ml of aqueous saline phase (0.9%Nacl)containing 0.04%PVA(20)mg and 10% methanol (5ml) .
- The system is stirred using propeller at 300 rpm room temperature for 2-3 hours the drug loaded floating microsphere formed filtered Whatman filtered paper

Process Flow Chart of micropsheres

Drug (Captopril) + Polymer (rosin)

↓

Dissolve in dichloromethane

Injected

↓

Nacl + PVA+ Methanol+ water containing solution

↓

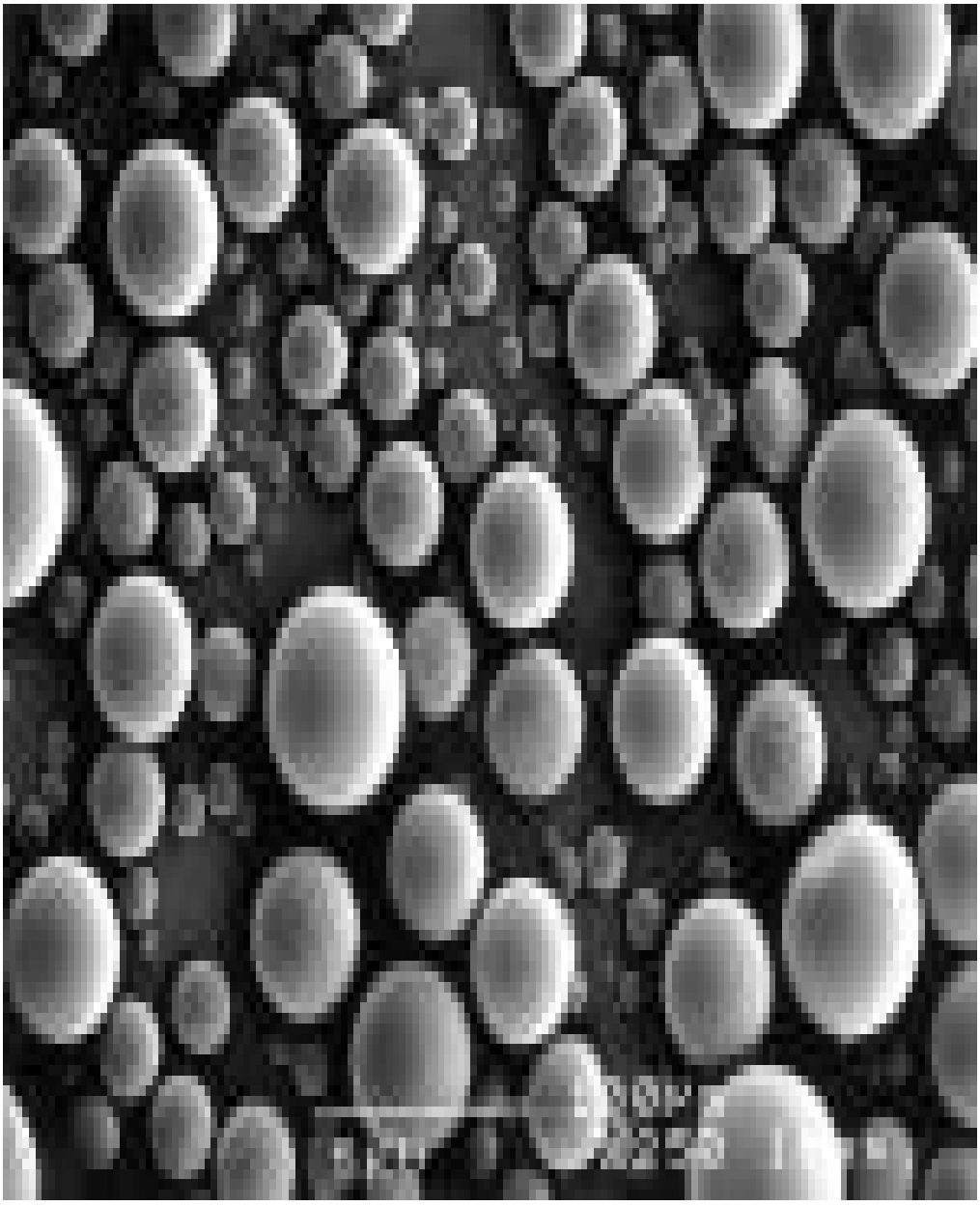
Stirred at 500 rpm for 2-3 hours

↓

Formation of microspheres

8.2 FORMULATION OF MICROSPHERES

Fig -7 microspheres



8.3 FORMULATION OF MICROSPHERES [22,32]

Table -5 Formula for Captopril Microspheres

Ingredients	Formulation Ratios				
	F1	**F2**	**F3**	**F4**	**F5**
Captopril	50 mg	50 mg	50 mg	50mg	50mg
Rosin	150 mg	200mg	250mg	300mg	350mg
Dichloromethane	5ml	5ml	5ml	5ml	5ml
Sodium chloride	450mg	450mg	450mg	450mg	450mg
Poly vinyl alcohol	20mg	20mg	20mg	20mg	20mg
Methanol	5ml	5ml	5ml	5ml	5ml
Water	50ml	50ml	50ml	50ml	50ml

CHARACTERIZATION OF MICROSPHERES[24,28]

The prepared captopril micropsheres were characterized for various characters such as particle size, surface morphology, entrapment efficiency, drug content, *in-vitro* drug release study.

Determination of particle size distribution by Particle size analyzer

The selected best metoclopramide microbeads formulation (F6) was subjected to laser particle counting method. Here the sample was injected into the sample delivery and controlling chamber. Then, suitable solvent was pumped through the chamber. Now a beam of laser light was allowed to fall on the sample cell. After required number of runs, they were directed towards the detector. From this the particle size range and the average mean particle size of the formulation can be studied.

The average particle size of F---------- formulation can be determined using particle size analyzer. The results are shown in the figure.----------

Scanning Electron Microscopy:

The purpose of the Scanning Electron Microscopy study was to obtain a topographical characterization of micropsheres. The micropsheres were mounted on brass stubs using double-sided adhesive tape. Scanning electron microscopy photographs were taken with a scanning electron microscope (JSM-5610LV, Joel Ltd, Tokyo, Japan) at the required magnification at room temperature. The working distance of 39 mm was maintained, and the acceleration voltage used was 15 kV, with the secondary electron image as a detector.

Yield of Microspheres

The prepared Microspheres were collected and weighed. The actual weight of obtained Microspheres divided by the total amount of all non-volatile material that was used for the preparation of the Microspheres multiplied by 100 gives the % yield of Microspheres .

This was calculated by the use of following formula.

