FORMULATION AND CHARACTERIZATION OF COLON TARGETED DRUG DELIVERY OF ACECLOFENAC FOR RHEUMATOID ARTHRITIS

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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND CHARACTERIZATION OF COLON TARGETED DELIVERY OF ACECLOFENAC TABLET FOR RHEUMATOID ARTHRITIS"** is a bonafide work done by **Mr.V.NAGASELVAN (261711306), Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-20** in partial fulfillment of The Tamilnadu Dr. M.G.R Medical University rules and regulation for award of **MASTER OF PHARMACY IN PHARMACEUTICS** under my guidance and supervision during the academic year 2018-2019.

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1.INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration, belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery and the design of dosage forms must be developed within the intrinsic characteristics of GIT physiology, pharmacokinetics and pharmacodynamics and formulation design to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

Among the various routes of administration, the oral route is considered to be most convenient for the administration of drugs to patients. On oral administration of conventional dosage forms drug normally dissolves in the gastro-intestinal fluids and is absorbed from regions of the gastro-intestinal tract, which depends upon the physicochemical properties of the drug. It has a serious drawback in conditions where localized delivery of the drug in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs in the colon rather than upper GIT has number of advantages.

Oral delivery of drugs in the colon is valuable in the treatment of diseases of colon where by high local concentration can be achieved while minimizing side effects. The colon is attracting of an interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon having a somewhat less hostile environment which is with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a long retention time and appears highly responsible to agents that enhance the absorption of poorly absorbed drugs.

The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coating or extremely slow releasing matrices. These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules, where they are needed most and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the Gastrointestinal tract, namely stomach and small intestine. Colon targeted drug delivery would ensures direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. For example, molecules that are degraded or poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more being environment of the colon.

There is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs. In such instances, the drug may be need to delivered in a pre-solubilized form or delivery should be directed to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon than in the distal colon. Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug. Moreover, the resident microflora could also affect colonic performance via degradation of the drug.

In the area of targeted delivery, the colonic region of the GI tract is the one that has been embraced by scientists and is being extensively investigated over the past two decades. Targeted delivery to the colon is being explored not only for local colonic pathologies, thus avoiding systemic effects of drugs or inconvenient and painful trans-colonic administration of drugs, but also for systemic delivery of drugs like proteins and peptides, which are otherwise degraded and or poorly absorbed in the stomach and small intestine but may be better absorbed from the more benign environment of the colon.

This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. Furthermore, there is urgent need for delivery to the colon of drugs that are reported to be absorbable in the colon, such as steroids, which would increase efficiency and enable reduction of the required effective dose. The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, crohn's disease and colon disease, where it is necessary to attain a high concentration of the active agent, maybe efficiently achieved by colon-specific delivery.[1]

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the GIT depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon rather than upper GIT proffers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, crohn's disease, carcinomas and infections) there by high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Apart from retarding or targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption of perorally applied, undigested, unchanged and fully active peptide drugs. As the large intestine is relatively free of peptidases such special delivery systems will have a fair chance to get their drug sufficiently absorbed after peroral application. The simplest method for targeting of drugs

to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coatings or extremely slow releasing matrices.[2]

The colon, as a site for drug delivery, offers distinct advantages on account of a near neutral pH, a much longer transit time, relatively low proteolytic enzyme activity, and a much greater responsiveness to absorption enhancers. These criteria favour this distal part of the gastrointestinal tract (GIT) as a site for the delivery of various drug molecules, including proteins and peptides. Colon-specific delivery systems should prevent the release of the drug in the upper-part of GIT and require a triggering mechanism to affect an abrupt release on reaching the colon. In the past, various primary approaches for colon specific delivery, such as pro-drugs, pH sensitive polymers, timed release delivery systems, and microbially degraded delivery systems, have achieved limited success. The majority of these systems developed during the past decade, were based on pH and time dependent mechanisms with limited in-vivo evaluation. Minor variation in pH between the small intestine and the colon makes the pH-dependent systems less specific, in terms of targeted release in the colon. Time-dependent formulations predominantly depend on the transit time of the delivery system in the GIT. A major limitation with these systems is that *in vivo* variation of the small intestinal transit time may lead to release of the bioactive in the small intestine or terminal part of the colon. The pathophysiological state of an individual will have a significant impact on the performance of these time-dependent systems. Patients with irritable bowel syndrome and ulcerative colitis exhibited accelerated transit through different regions of the colon.[3]

Colon-specific drug delivery has been approached by a number of methods exploiting changes in the physiological parameters along the gastrointestinal tract. The GIT transit time was utilized to formulate colon specific drug delivery systems which are so designed that their drug release is delayed to the time required for transiting drug from mouth cavity to distal part of small intestine i.e., ileum and subsequently drug release in the colon. Factors influencing the transit time of pharmaceutical dosage forms in the various regions of the gastrointestinal tract appear to depend on diet, gastrointestinal motility and physical activity of the person, fasted or fed state of the person. The change

in pH along the gastrointestinal tract was also used to develop colon specific drug delivery systems by applying coatings that were intact at low pH and dissolved at neutral pH. The pH of the colon is however; often lower than the pH of the small intestine, which in turn may be as high as 8 or 9, resulting in a too early release of a drug.

A number of specific regional characters of the colon can be explored for site specific drug delivery to the colon. In the colon, an extensive growth of anaerobic microorganisms is observed. These colonic micro flora produce a large number of hydrolytic as well as reductive enzymes which can potentially be utilized for colon-specific drug delivery. Prodrugs and coatings based on azo aromatic polymers and matrices containing azo aromatic cross-links are examples of systems that are potentially degradable by reductive enzymes released by colonic bacteria. Apart from azo reductase enzyme release other polysaccharidases like glucosidases, glycosidases are also released by colonic microflora, which are responsible for the degradation of polysaccharides. Hence drug delivery systems based on polysaccharide can also be used for colon specific drug delivery.[3]

1.1.Chronobiology and Chronopharmacotherapy of disease[4,5]

Until today design of drug delivery systems has been governed by the homeostatic theory. This theory is based on the assumption of biological functions that display consistency over time. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g. heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function.

It has become apparent that rhythmic processes are indispensable for treatment of human diseases as well as physiological functions vary over time and pathological state of disease has circadian rhythms. Epidemiological studies document the elevated risk of disease symptoms during 24 h cycle. The diseases commonly affecting human body, like asthma, arthritis, angina, myocardial infarction, allergy, inflammation, cancer and other such diseases follow circadian rhythmic pattern. The exacerbation of such diseases peak at only certain times of the day.

Morning stiffness observed in rheumatoid arthritis is one of the diagnostic criteria of the disease. Joint size, stiffness and pain are more on awakening and in the early morning hours when grip strength is lowest. Circadian rhythm of levels of interleukin- 6 might correspond to the rhythm of symptoms of rheumatoid arthritis.

In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of diseases drug effect can be optimized and side effects can be reduced. If symptoms occur at daytime, a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease become worse during the night or in the early morning, the timing of drug administration and nature of the drug delivery system need careful consideration.