% yield= (Actual weight of the product / Total weight of excipients and drug) × 100

Determination of Drug Content and Entrapment Efficiency

100 mg of accurately weight microspheres were suspended in a phosphate buffer pH 7.2 upto 24 hours. Next day, the sample was shaken using mechanical shaker for few hours. Then it was filtered and from the filtrate, few ml of aliquot was taken and made the suitable dilutions and analyzed for the drug content at 202.4 nm by spectrophotometry. The % of Entrapment Efficiency was calculated. Taking into the consideration the dilution factor and the amount of micro beads takes, the amount of drug entrapment per unit weight of micro beads were calculated.The drug entrapment efficiency was calculated using for the formula

$$\text{Percentage entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoritical drug content}} \times 100$$

Dissolution studies

The dissolution studies were carried out using basket type apparatus at 50 rpm and 37±0.5°C. 20 mg of drug were filled into colorless hard gelatin capsules and placed in basket separately. The dissolution medium was phosphate buffer pH 7.2 as simulated intestinal fluid (SIF) for 12 hrs. 5 ml samples were withdrawn at specified time intervals and same volume was replaced immediately with an equal volume of fresh medium. Samples were analyzed at 202.4 nm (Shimadzu 1700). The *In-vitro* drug release studies results were mentioned in the following table.

Dissolution Study

Apparatus	:	USP (basket)
Speed	:	50 rpm
Time	:	1,2,3,4,5,6,7,8,9,10,11,12th hour
Temperature	:	37°C ± 0.5°C
λ_{max}	:	308.2 nm

Kinetics of drug Release[34.39]

Several theories and kinetic models describe the dissolution of drug from immediate release and modified release dosage forms. There are several models to represent the drug dissolution profiles where f (t) is a function of time related to the amount of drug dissolved from the pharmaceutical dosage form.

The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve function of some parameters related with the pharmaceutical dosage forms. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time't' or Q(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models, Weibull models. These models are used to characterize drug dissolution/release profiles.

(i) Zero Order Kinetics

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (that is, a constant release rate). The following equation is used to express the model:

$$\mathbf{Q_t = Q_o + K_o t}$$

Where, Q_t is the amount of drug dissolved in time t

Q_o is the initial amount of drug in the solution

K_o is the zero order release constant

For practical purposes the equation is rearranged:

Percent drug released = Kt

This is applicable to dosage forms like transdermal systems, coated dosage forms, osmotic systems as well as matrix tablets with low soluble drugs.

(ii) First Order Kinetics

First order release constitutes drug release in a way that is proportional to the amount of drug remaining in its interior; in such a way that amount of drug released by unit time diminish. The following equation is used to express the model:

$$\log Q_t = \log Q_o + Kt/2.303$$

Where, Q_t is the amount of drug dissolved in time t

Q_o is the initial amount of drug in the solution

K is the first order release constant

For practical purposes the equation is rearranged:

Log % of drug unreleased = Kt/2.303

This model is applicable to dosage forms such as those containing water-soluble drugs in porous matrices.

(iii) Higuchi Model [25]

Higuchi describes drug release as a diffusion process based in Fick's law,square root dependent. The following equation is used to express the model:

$$Q_t = K_h t^{1/2}$$

Where,

Q_t is the amount of drug dissolved in time t

K_h is the first order release constant

For practical purposes the equation is rearranged:

Percent drug released = $Kt^{1/2}$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug

(iv) Peppas-Korsmeyer Model[32]

This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved

The following equation is used to express the model

$$\mathbf{Q_t/Q_\infty = Kt^n}$$

Where,

Q_t is the amount of drug dissolved in time t

Q_∞ is the amount of drug dissolved in infinite time

n is the release exponent indicative of drug release mechanism

K is the kinetic constant

For practical purposes the equation is rearranged:

Log percent drug released = log k +n log t

Peppas used n value in order to characterize different release mechanism concluding for values of n = 0.5 for Fickian diffusion and values of n, between 0.5 to 1.0 for anomalous transport (corresponds to diffusion, erosion and swelling mechanism or mixed order kinetics) and higher values of n, n=1 or n>1 for case-II transport (corresponds to erosion and relaxation of swollen polymer layer).

Stability Study

Accelerated Stability Studies[38]

Stability

Stability is officially defined as the time lapse during which the drug product retains the same property and characteristics that it possessed at the time of manufacture. This process begins at early development phases.

Definition

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation (dosage form or drug product) in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life.

Instability in modern formulation is often undetectable only after considerable storage period under normal conditions. To assess the stability of a formulated product it is usual to expose it to high stress conditions to enhance deterioration and therefore the time required for testing is reduced. Common high stress factors are temperature and humidity. This will eliminate unsatisfactory formulation.

Purpose of stability testing:

- To study of drug decomposition kinetics
- To develop stable dosage form
- To establish the shelflife or expiration date for commercially available drug product.
- To ensure the efficacy, safety and quality of active drug substance and dosage forms.

Table - 6 Stability Conditions Chart

S.NO	STUDY	STORAGE CONDITION	MINIMUM PERIOD
1	Long term	25ºC ± 2ºC 60% ± 5% RH	12 months
2	Intermediate	30ºC ± 2ºC 65% ± 5% RH	6 months
3	Accelerated	40ºC ± 2ºC 75% ± 5% RH	6 months

The stability studies of formulation F1 to F2 were carried out at 45° C ± 2°C 75% ± 5% RH and leakage of the drug from the microspheres were analyzed in terms of percentage drug content.

9.RESULTS AND DISCUSSION

PREFROMULATION:

Description - White, Odourless powder.

Melting point - 106°C

Solubility

Table - 7

Solubility Profile of Captopril

S.NO	SOLVENT	SOLUBILITY
1.	Distilled water	Very Soluble
2.	Alcohol	freely soluble
3.	Ether	Practically insoluble