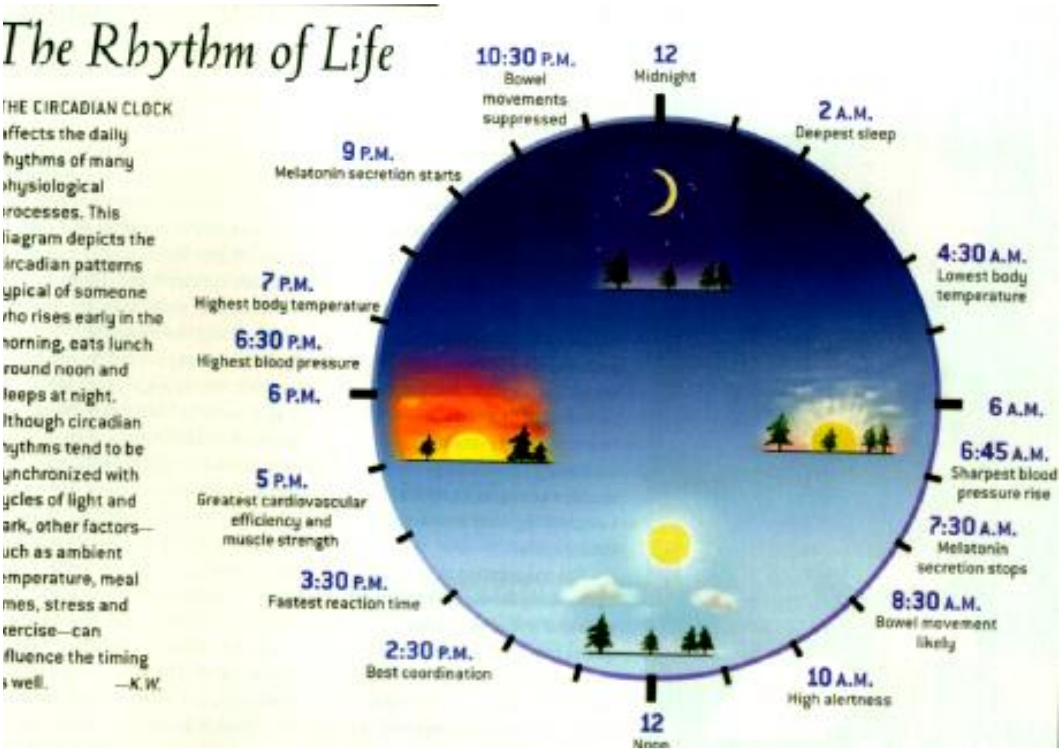


Fig.1. The Rhythm of life

Factors affecting Chronopharmacotherapy[5]

- Time of drug administration (morning, evening and bed time)
- Temporal and biological factors like seasonal allergies and other disorders
- Patient routines (exercise, work, sleep, and food consumption pattern)

Chronopharmacokinetics[6]

Chronopharmacokinetics involves study of temporal changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, GI motility, GI blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play a role in time dependent variation of drug concentration in plasma. Time of drug administration has to be regarded as an additional variable to influence the kinetics of a drug.

Arthritis[7]

"Arthritis" literally means "inflamed joints". Arthritis primarily affects the joints; it also attacks muscles and connective tissues of the surrounding organs. Arthritic disease stems from injuries, defects in the immune system, wear and tear on the joints, infections or genetic predisposition.

Osteoarthritis

A degenerative joint disease and the most common form of arthritis and joint disorders, is the gradual deterioration of cartilage, usually in the larger, weight bearing joints such as the hips, knees, and spine. This wear and tear is normal process predominantly found in people of age 55 and older. Among those younger than 45, it occurs more often in men. The joints are not always inflamed; the articular cartilage may begin to flake and crack, due to over use or injury. In severe cases the underlying bone becomes thickened and distorted. Scar tissue may then replace damaged cartilage. If movement becomes painful and restricted, lessened use of the associated muscles will lead to their atrophy.

Rheumatoid arthritis[7]

Rheumatoid arthritis (RA) is traditionally considered a chronic, inflammatory autoimmune disorder that causes the immune system to attack the joints. It is a disabling and painful inflammatory condition, which can lead to substantial loss of mobility due to pain and joint destruction. RA is a systemic disease, often affecting extra articular tissues throughout the body including the skin, blood vessels, heart, lungs and muscles.

The joint lining, called the synovium, becomes inflamed in cases of rheumatoid arthritis, leading to pain, stiffness, warmth, redness and swelling. These inflamed cells release an enzyme that may even digest cartilage and bone.

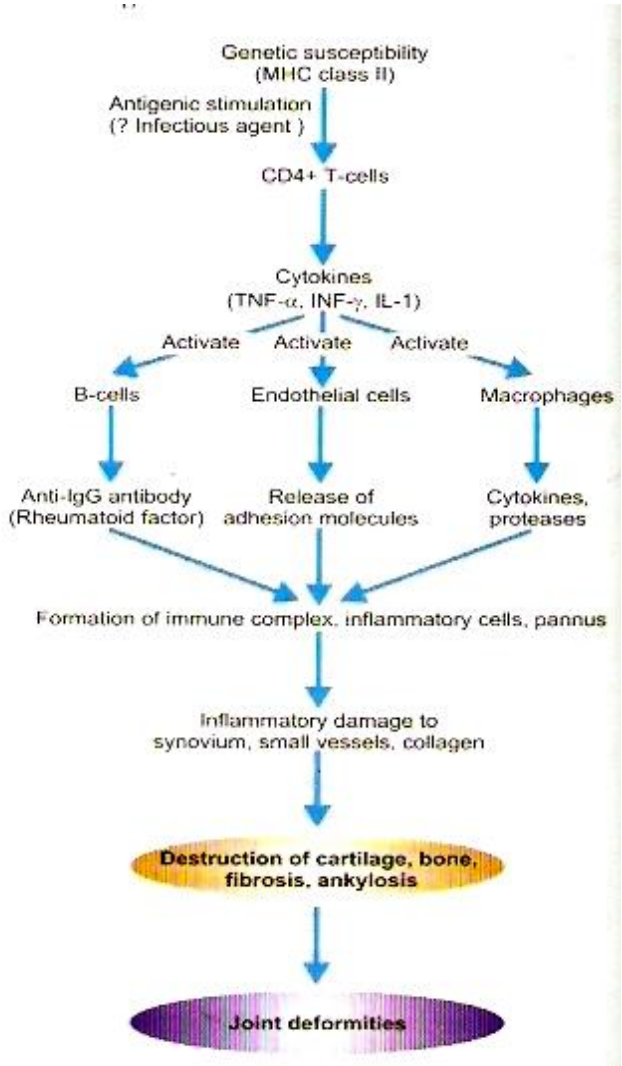


Fig.2. Causes of joint deformities

Biochemical mechanism[8]

The normal synovial lining of diarthodial joints is a delicate tissue layer up to three cells thick and a loosely arranged stroma with connective tissue, microvasculature and lymphatics. Inflammatory synovitis is the key pathological feature in rheumatoid arthritis. Its characteristics are synovial hyperplasia, inflammatory cell infiltration and vascularity. Initially edema and fibrin deposition predominate. Subsequently, there is synovial lining layer hyperplasia involving macrophage and fibroblast like synoviocytes. This hyperplasia is accompanied by infiltration of T cells, B cells, macrophages and plasma cells in the sublining layer.

Pannus formation with the formation of locally invasive synovial tissue is the other characteristic feature of rheumatoid arthritis and it is composed of mononuclear cells and fibroblasts. It has high levels of proteolytic enzyme expression, which allow the pannus to penetrate cartilage.

A number of different pathological mechanisms are involved in rheumatoid arthritis. Lymphocytes have an important role and many inflammatory cells in the synovial sublining layer are lymphocytes, especially T cells. Two cytokines, TNF-α and interlukin-1 are present in large quantities in rheumatoid arthritis synovial fluid and tissue and they have therapeutic targets for disease modifying drugs. Additionally, there are high levels of matrix metalloproteinase enzymes, which are destructive enzymes that are produced by rheumatoid arthritis synovial lining cells.

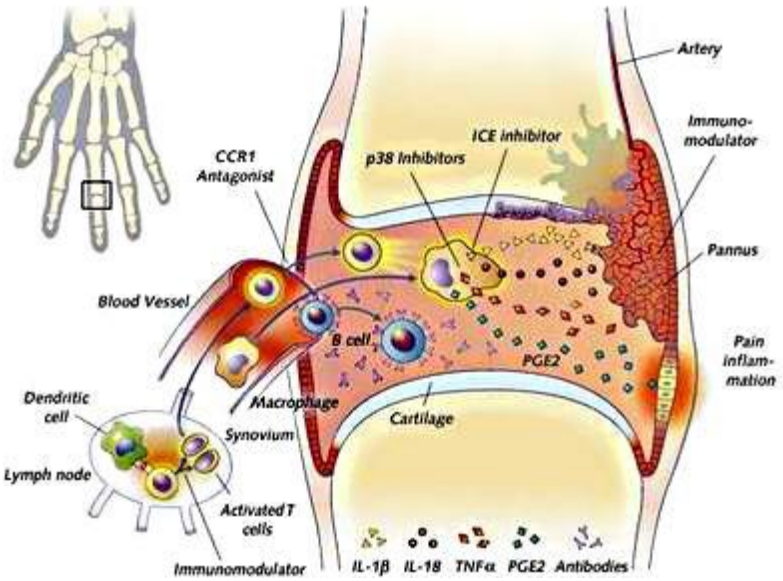


Fig.3. The Pathophysiology of Rheumatoid Arthritis

Symptoms[9,10]

- The exacerbation of the disease peaks at only certain times of the day and the cardinal symptoms of rheumatoid arthritis include:
- Stiffness, swelling and pain of one or more joints of the body characteristically severe in the morning, fatigue and weakness.
- Stiffness following periods of immobility, which gradually improves with movement.
- Rheumatoid nodules (lumps of inflamed cells) under the skin usually found on the bony part of the fore arm, ankle and fingers.
- Minor fever, anemia and weight loss.

Treatment

Pharmacological treatment of rheumatoid arthritis can be divided into

- Disease modifying anti-rheumatic drugs (DMARDs)
- Anti-inflammatory agents and analgesics.
- Exercise

DMARDs have been found to produce durable remissions and delay or halt disease progression. In particular they prevent bone and joint damage from occurring secondary to the uncontrolled inflammation.

Disease modifying anti-rheumatic drugs (DMARDs) [11]

DMARDs can be further subdivided into xenobiotic agents and biological agents. Xenobiotic agents are those DMARDs that do not occur naturally in the body, as opposed to biologicals.

Anti-inflammatory agents and analgesics[12]

The treatment of arthritic conditions relies on medicines that fight joint swelling, stiffness and pain. Circadian rhythm affects the arthritic medication. NSAIDs reduce the swelling, stiffness and pain of arthritis. Taking the medicines at the wrong time of day compromises their effectiveness and increases the risk of side effects such as indigestion, stomach ulcers, headache, anxiety and dizziness. Chronotherapy provides ways of increasing the effectiveness and safety of arthritic medications. The chronotherapy of arthritic disease involves determining the best time to take NSAIDs or other types of medicines to enhance their desired effects and avoid or minimize the side effects.

Non-steroidal anti -inflammatory drugs

NSAIDs are drugs with analgesic, antipyretic and anti-inflammatory effects that reduce pain, fever and inflammation. The term "non-steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eiconoside depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic.

Mechanism of action

Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) iso-enzymes. Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (Derived from the cellular phospholipid bilayer by phospholipase

A2). Prostaglandins act (among other things) as messenger molecules in the process of inflammation.

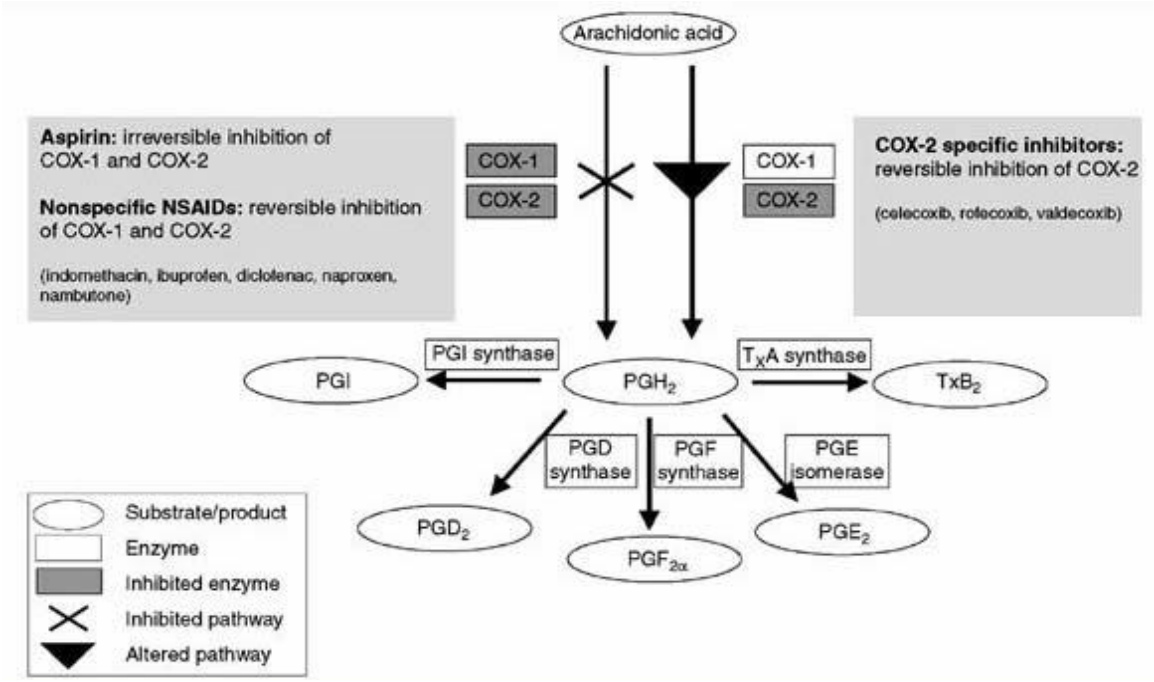


Fig.4. Mechanism of action of NSAIDs

Exercise

In some cases, surgery may be necessary. Surgery, such as joint replacement, is considered only when the previous treatments for pain and mobility have been unsuccessful and the quality of life is suffering. In addition to joint replacement surgery, other types of surgery include the reconstruction or fusion of a joint and the removal of diseased tissue from the joint (synovectomy).