Identification of Drug Sample - Absorption Maxima of

Fig – 8 Captopril in Phosphate buffer pH 7.2

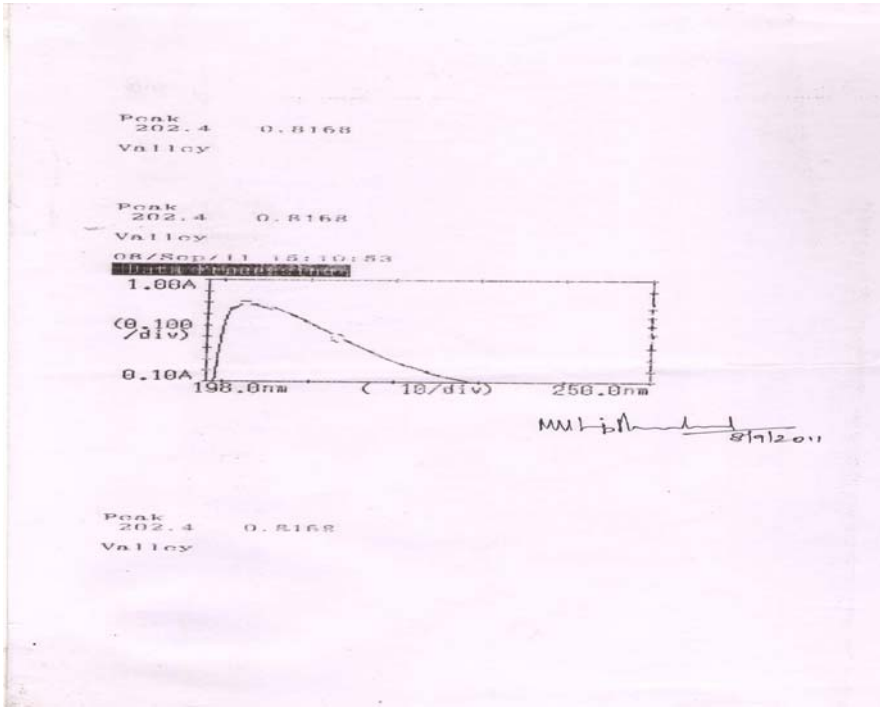
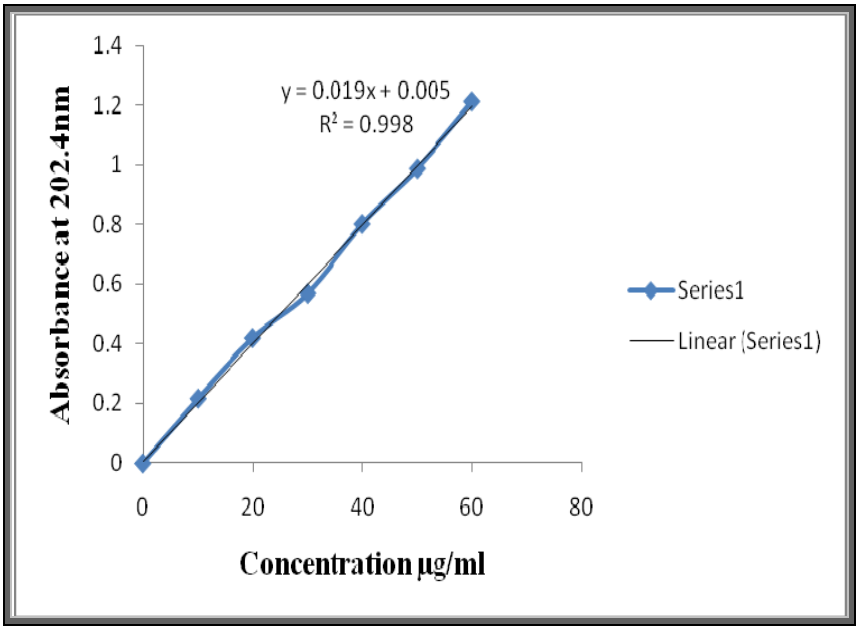


Table - 8

Standard curve in phosphate buffer pH 7.2

S.No	Concentration µg/ml	Absorbance at 202.4 nm
1	10	0.2177
2	20	0.4209
3	30	0.5698
4	40	0.8021
5	50	0.9877
6	60	1.2128

Fig- 9 Standard curve



FTIR

Fig – 10 IR Spectra of Captopril

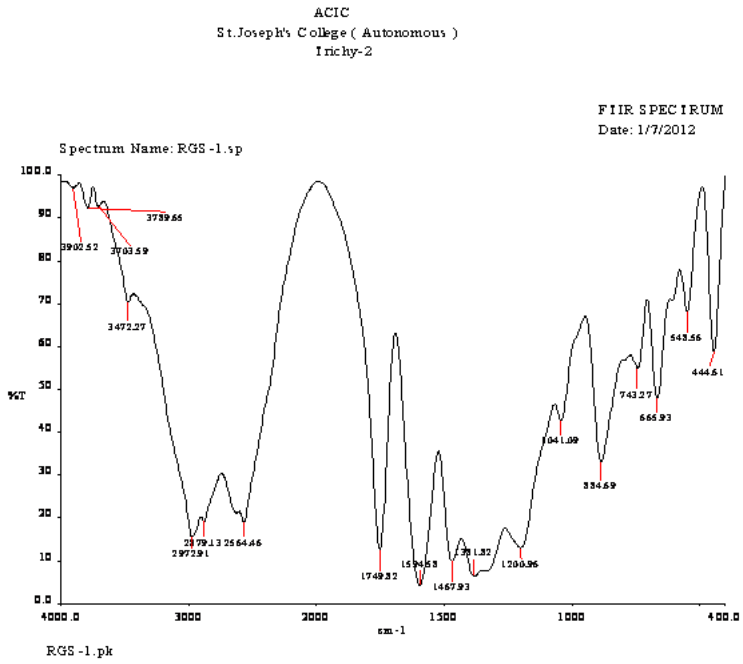


Table – 9

FTIR spectral Assignment of captopril

S.No	Wavenumber(cm^{-1})	Assignment
1	3943.39	N-H stretching
2	2700.25	O-H stretching
3	2452.86	C-H stretching
4	2066.73	CH stretching
5	1600.09	C=O stretching
6	1399.60	C-O stretching

Fig – 11 IR spectra of Rosin

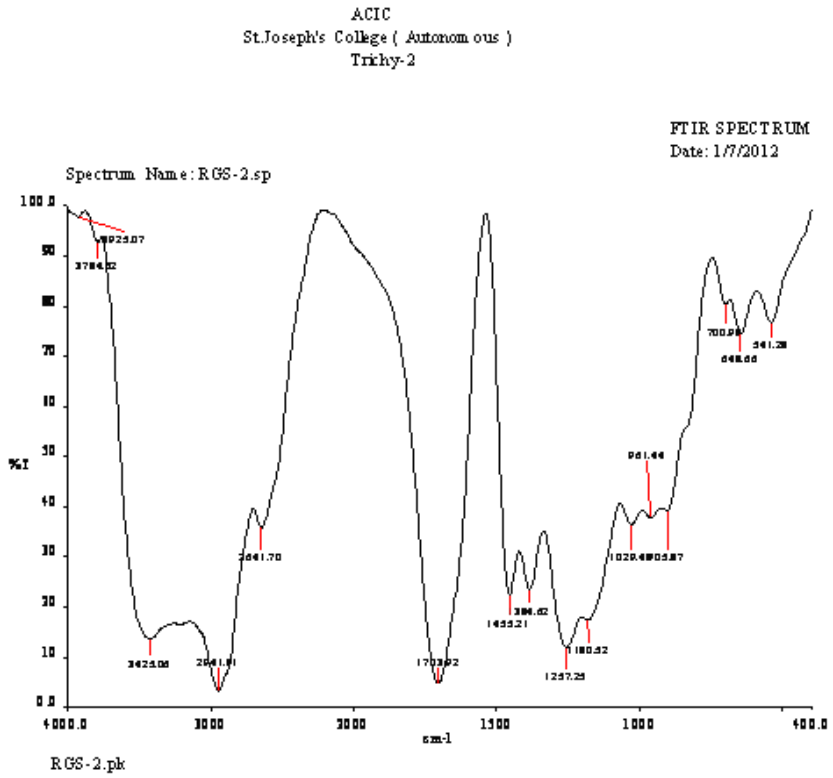


Table - 10 IR Spectral Assignment of Rosin

S.No	Wave number (cm^{-1})	Assignment
1	3398.97	O-H stretching
2	2967.72	C-H stretching
3	1550.90	C=O stretching
4	1383.84	C-O stretching
5	1228.17	C-C stretching

Fig – 12 IR Spectra of Captopril and Rosin

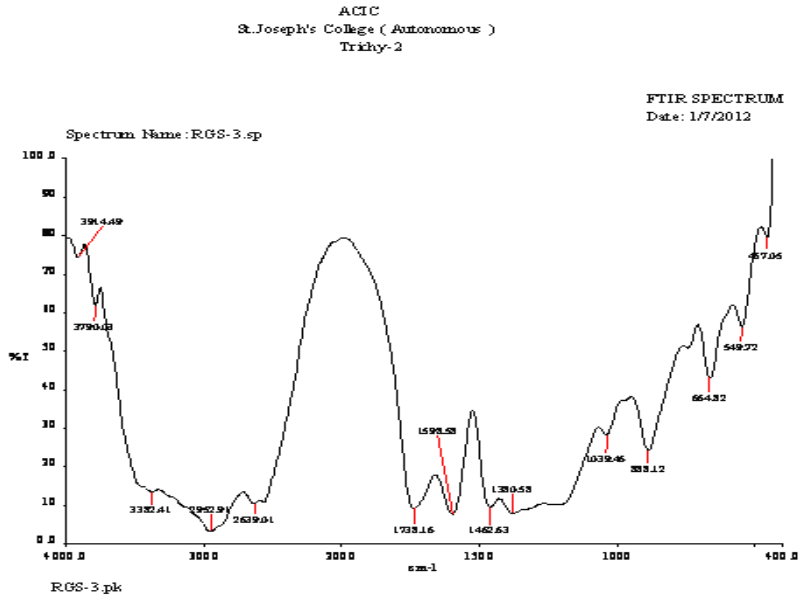


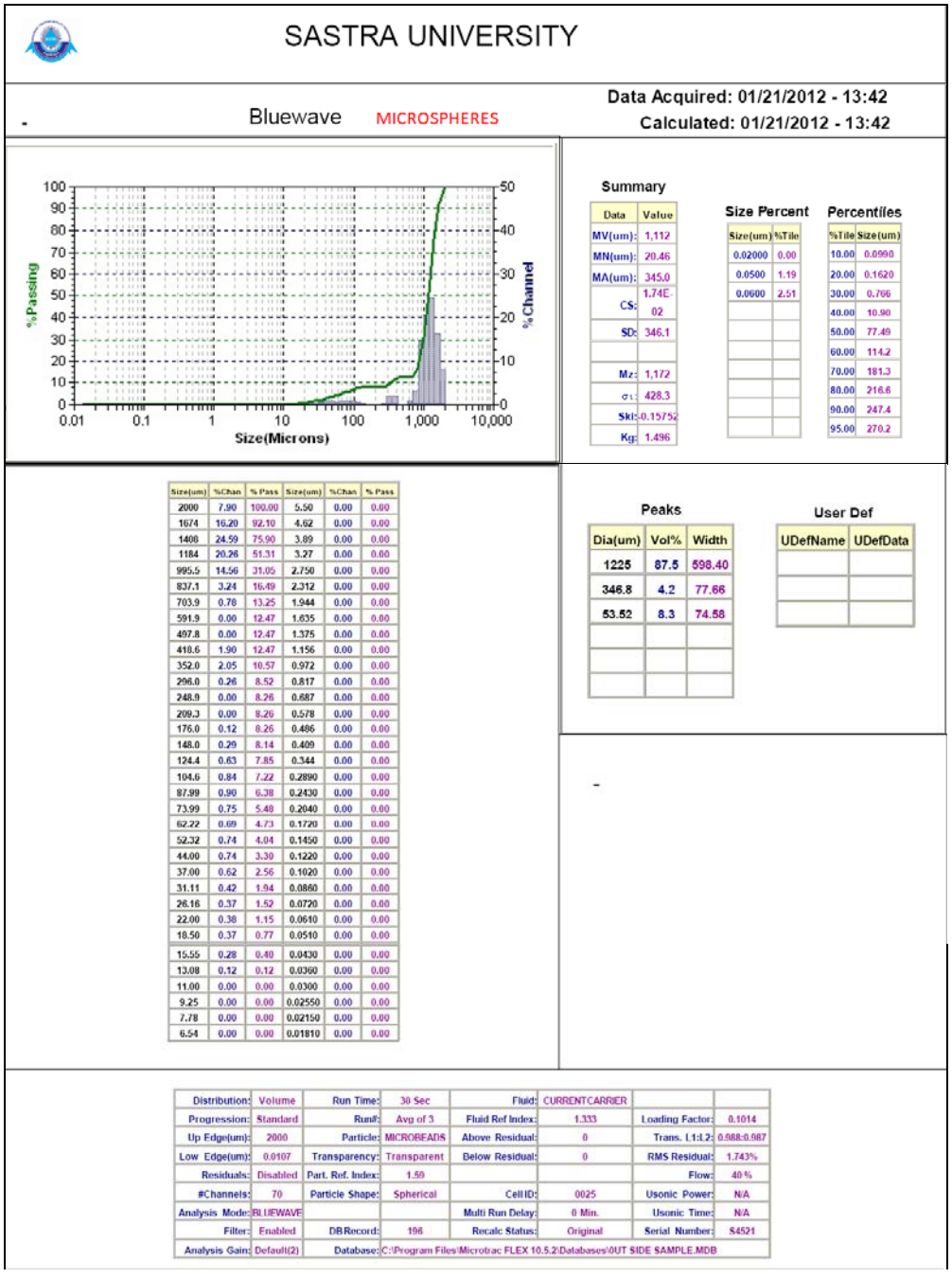
Table -11 IR Spectral Assignment of Captopril and rosin

S.No	Wave number (cm^{-1})	Assignment
1	2872.37	O-H stretching
2	2554.90	C-H stretching aromatic
3	2066.99	C-H stretching
4	1598.81	C=O stretching
5	1239.16	C-O stretching
6	1112.13	C-C stretching
7	963.66	C-H outplane bending

FTIR RESULT:

There are no extra peaks seen other than the normal peak in the spectra of the mixture of the drug and polymers and so there is no interaction with the drug and polymer and they are compatible with each other.

Particle size analysis



SASTRA UNIVERSITY

Bluewave MICROSPHERES

Data Acquired: 01/21/2012 - 13:42
Calculated: 01/21/2012 - 13:42

Summary

Data	Value
MV(um):	1.112
MN(um):	20.46
MA(um):	345.0
CS:	1.74E-02
SD:	346.1
Mz:	1.172
σ:	428.3
Ski:	-0.15752
Kg:	1.496

Size Percent

Size(um)	%Tile
0.02000	0.00
0.0500	1.19
0.0600	2.51

Percentiles

%Tile	Size(um)
10.00	0.0990
20.00	0.1620
30.00	0.766
40.00	10.90
50.00	77.49
60.00	114.2
70.00	181.3
80.00	216.6
90.00	247.4
95.00	270.2