1.2. COLON TARGETED DRUG DELIVERY SYSTEM

Colon Targeted Drug Delivery System (CTDDS) may be following the concept of Controlled or Sustained drug Delivery System. For CTDDS oral route of administration has received most attention. Local delivery allows topical treatment of inflammatory bowel disease. Colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs.[13,14]

For effective and safe therapy of these colonic disorders, colon specific drug delivery is necessary i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon[15]. Today, colon specific drug delivery is challenging task to pharmaceutical technologist. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons,

i. Less diversity,
ii. Intensity of digestive enzymes,

Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CTDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability[16]. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time[17]. Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery [18]

The bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the reaches the colon. Because the colon has a long residence time 72 hours and high water content it favors absorption of poorly absorbed drug

molecule may have an improved bioavailability, CTDDS has been employ to achieve following objectives

i) Sustained delivery to reduce dosing frequency

ii) Delay delivery of drug to achieve high concentration in treatment of disease of distal.

iii) To delay deliver to a time appropriate to treat acute phase of disease

iv) Deliver drug to that region that is less hostile metabolically, drug which is acid and enzyme labile such as proteins[19].

Benefits of Colon Target Drug Delivery System [20,21]

a) Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, Crohn's disease etc.)

b) Minimizing extensive first pass metabolism of steroids.

c) High retention time thus increasing the bioavailability of poorly absorbable drugs.

d) Increased patient compliance.

e) Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.

f) Decreases the side effects in the treatment of colon diseases.

g) Prevents gastric irritation resulting due to the administration of NSAIDs.

h) Minimizes first pass metabolism.

i) Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.

j) Decreased frequency of administration. Hence decreased cost of drugs.

k) High retention time thus increasing the bioavailability of poorly absorbable drugs.

l) Targeted drug delivery to the colon in treatment of colonic disease ensures direct treatment at the affected area with lower dose and less systemic side effects.

m) The colonic drug delivery can also be utilized as the threshold entry of the drugs into blood for proteins and peptides which degraded or poorly absorbed in upper GIT.

n) The colon targeted drug delivery can also be used for chrono-therapy for effective treatment of diseases like asthma and angina.

o) High retention time thus increasing the bioavailability of poorly absorbable drugs.

Limitations of colon target Drug Delivery System[20-22]

a) Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.

b) Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.

c) There are variations among individuals with respect to the pH level in the small intestine and colon which may allow drug release at undesired CSDDS site.

d) The pH level in the small intestine and caecum are similar which reduces site specificity of formulation.

e) The major disadvantage of colonic delivery of drug is poor site specificity.

f) Diet and diseases can affect colonic micro flora which can negatively affect drug targeting to colon.

g) Nature of food present in GIT can affect drug pharmacokinetics.

h) Enzymatic degradation may be excessively slow which can cause interruption in polymer degradation and thus alters the release profile of drugs.

Need for colon targeting drug delivery: [23,24,25,26]

- ✓ Targeted drug delivery to the colon to ensure that direct treatment at the disease site (local delivery), at lower dosing and fewer systemic side effects.
- ✓ Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- ✓ Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
- ✓ The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sufasalazine .
- ✓ A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon .
- ✓ Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides

1.2.1 ANATOMY AND PHYSIOLOGY OF COLON [27]

In GIT, large intestine starts from the ileo-cecal junction to the anus having a length of about 1.5m (adults) and is divided into three parts, viz. colon, rectum and anal canal. The colon consists of caecum, ascending colon, transverse colon, descending colon and sigmoid colon. Colon is made up of four layers, serosa, muscularis externa, sub-mucosa and mucosa. The epithelium consists of a single layer of cells, which lines the crypts and covers the surface of the mucosa. Three major cell types found in the epithelium are the columnar absorptive cells, goblet (mucous) cells and entero endocrine cells. Adjacent columnar absorptive cells are attached to one another near apical margins by a junctional complex. Mucus production in the colon is a function of goblet cells and the proportion of goblet cells increases in the elderly. The colon and the rectum have an anatomic blood supply. The arterial blood supply to the proximal colon is from the

superior mesenteric artery and the inferior mesenteric artery supplies the distal colon. The venous drainage is via the superior (proximal colon) and inferior (distal colon) veins. The arterioles and capillary branches pass to the epithelial surface between the crypts and form an extensive network of capillary plexi. The mucus lining of GIT forms a barrier against bacterial invasion of the gut wall.

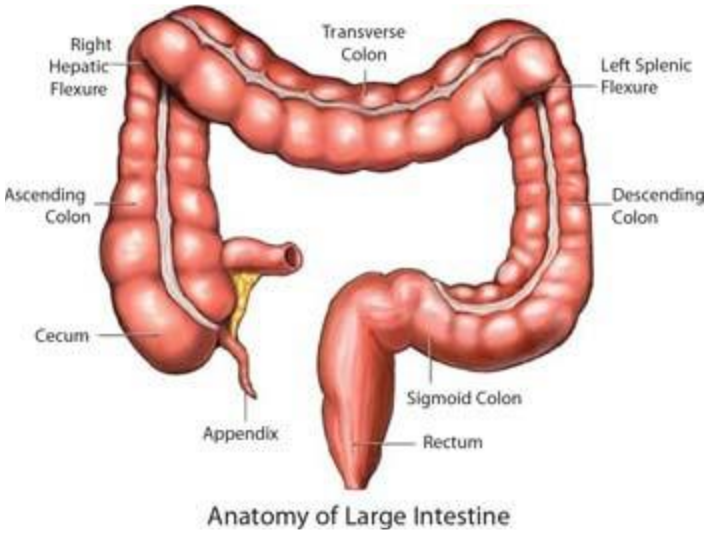


Fig.5. Anatomy of Colon.

1.2.2. COLONIC MICRO FLORA [28]

The sluggish movement of material through the colon allows a large microbial population to succeed there. Over 400species of bacteria found, for the most part anaerobes and a small number of fungi. The bacterial count (colony forming unit/mL, CFU/mL) is 1011-1012CFU/mL in colon. Most of them are anaerobes. E.g.: Bacteroides, Bificlobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus and Clostridium; others are facultative anaerobes e.g.: E.Coli. Among all of them 20-30% are Bacteroides.

1.2.3. pH IN THE COLON

Radio telemetry has been used to measure the gastrointestinal pH in healthy human subjects. The average pH of the caecum and colon lumen is 6.8 – 7.0. The highest pH levels (7.5 – 8.0) were found in the terminal ileum. On entry into the colon, the pH dropped to 6.4 –7.0. The pH in the mid-colon was measured at 6.6 – 7.4 and in the left

colon, 7.0 – 7.7. The fall in pH on entry into the colon is due to the presence of short chain fatty acids arising from the bacterial fermentation of polysaccharides. Colonic pH has been shown to be reduced in disease.

1.2.4. FUNCTIONS OF THE COLON

The major function is the consolidation of the intestinal contents into feaces by the absorption of water and electrolytes. The absorptive capacity is very high. In healthy human colon, sodium and chloride ions are usually absorbed and potassium and bicarbonate ions are usually secreted. Activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements caused by circular muscle and causing the appearance of the sac-like haustra, predominate and resulting in mixing of the luminal contents. Significant propulsive activity, associated with defecation and affected by longitudinal muscle, is less common and occurs an average of three or four times daily.