Size(um)	%Chan	% Pass	Size(um)	%Chan	% Pass
2000	7.90	100.00	5.50	0.00	0.00
1674	16.20	92.10	4.62	0.00	0.00
1408	24.59	75.90	3.89	0.00	0.00
1184	20.26	51.31	3.27	0.00	0.00
995.5	14.56	31.05	2.750	0.00	0.00
837.1	3.24	16.49	2.312	0.00	0.00
703.9	0.78	13.25	1.944	0.00	0.00
591.9	0.00	12.47	1.635	0.00	0.00
497.8	0.00	12.47	1.375	0.00	0.00
418.6	1.90	12.47	1.156	0.00	0.00
352.0	2.05	10.57	0.972	0.00	0.00
296.0	0.26	8.52	0.817	0.00	0.00
248.9	0.00	8.26	0.687	0.00	0.00
209.3	0.00	8.26	0.578	0.00	0.00
176.0	0.12	8.26	0.486	0.00	0.00
148.0	0.29	8.14	0.409	0.00	0.00
124.4	0.63	7.85	0.344	0.00	0.00
104.6	0.84	7.22	0.2890	0.00	0.00
87.99	0.90	6.38	0.2430	0.00	0.00
73.99	0.75	5.48	0.2040	0.00	0.00
62.22	0.69	4.73	0.1720	0.00	0.00
52.32	0.74	4.04	0.1450	0.00	0.00
44.00	0.74	3.30	0.1220	0.00	0.00
37.00	0.62	2.56	0.1020	0.00	0.00
31.11	0.42	1.94	0.0860	0.00	0.00
26.16	0.37	1.52	0.0720	0.00	0.00
22.00	0.38	1.15	0.0610	0.00	0.00
18.50	0.37	0.77	0.0510	0.00	0.00
15.55	0.28	0.40	0.0430	0.00	0.00
13.08	0.12	0.12	0.0360	0.00	0.00
11.00	0.00	0.00	0.0300	0.00	0.00
9.25	0.00	0.00	0.02550	0.00	0.00
7.78	0.00	0.00	0.02150	0.00	0.00
6.54	0.00	0.00	0.01810	0.00	0.00

Peaks

Dia(um)	Vol%	Width
1225	87.5	598.40
346.8	4.2	77.66
53.52	8.3	74.58

User Def

UDefName	UDefData

Distribution:	Volume	Run Time:	30 Sec	Fluid:	CURRENTCARRIER		
Progression:	Standard	Runs:	Avg of 3	Fluid Ref Index:	1.333	Loading Factor:	0.1014
Up Edge(um):	2000	Particle:	MICROBEADS	Above Residual:	0	Trans. L1:L2:	0.888:0.987
Low Edge(um):	0.0107	Transparency:	Transparent	Below Residual:	0	RMS Residual:	1.743%
Residuals:	Disabled	Part. Ref. Index:	1.59			Flow:	40 %
#Channels:	70	Particle Shape:	Spherical	Cell ID:	0025	Usonic Power:	N/A
Analysis Mode:	BLUEWAVE			Multi Run Delay:	0 Min.	Usonic Time:	N/A
Filter:	Enabled	DB Record:	196	Recalc Status:	Original	Serial Number:	S4521
Analysis Gain:	Default(2)	Database:	C:\Program Files\Microtrac FLEX 10.5.2\Databases\0UT SIDE SAMPLE.MDB				

Fig- 13 Particle size analysis

OPTICAL VIEW OF MICROSPHERE

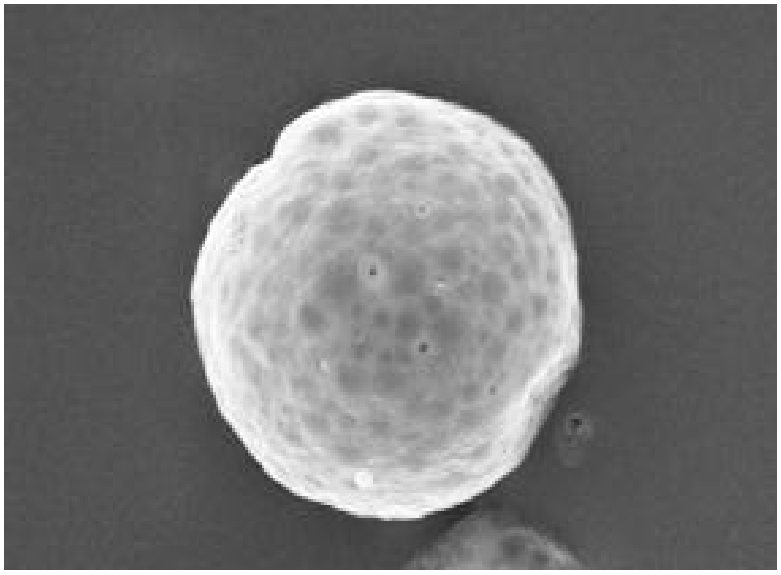


Fig- 14

SEM PHOTOMICROGRAPH OF CAPTOPRIL MICROPSHERES F5

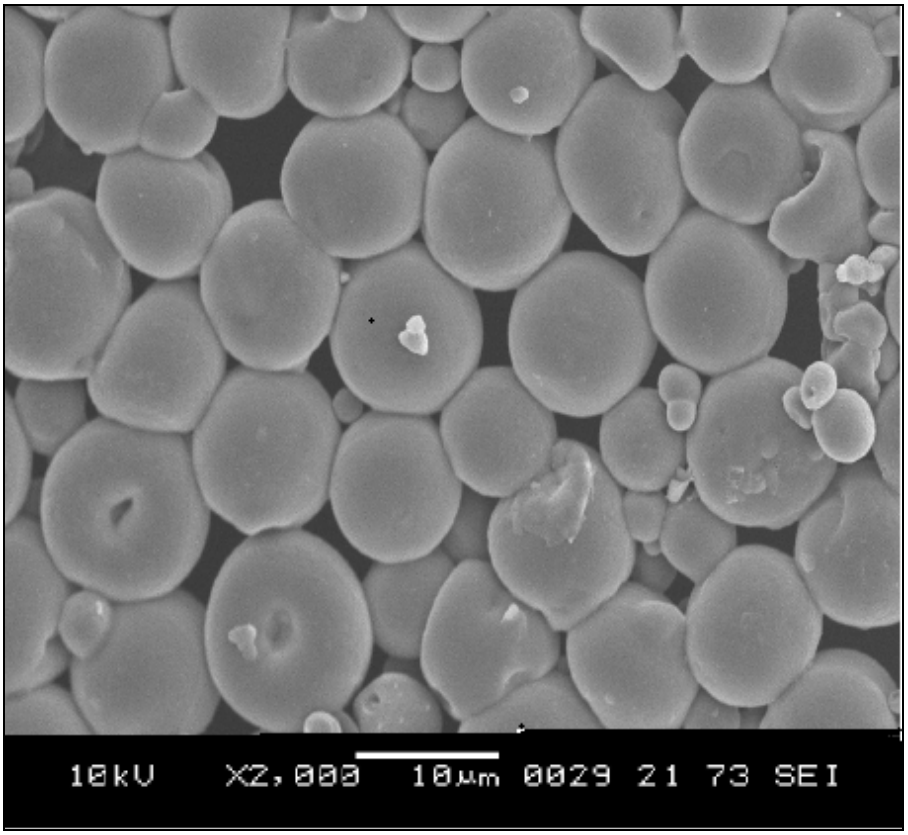


Fig – 15 SEM F 5

Percantage Yield

Table – 12

Percentage Yield

S.NO	Formulation code	% Yield[a]
1	F1	76.4 ± 2.72
2	F2	74.4 ± 1.39
3	F3	72.84 ± 0.84
4	F4	78.33 ± 0.93
5	F5	80.64 ± 1.12

Values are mean ± SD, n=3.

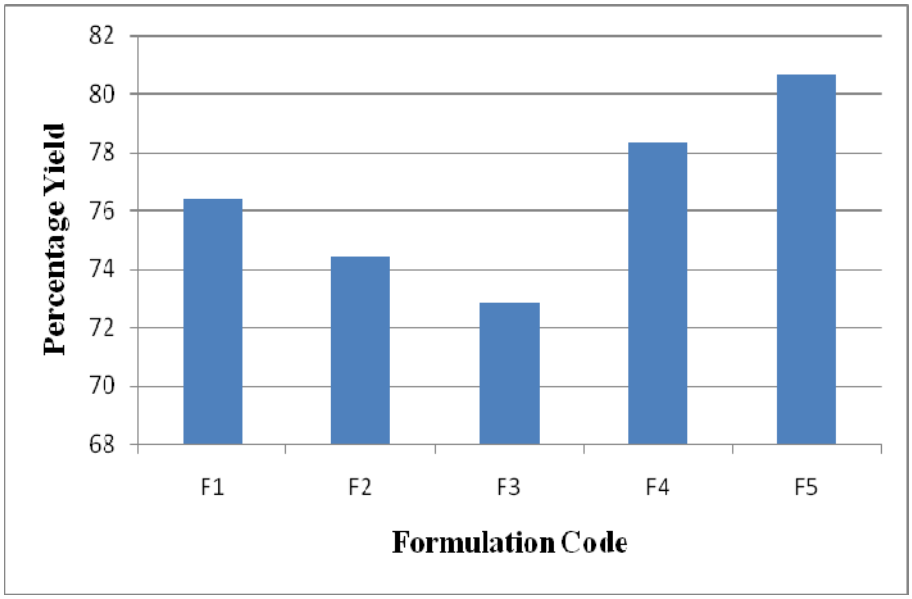


Fig - 16 Percentage yield

Determination of drug content

Table – 13

Drug Content

S.NO	Formulation code	Drug content[a]
1	F1	87.64± 0.64
2	F2	90.47± 0.46
3	F3	89.84± 0.62
4	F4	88.84± 0.74
5	F5	92.63± 0.48

Values are mean ± SD, n=3.

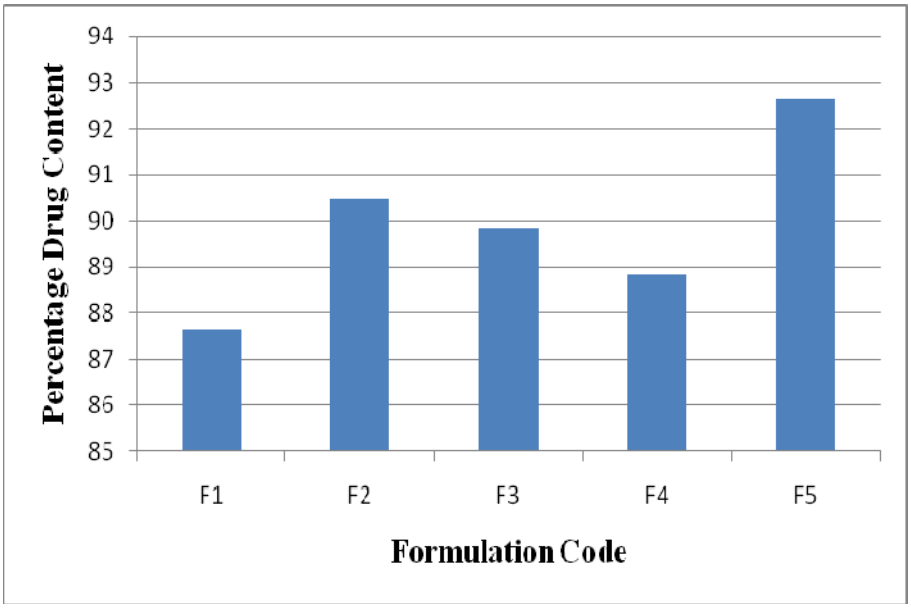


Fig – 17 Percentage drug content

Table – 14

Percentage entrapment efficacy

S.NO	Formulation	% Entrapment Efficienc[y]
1	F1	81.74± 0.02
2	F2	82.64± 0.53
3	F3	81.73± 0.64
4	F4	84.83± 0.74
5	F5	89.94± 0.25

Values are mean ± SD, n=3.

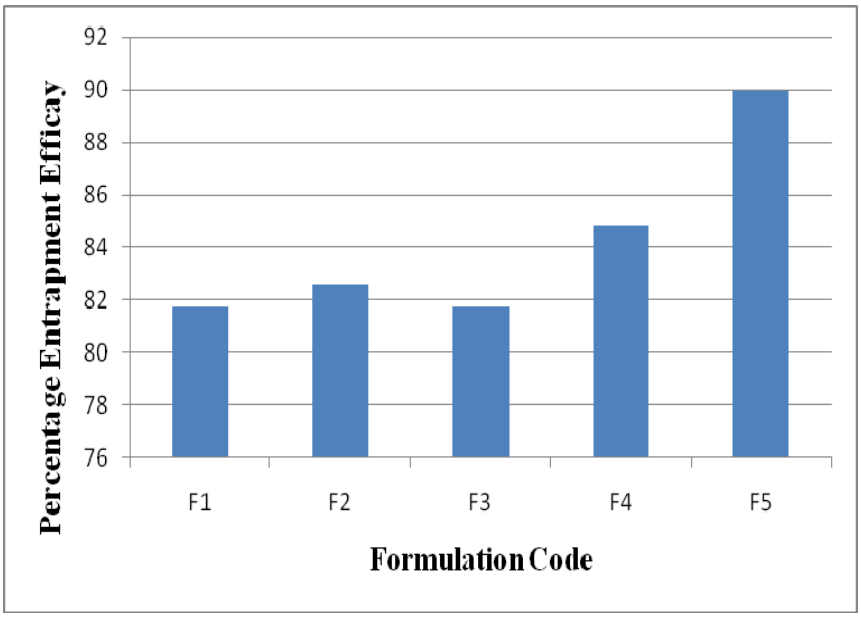


Fig – 18 Percentage entrapment efficacy

Dissolution Study

Table – 15

Comparative Invitro drug release of Micropshere Formulations

Time in hours	Formulation code				
	F1	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
1	34.04	30.68	28.92	22.48	21.46
2	41.16	36.92	30.06	28.85	25.46
3	49.52	42.08	40.56	37.95	35.93
4	57.04	51.88	49.00	43.24	41.41
5	63.64	59.72	57.84	51.84	49.42
6	82.08	70.28	66.64	60.53	57.34
7	98.27	81.64	74.04	68.84	64.94
8		99.84	82.47	71.48	78.48
9			97.12	73.95	82.98
10				77.95	85.85
11				80.04	87.95
12				82.36	89.83