1.2.5. BARRIERS TO COLONIC DRUG ABSORPTION[27]

Drug absorption through the colon can be limited by number of barriers. In the lumen itself, specific and non-specific drug binding can occur through the interaction of drug with dietary components and products released from bacteria residing in the colon. The mucus barrier at the epithelial surface can present a formidable physical barrier to uptake as a result of specific and non-specific drug binding. Mucus-drug incompatibility can be compounded if the delivered drug stimulates the mucus secreting goblet cells because the transit through mucus is diffusion limited, the greater the thickness of this barrier, longer the time required for an individual molecule to reach the epithelial surface.

The unstirred water layer (the space between mucus layer and epithelial cells) presents another barrier to colonic absorption, particularly for lipophilic drugs. A pH gradient may also exist across the unstirred water layer. This lower pH at the colonocyte surface may dramatically alter drug solubility and since drug transport within the unstirred layer is driven by chemical potential, altered drug solubility can affect absorption. Probably the most significant barrier to epithelial transport of drugs in the

colon occurs at the level of the epithelium. Here, the lipid bilayers of the individual colonocytes and the occluding junctional complex (OJC) between these cells provide a physical barrier to drug absorption.

1.2.6. FACTORS AFFECTING COLONIC DRUG DELIVERY

There are many factors that influence the drug delivery to colon. They include

1. Transit through GIT

In order to reach colon in an intact form, the drug delivery systems should surpass the barriers in the stomach and small intestine. Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hours to reach the ileocecal junction. During this period the dosage form is exposed to enzymes present in small intestine. Compared to the other region of GIT, movement of material through the colon is slow. The colonic transit time of a capsule in adult is 20-35 hrs. Improved residence time with subsequent longer transit time and the contact of dosage form with microflora in colon govern the release and absorption of drug from dosage form.

2. Gastric emptying

Once the dosage form enters the stomach, the primary concern is how long it will remain there before being discharged into the duodenum. Emptying generally completes in 5-10 min up to 2 hours depending on phase of the stomach at the time of drug administration. It is preferable for a colonic delivery system to spend little time in the stomach. Such system may release the drug at a distant locus from the colon.

3. Stomach and intestinal pH

The pH of GIT must be considered when enteric coatings (bio-erodible polymers) are used to deliver drugs to colon. Since, in such systems, GIT pH gradient is used to trigger drug release.

4. Colonic microflora

Microflora of the colon has a number of implications in health and the treatment of diseases such as IBD. The concentration of gut microflora rises considerably in the terminal ileum to reach extraordinarily high levels in the colon. The gut bacteria are capable of catalyzing a wide range of metabolic events. Many colon-specific drug

delivery systems rely on enzymes unique to gut microflora to release active agents in the colon. However, only two or three enzyme systems namely azo-reductases and glycosidases (including glucuronidase) have been explored in this area. A large number of polysaccharides are actively hydrolysed by gut microflora leading to the possibility of using naturally occurring biopolymer as drug carriers. The second class of enzymes used to trigger the release of drugs in the colon is glycosidases (including glucuronidases). The main bacterial groups responsible for β- glycosidases activity are *lactobacilli*, *bacteroides* and *bifidobacteria*.

5. Gastrointestinal Disease State

Gastrointestinal diseases such as IBD (inflammatory bowel disease), crohn's disease,constipation, diarrhoea and gastroenteritis may affect the release and absorption of drug from colon-specific drug delivery system.

1.2.7. COLONIC ABSORPTION

As absorption capacity of colon is very high which is attributed to the colon transit time, which can be as long as 20-35 hours, hence it is ideally suited for absorption. The absorption is influenced by the transport of water, electrolytes and ammonia across the mucus and it is more in the proximal colon than the distal colon. Drug molecules pass from the apical to baso lateral surface of epithelial cells by

- ✓ Passing through Colonocytes (trans-cellular transport), or
- ✓ Passing between adjacent Colonocytes (Para-cellular transport)

Small amphipathic drugs may pass this barrier through transcellular transport. Paracellular transport may be the most promising means of general drug absorption in colon. Additionally, carrier mediated uptake of the drug in the colon is not extensive and usually related to the metabolic events of the resident bacteria. Receptor mediated endocytosis and pinocytosis could, however lead to transcellular transport of drug.

1.3. ORAL SOLID DOSAGE FORMS - A CONVENIENT DRUG DELIVERY SYSTEM [29-31]

A drug can be administered through various routes to produce prompt therapeutic action. An Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient, most economical method and having the highest patient compliance. The conventional oral drug delivery is the most widely utilized route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drugs. The popularity of oral route will provide patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improve the shelf life of the product.

Oral solid forms such as Tablets and Capsules are most useful dosage forms for the administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter products are mostly Immediate-release type, which are designed for Immediate-release of drug for rapid absorption.

1.3.1. TABLETS – Ruling dosage form since year's overview[30]

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopeia Pharmaceutical Tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without excipients. They vary in shape and different greatly in size and weight, depending on amount of Active Pharmaceutical Ingredient (API) and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablets.

Advantages of the Tablet dosage form

- Tablets are unit dosage form and greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.

- Less economic formulation.
- Lighter and compact.
- Easy to swallowing with least tendency for hang-up.
- Modified release products can be formed easily by utilizing polymers.
- Objectionable odour and taste can be masked by coating the Tablets.
- Suitable for dosage form for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid requiring, no additional steps when employing an embossed and / or monogrammed punch face.

Disadvantages of Tablet dosage form

- Difficult to swallow the Tablets in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Drugs with poor wetting, slow dissolution properties, may difficult to formulate as a Tablet that will still provide adequate or full drug bioavailability.

1.3.2. Different types of Tablets

A. Tablet ingested orally

1. Compressed Tablets
2. Multiple compressed Tablets
    - Compression Coated Tablets
    - Layered Tablets

- Inlay Tablets

3. Repeat action Tablets
4. Delayed release Tablets
5. Sugar coated Tablets
6. Film coated Tablets
7. Chewable Tablets
8. Targeted Tablets

B. Tablets used for oral cavity

1. Buccal Tablets
2. Sublingual Tablets
3. Troches or Lozenges
4. Dental cones

C. Tablets administered by other route

1. Implantation Tablets
2. Vaginal Tablets

D. Tablets used to prepare solution

1. Effervescent Tablets
2. Hypodermic Tablets
3. Tablet Triturates

1.3.3. COMPRESSION COATED TABLETS (CCT)[29,32,33,34]

Tablets are coated in number of ways. Coating is one of the important part in the formulation of pharmaceutical dosage form to achieve excellent formulation quality (e.g., color, texture, mouth feel, and taste masking), to provide physical and chemical protection to drugs in the dosage forms and to modify release characteristics. Coating techniques mostly used in pharmaceutical industry are aqueous or organic coating, which has some disadvantages. They are time consuming, stability for heat labile and hydrolysis of degradable drug and polluted environment problem. So the non-solvent coating method is introduced as alternative technique to overcome these disadvantages. Non-solvent coatings have been categorized as Press coating, Hot melt coating, Supercritical fluid spray coating, Electrostatic coating, Dry powder coating. Among these techniques, Compression coating or Press coating is the absolute dry coating without solvent and heat use. Additionally Compression coating technique has no limitation for the Core Tablets and hence overcomes the adhesion problem found in spraying methods.