Fig – 19 *In-vitro* release

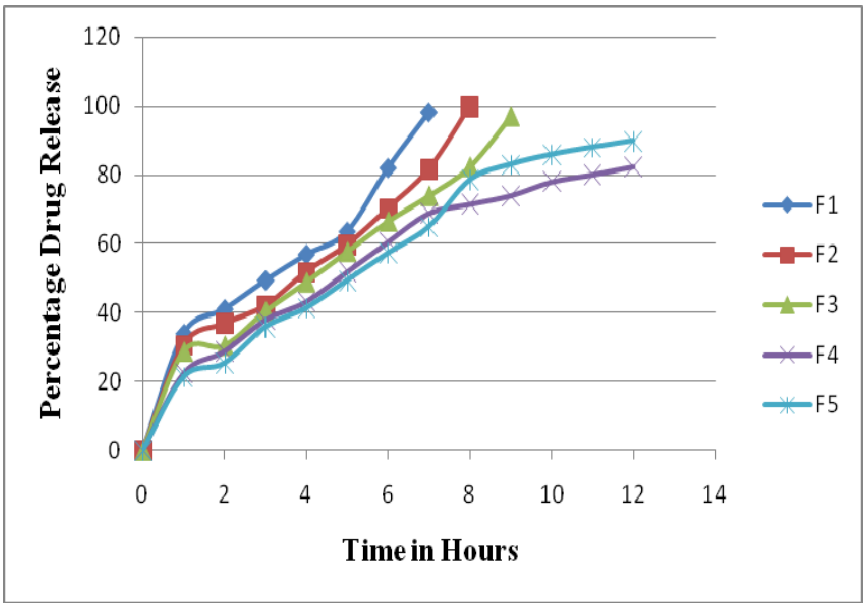


Table- 16

Model fitting data for in-vitro release kinetic parameters of microspheres

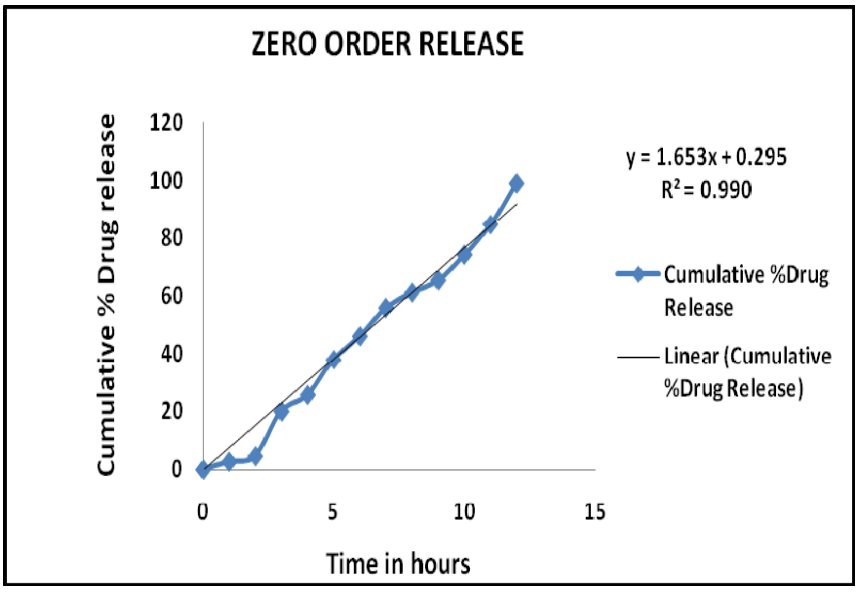
Formulation Code	Zero order [r]	First order [r]	Higuchi [r]	Hixson Crowell [r]	Korsmeyer-Peppas [r]	'n '-Values
F1	0.923	0.953	0.991	0.804	0.651	0.520
F2	0.971	0.884	0.991	0.815	0.704	0.6492
F3	0.981	0.910	0.981	0.830	0.746	0.744
F4	0.990	0.86	0.926	0.933	0.942	0.902
F5	0.993	0.822	0.935	0.921	0.951	1.079

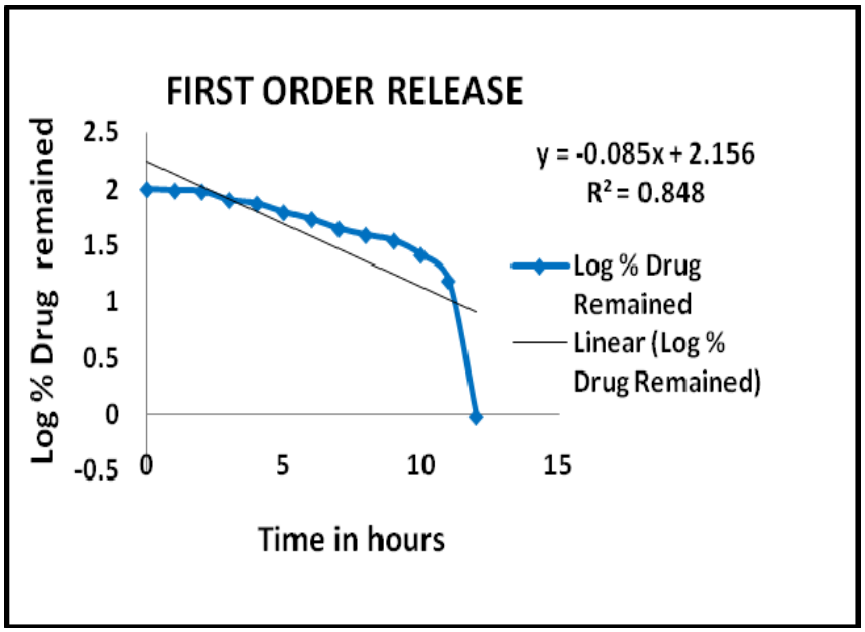
n= Diffusion exponent related to mechanism of drug release, according to equation $Mt/M\infty == Ktn$,