Tablet-in-a-Tablet technology gained increased interest in the recent years for creating modified released products. It involves the compaction of granular materials around a preformed Tablet core using specially designed tableting equipment. Compression coating is completely dry coating process. The Compression Coated Tablet has two parts, internal core and surrounding coat. The Core Tablets are generally small in size and prepared on one turret. Then the prepared Core Tablets are transferred (centrally positioned) to another slightly larger die that is partially filled with coating powder (half of the amount), remaining coating powder is filled on the top of the core and compressed again resulting to form Tablet-in-a-Tablet. Mostly, the coat is water soluble and disintegrates easily after swallowing, in order to achieve Immediate-release product. This Tablet readily lend itself in to a Repeat action Tablet as the outer layer provides the initial dose while the inner core release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose and toxicity occurs. To avoid Immediate-release of both the layers, the Core Tablet is coated with enteric polymer so that it will not release the drug in Stomach while, the first dose is added in outer sugar coating.

Fig.6. Compression Coated Tablet

Advantages of Tablet-in-a-Tablet technology

- Simple and in-expensive.
- It is useful for formulation of Tablets containing two incompatible materials (one in the core and the other in the coat).
- Can be used to formulate Modified-release products such as Delayed-release (i.e. drug release in Intestine, Colon).
- It is not hazardous to the environment since it does not require the use of high amounts of organic solvents.
- Compression Coated Tablet (CCT) can also be used to avoid pharmacokinetic Drug–Drug interactions between concomitantly administered medications, creating a time interval between their releases into the gastrointestinal tract.
- To protect hygroscopic, light-sensitive, oxygen labile or acid-labile drugs

1.3.3.1. CLASSIFICATION OF COMPRESSION-COATED TABLETS BASED ON CORE SURFACE COATING[32]

A compression Coated Tablet is a system in which the all surface of an inner core is completely surrounded by coat. These coats prevent drug release from the core until the polymeric coat is entirely eroded, dissolved or removed (breaking down). Different drug release fashion could be obtained depending on coating layer and core composition.

1) Controlled release systems from Compression Coated Tablets

Compression Coated Tablet consists of a core (rapid release or modified release) which is coated by compression with a coating layer which contains polymeric material, diluent etc., and drug. Compression Coated Tablets could be modulated to provide different release patterns depending on the drug distribution and different type of controlling polymer used in core and coat. Extended release and Delayed release (time, pH and microbial control) for specific region of gastrointestinal tract, products can be formulated by using this concept.

2) Multiphasic release

Multiphasic release is a delivery system designed for many diseases which have marked diurnal rhythms, while constant drug release does not meet the optimum therapeutic efficiency. In such diseases, drug concentrations are needed to vary during the day. Drug levels need to be highest when symptoms are most severe. In the system, drug is presented in coat and core as a non-uniform drug distribution matrix which results in biphasic drug release. With the combination of therapeutic drugs in one Tablet, a variety of drug release. i.e. sequential release of different drugs or multi-phasic release of drugs is achievable. Compression Coated Tablets with multiple layers for desirable therapeutic use can be prepared.

3) Delayed release

Delayed-release defined with lag phase and followed with release phase, is obtained when all surface of core is compression-coated. Pulsatile release defined by fast drug release after a certain lag time could be categorized within this group as well. Lag

time for drug release could be controlled by the application of different polymeric coats which were differentiated with triggering factors to control drug release as mainly mentioned in Colonic Drug Delivery System.

4) Time-controlled release

A delayed-release Tablet consists of a drug core which is Compression coated with different polymeric (pH-independent) barriers. This delayed drug release is programmed for the treatment of disease that depends on circadian rhythms. The lag time of drug release is controlled by the compression coating, which prevents drug release from the core until the polymer coat is completely eroded, swollen or ruptured. Drug release pattern depends on the compression-coat properties.

5) pH-controlled release

A delayed release system using enteric polymers as a coating can provide site-specific drug delivery especially for Colon. This system has attracted a great interest for improving systemic absorption of therapeutic agents susceptible to enzyme digestion in the upper gastrointestinal (GI) tract, while time controlled release cannot achieve owing to large variations in gastric emptying time.

6) Microbial controlled release

A delayed release system may be aimed for Colon targeting. This system is based on the degradation of the polymeric compression-coat by specific enzymes produced by entero-bacteria in the Colon. Microbial degradable polysaccharides containing glycosidic bonds such as alginates, arabinogalactan, arabinoxylan, cellulose, chitosan, amylase, chondroitin sulfate, dextran, inulin, galactomannan (guar gum, locust bean gum), karaya gum, laminarin, pectins, starch, tragacanth gum, xanthan gum and xylan, could be employed as a coat. The investigated polysaccharides used for Colon-specific drug delivery which could also be used in Compression Coated Tablet included Methoxy pectin, pectin plus HPMC.

1.3.3.2. FORMULATION CONSIDERATION OF COMPRESSION COATING TECHNIQUE[32]

1) Compression coating amount

Coating amount is the most important parameter to achieve a coating uniformity in compression Coated Tablets. Generally, Compression Coated Tablet requires a coating material which is about twice the weight of the Core Tablet or more, the volume must be greater than that of the core itself. If the Core Tablet contains low density materials, such as fats and waxes, the amount or weight of coating must be even greater to assure a uniform volume of coating material for covering the core and adhesion of core and coating. Recently, increasing the drug loading by decreasing the compression coat could be performed with a novel compression tool (one-step dry coated tablet manufacturing method; OSDRC-system).

2) **Position of core in coated layer**

The main drawback of this system is to centralize the core in the Compression Coated Tablets. The reproducibility of drug release from Compression Coated Tablet is questionable, since the faults of press-coating may occur. Examples of press-coating fault are unequal coating, cocking and off-center. However, this drawback has been recently overcome by the novel compression tools (OSDRC-system) which placed a Core Tablet in a certain position. X-ray computed tomography as non-invasive and rapid characterization method in online processing control for Press Coated Tablets (PCT).

3) **Compression force and Compressibility of materials**

The compressibility of coated Tablets is mainly depended on the coating material. Thus, cohesiveness and plasticity of the powder coat are needed to obtain satisfactory mechanical strength of the coating. The cohesiveness indicates the continuity of the coating around the edge of the core, which depends on its strength and the plasticity responses for the expansion of the core after the final Tablets are released from the die. The final compression force applied to prepare Compression Coated Tablets need to be higher than the compression force which was applied to the core, to ensure the adhesion

between core and coat. Tablets with adhesive coating can be applied as core to ensure adhesion of compression coat and core.

4) **Interaction between drug and compression coat**

The interaction of drug and coating is needed to be considered especially when gellable coating materials are used for drug release control. Drug in Compression Coated Tablets diffuses through the swollen coat. This process might enhance some possible interaction between drug and coat. The difference in drug release of the enantiomers of verapamil hydrochloride from Compression Coated Tablets containing chiral polymers (pectin, galactomannan and sclera glucan) as the coat has been found.

1.3.3.3. FACTORS AFFECTING DRUG RELEASE IN COMPRESSION COATED TABLETS[32]

1. Tablet cores

- Drug solubility
- Release modifiers used in Core Tablet formulation

2. Compression coating

- Polymer type
- Particle size of polymer used
- Porosity or release modifier incorporated in coat
- Core-Coat ratio
- Compression force

1.3.3.4. RECENT TECHNOLOGIES USED IN COMPRESSION COATING METHOD[32]

- 1. One -Step Dry Coated Tablet manufacturing method (OSDRC**)**
- 2. Dividable Compression Coated Tablets
- 3. Inlay Tablets

2.REVIEW OF LITERATURE

1. Guoqiang Liu *et al.*, (2016) [35], Astragalus polysaccharide (APS) (used for intestinal protection) was added to formulate the Tongshu suppository to improve the pharmacokinetics of Aceclofenac, which were assessed in New Zealand rabbits using an orthogonal experimental design. The single-agent Aceclofenac was taken as the control formulation. The concentration-time and drug release curves were drawn, and Tmax (min), Cmax (μg·mL−1), AUC0→∞, and MRT were compared using a pharmacokinetic systems program. The formulated Tongshu suppository had moderate hardness, a smooth surface with uniform color, and theoretical drug-loading rate of 8%. Its release rate was in accordance with the drug preparation requirements. The concentration-time curves and drug release curves revealed that the maximum concentrations (Cmax) were 4.18 ± 1.03 μg·mL−1 and 3.34 ± 0.41 μg·mL−1 for the Tongshu and Aceclofenac suppositories, respectively, showing statistically insignificant difference, while the peak times were 34.87 ± 4.69 min and 34.76 ± 6.34 min, respectively, also showing statistically insignificant difference. Compared with the Aceclofenac suppository, the relative bioavailability of the Tongshu suppository was 104.4%, and the difference between them was statistically insignificant. In this experiment, the Tongshu suppository was prepared using the hot-melt method. In vivo pharmacokinetic studies confirmed it had higher bioavailability than the Aceclofenac suppository.

2. Semalty, *et al*., (2010),[36] Pharmacosomes were amphiphilic lipid vesicular systems containing phospholipid complexes with a potential to improve bioavailability of poorly water soluble as well as poorly lipophilic drugs. To improve the water solubility, bioavailability and minimize the gastrointestinal toxicity of aceclofenac, its pharmacosomes were prepared. Aceclofenac was complexed with phosphatidylcholine (80%) in two different ratios (1:1 and 2:1) using conventional solvent evaporation technique. Pharmacosomes thus prepared were subjected to solubility and drug content evaluation, scanning electron microscopy, differential scanning calorimetry, X ray powder diffraction and *in vitro* dissolution study. Pharmacosomes of aceclofenac were

found to be disc shaped with rough surface in scanning electron microscopy. Drug content was found to be 91.88% (w/w) for aceclofenac phospholipid complex (1:1) and 89.03% (w/w) aceclofenac phospholipid complex (2:1). Differential scanning calorimetry thermograms and X ray powder diffraction datas confirmed the formation of phospholipid complex. Solubility and dissolution profile of the prepared complex was found to be much better than aceclofenac**.**

3. Shivani Kala and Divya Juyal. (2016),[37] Aceclofenac is a potent analgesic, anti-pyretic and anti-inflammatory agent used in the management of moderate-to-severe pain and in rheumatoid disorder, rheumatoid arthritis and ankylosing spondylitis. Almost all drugs are marketed as tablets, capsules or both. The current aim of the study was to systematically investigate some of the important physicochemical properties of Aceclofenac. Before the development of any dosage form, it is essential to find some fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. It helps to decide many of the approaches in formation and development. Thus before selection of excipients, the Preformulation study of any API should be completed for any successful formulation. Preformulation Studies like solubility, pKa, dissolution, melting point, stability in solid state; bulk density, flow properties, were investigated and reported.

4. Kaisar Raza,*et al* (2014)[38] Osteoarthritis (OA), a common musculoskeletal disorder, is projected to affect about 60 million people of total world population by 2020.The associated pain and disability impair the quality of life and also pose economic burden to the patient. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed in OA, while diclofenac is the most prescribed one. Oral NSAIDs are not very patient friendly, as they cause various gastrointestinal adverse effects like bleeding, ulceration, and perforation. To enhance the tolerability of diclofenac and decrease the common side effects, aceclofenac (ACE) was developed by its chemical modification. As expected, ACE is more well-tolerated than diclofenac and possesses superior efficacy but is not completely devoid of the NSAID tagged side effects. A series of chemical modifications of already planned drug is unjustified as it consumes quanta of time, efforts, and money,

and this approach will also pose stringent regulatory challenges. Therefore, it is justified to deliver ACE employing tools of drug delivery and nanotechnology to refine its safety profile. The present review highlights the constraints related to the topical delivery of ACE and the various attempts made so far for the safe and effective topical delivery employing the novel materials and methods.

***5. Rabia Bushra., et al.,*(2013)[39]** Non-steroidal anti-inflammatory drugs (NSAIDs) were being widely used all over the world for their anti-inflammatory, analgesic and anti-pyretic activities. Aceclofenac is relatively a new NSAID belongs to phenyl acetic acid group. It is a potent COX-II blocker and inhibits the synthesis of prostaglandin E2. The anti-inflammatory properties are comparable to other NSAIDs like diclofenac. This review was significant in terms of information about the therapeutic application, adverse effects and the safety profile of aceclofenac.

6. Puratchikody A., *et al* (2011)[40] Microspheres were one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Aceclofenac is a potent analgesic, anti-pyretic and anti-inflammatory agent used in the management of moderate-to-severe pain and in rheumatic disorders such as rheumatoid arthritis and ankylosing spondylitis. The primary aim of this study is to formulate and characterize the aceclofenac loaded microsphere using Eudragit RL100, Eudragit RSPO and Ethyl Cellulose. Another objective of this study is to evaluate the marketed brands of modified release aceclofenac tablets. The formulated microspheres showed the percentage yield of 69.1 – 76.56%, mean particle size of 86.32 – 114.3 μm and drug entrapment efficiency as 79 – 88%. The *invitro* release of microspheres at phosphate buffer pH 7.4 showed 66.37 – 74.03% after 6 hours. The commercially available marketed brands of modified release aceclofenac [Zerodol CR (IPCA), Aceclo SR (Aristo) and Aceclan SR (Anthus)] were evaluated for uniformity of weight, friability and hardness all the results were within the acceptable limit. The *invitro* release studies with 0.1N HCl for 2 hours showed 10% release and further upto 24 hours in phosphate buffer pH 7.4 showed 61.18 – 66.68% release.