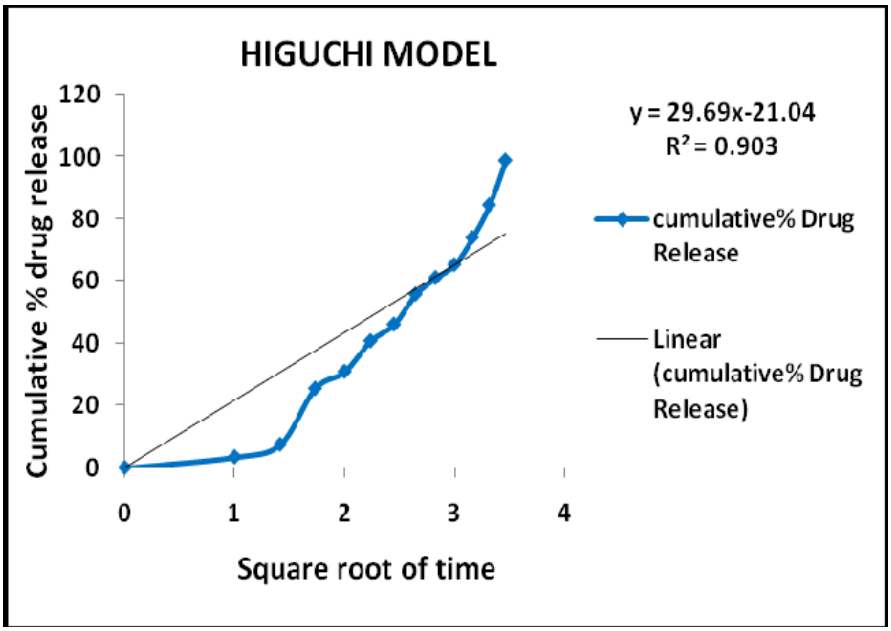
r = Correlation coefficient

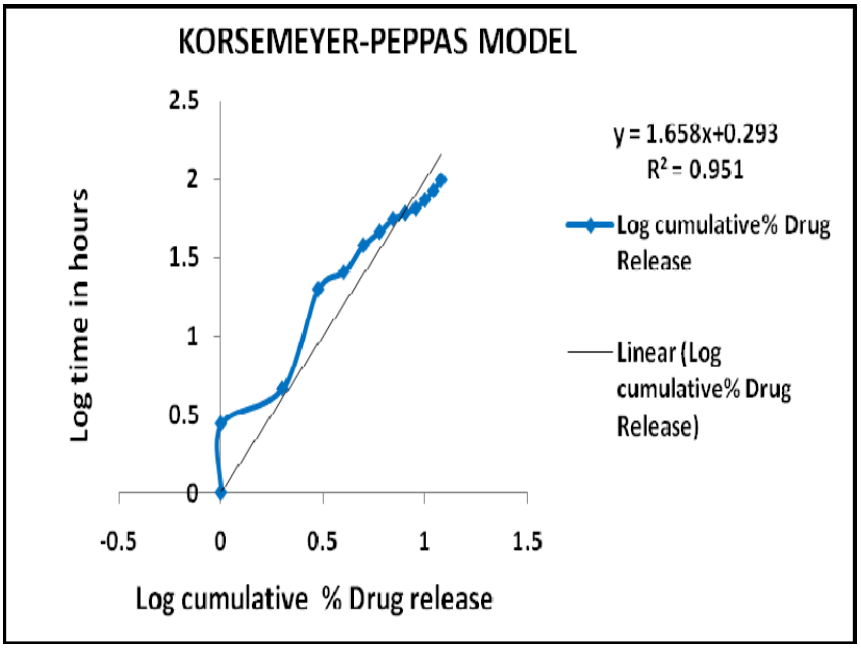
Drug kinetics release

Fig – 20 Drug kinetics release






HIGUCHI MODEL
Cumulative % drug release
120
100
80
60
40
20
0
0
1
2
3
4
Square root of time
y = 29.69x-21.04
R² = 0.903
cumulative% Drug Release
Linear (cumulative% Drug Release)


KORSEMEYER-PEPPAS MODEL
Log time in hours
2.5
2
1.5
1
0.5
0
-0.5
0
0.5
1
1.5
Log cumulative % Drug release
y = 1.658x+0.293
R² = 0.951
Log cumulative% Drug Release
Linear (Log cumulative% Drug Release)

10.7 Stability Study

Table -17

Stability Study for F5 formulation

S.No	Formulations	Before storage	Stored at 40°C ± 2°C and 75% ± 5% RH		
			1st month	2nd month	3rd month
1	F5	92.63±0.74	91.63±0.74	90.63±0.74	89.63±0.74

The results showed that F5 formulation is stable for the period of 3 months without showing significant change in the drug content.

Discussion

Captopril, an antihypertensive agent, with short half-life, low single dose administration and oral bioavailability is 65 %, was selected as a model drug to formulate a sustained release formulation with improved oral bioavailability. The drug captopril was identified by UV method. The maximum absorption was found at 202.4nm. Therefore further measurements were taken ta 202.4nm.

The IR spectra of the drug and polymer combination were compared with the spectra of the pure drug and individual polymers in which no shifting of peaks was significantly found, indicating the stability of the drug during encapsulation process. The results were show in table 9 to 11.

Microspheres were successfully prepared for the delivery of Captopril to enhance absorption and bioavailability. In concern to this approach, five formulations were prepared. In each formulation, the polymer concentration was varied. Rosin is a natural polymer. Incorporation of NaCl to the aqueous phase was necessary to prevent the dispersed phase from settling due to high density of dichloromethane, thereby making the dispersion and stabilization of the droplets by stirring difficult. Percentage yield of all formulation F1 to F5 were calculated and results are shown in Table 12.

All formulations F1 to F5 micropheres were evaluated for particle size analysis (fig – 13)mean particle size range 40µm - 50µm.

The microspheres of Captopril with rosin were smooth, spherical and no aggregated (F5) results shown in fig – 15.

As shown in table – 13, the F5 shows the maximum drug content values of 92.63 %. Percentage Entrapment efficiency were shown in Table – 14, the F5 – 89.94 %. As the polymer concentration was increased the drug entrapment efficiency % was increased due to increase in the viscosity of the solution. The

present investigation state that if the drugs are soluble in the solvent system, it results in high drug entrapment efficiency than that of dispersed in the solvent system. The elimination of the drugs from the prepared microspheres highly dependent on the concentration of the polymer used, as the amount of the polymer increased the entrapment efficiency of the microsphere increased because of the good matrix formation.

Dissolution studies on all the five formulations of Captopril microspheres were carried out using a USP dissolution apparatus Type I. The *In vitro* drug release data for all formulations shown in Table - 15 and Fig - 19. The cumulative percent drug release for F5 after 12 h was found to be 89.83 %. The cumulative drug release significantly decreased with increase in polymer concentration. The increased density of the polymer matrix at higher concentrations results in an increased diffusional pathlength. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release.

The data obtained from in vitro dissolution studies were fitted to zero-order, first-order and Korsemeyer-Peppas equations. Fitting of the release rate data to the various models revealed that the formulation F1, F2, F4 and F5 followed first order release kinetics.

In the case of the Fickian release mechanism, the rate of drug release is much less than that of polymer relaxation (erosion). So the drug release is chiefly dependent on the diffusion through the matrix. In the non-Fickian (anomalous) case, the rate of drug release is due to the combined effect of drug diffusion and polymer relaxation. Case II release generally refers to the polymer relaxation. The n values for formulations F1 to F5 ranged from 0.520 to 1.079, indicating that the release mechanism was non-Fickian or anomalous release ($0.5 < n < 1$). Based on

the n values, F1 to F5, drug release from microsphere were controlled by polymer relaxation (erosion) as well as diffusion.

For the best formulation F5 were subjected to stability studies at 40^0 C/75% RH up to 3 months. The microspheres potency under accelerated stability conditions were within 90% to 110% of the label claim. Overall, results from the stability studies indicated that the spheres were chemically stable for more than 3 months

10. CONCLUSION

In this study sustained release Captopril Microspheres were prepared successfully using solvent evaporation method. It may be concluded that Captopril microspheres would be promising drug delivery system for oral administration of Captopril to sustained the drug release upto 12 h.

The formulation was found to be efficient with good recovery yield, percentage drug entrapment. FT-IR studies did not reveal any significant drug interactions.

Captopril microspheres are promising pharmaceutical dosage forms by providing sustained release drug delivery systems and avoiding the dose related side effects in the entire physiological region.

Among the different formulations, microspheres containing F-5 was found to be it has higher release the drug of 89.83 ± 0.21 % at 12th hour.

The diffusion of F5 formulation follows Zero order kinetics and fit into the Korsemeyer- peppas model and follows non-fickian,

Formulating Captopril microspheres (F5) was successfully achieved. The drug release in a sustained manner upto 12 hours with less dose dumping.

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