7. Umadevi Subbaih Khandasamy., *et al.*, (2011)[41] The aim of the present study was to develop a single unit, site-specific matrix tablets of aceclofenac allowing targeted drug release in the colon with a microbially degradable polymeric carrier, chondroitin suphate (CS) and to coat the optimized batches with a pH dependent polymeric. The tablets were prepared by wet granulation method using starch mucilage as a binding agent and HPMC K-100 as a swellable polymer. Chondroitin Sulphate and drug and physical mixture were characterized by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). The tablets were tested for their *in-vitro* dissolution characteristics in various simulated gastric fluids for their suitability as a colon-specific drug delivery system and also the tablets were evaluated for physicochemical properties, drug content, water percentage swelling and erosion characteristics. The dissolution data demonstrates that the 10% w/w increase in coating level of the pH dependent polymer (Eudragit L-100 and Eudragit S-100 in a ratio of 1 : 4 prevented the drug release in the simulated gastric fluid (pH 1.2-SGF) and the simulated intestinal fluid (pH 7.4-SIF). The dissolution rate of the tablet is dependent upon the concentration of Chondroitin sulphate in the simulated colonic fluid (SCF). The rapid increase in release of aceclofenac in SCF was revealed as due to the degradation of the Chondroitin sulphate membrane by bacterial enzymes. The studies confirmed that, the designed system could be used potentially as a carrier for colon delivery of aceclofenac by regulating drug release in stomach and the small intestine.

8. Santanu Ghosh *et al.*, (2010)[42]The objective of the study was to develop matrix tablets for oral controlled release of aceclofenac using ethyl cellulose, guar gum and various grades of cellulose polymers. Possible drug-excipient interaction was evaluated by high performance liquid chromatography (HPLC) and Fourier infrared spectroscopy (FTIR). The tablets prepared were assessed for their physicochemical, *in vitro* drug release at pH1.2, 4.5, 6.8 and 7.5 and stability characteristics. Comparison with a 'once daily' commercial aceclofenac product was made in the in vitro studies. There was no interaction between aceclofenac and the polymers used as excipients. Furthermore, the physicochemical properties of the tablets were satisfactory. The release profile of one of the formulated aceclofenac tablets (F7), which contained hydroxyl propyl methyl

cellulose (HPMC K4M), was statistically similar ($p < 0.05$) to that of the commercial aceclofenac brand in all the dissolution media. The formulated products ware stable and showed no changes in physical appearance, drug content, or dissolution pattern after storage at 40°C /75 %RH for 6 months. The results indicate that it is feasible to achieve a stable 'once daily' sustained release aceclofenac tablet formulation by using HPMC K4M of 4000cps viscosity grade as matrix material.

9. Sanjay Singh *et al*., (2010)[43] The objective of this work was to develop bio-adhesive topical gel of Aceclofenac with the help of response-surface approach. Experiments were performed according to a 3-level factorial design to evaluate the effects of two independent variables [amount of Poloxamer 407 (PL-407 = X1) and hydroxyl propyl methyl cellulose K100 M (HPMC = X2)] on the bio-adhesive character of gel, rheological property of gel (consistency index), and *in-vitro* drug release. The best model was selected to fit the data. Mathematical equation was generated by Design Expert® software for the model which assists in determining the effect of independent variables. Response surface plots were also generated by the software for analyzing effect of the independent variables on the response. Quadratic model was found to be the best for all the responses. Both independent variable (X1 and X2) were found to have synergistic effect on bio-adhesion (Y1) but the effect of HPMC was more pronounced than PL-407. Consistency index was enhanced by increasing the level of both independent variables. An antagonistic effect of both independent variables was found on cumulative percentage release of drug in 2 (Y3) and 8 h (Y4). Both independent variables approximately equally contributed the antagonistic effect on Y3 whereas antagonistic effect of HPMC was more pronounced than PL-407. The effect of formulation variables on the product characteristics can be easily predicted and precisely interpreted by using a 3-level factorial experimental design and generated quadratic mathematical equations.

10. Maheshwari *et al*.,(2010)[44] Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic, antipyretic and anti-inflammatory activities. It is practically insoluble in water. The effect of hydrotropes such as urea and sodium citrate and blends (urea + sodium citrate) on the solubility of aceclofenac was investigated. The

enhancement in the solubility of aceclofenac was more than 5 and 25 folds in 30% sodium citrate solution and 30% urea solution, respectively, as compared to its solubility in distilled water. The enhancement in the solubility of aceclofenac in a mixed hydrotropic solution containing ≥ 20% urea and 10% sodium citrate solution was more than 250 folds (compared to its solubility in distilled water). This proved a synergistic enhancement in solubility of a poorly water- soluble drug due to mixed hydrotropy. Synergistic combination of hydrotropic agents can minimize the amount of hydrotropic agents employed, minimizing the chances of their toxicities. Aqueous injection of aceclofenac, using the mixed hydrotropic solubilization technique, was developed and by using the lyophilization method, the problem of inadequate stability of aceclofenac in aqueous solution was overcome. The developed formulation was studied for physical and chemical stability.

11. Rohit Ramesh Shah *et al*.,(2009)[45] A topical preparation containing aceclofenac was developed using an o/w microemulsion system. Isopropyl myristate was chosen as the oil phase as it showed a good solubilising capacity. Pseudo-ternary phase diagrams were used to obtain the concentration ranges of the oil, surfactant (Labrasol) and co-surfactant (plurol oleique) for microemulsion formation. Five different formulations were formulated with various amount of the oil (5-25%), water (10-50%), and the mixture of surfactant and co-surfactant at the ratio of 4 (45-65%). In vitro permeability of aceclofenac from the microemulsions was evaluated using Keshary Chien diffusion cells with 0.45-μm cellulose acetate membrane. The amount of the aceclofenac permeated was analyzed by HPLC and the droplet size and zeta potential of the microemulsions was determined using a Zetasizer Nano-ZS. The mean diameters of the microemulsion droplets approximately ranged between 154 - 434 nm, and the permeability of aceclofenac incorporated into the microemulsion systems was 3 folds higher than that of the marketed formulation. These results indicate that the microemulsion system studied is a promising tool for percutaneous delivery of aceclofenac.

12. Hitesh Ranchhodbhai Patel *et al*.,(2009)[46] The aim of the present study was to prepare and evaluate an osmotically controlled muco-adhesive cup-core (OCMC)

containing aceclofenac. A special technique was used while preparing an OCMC. Stability of OCMC was determined in natural human saliva, and it was found that both pH and device are stable in human saliva. OCMC was evaluated by weight uniformity, thickness, hardness, friability, swelling, muco-adhesive strength and in vitro drug release. Swelling index was higher with formulations containing hydroxyl propyl methylcellulose (HPMC) K4M alone, and it decreases with its decreasing concentration in the OCMC. The in vitro drug release studies showed a release with the composition of formulation up to 12 h. The mechanism of drug release was found to be zero order kinetics with diffusion controlled drug release. It has shown significant anti-inflammatory activity ($P<0.001$) and no hypersensitive reaction. It can be concluded that by changing the content of OCMC system, a desire effect is generated and it overcomes the drawback associated with the conventional buccal adhesive tablet.

13. Neha Singh Raghuvanshi *et al.*, (2014)[47] Formulated and evaluated matrix tablets of Prednisolone by wet granulation method using various proportions of Sterculia gum with Carbopol 934P and Sterculia gum with Ethyl cellulose at 1:1, 1:5 and 1:2 ratio. Coating was carried out by using 1:1 ratio of Eudragit L100 and Eudragit S100. All the preparation were evaluated for Pre compressional properties, Post compressional properties and *in-vitro* dissolution study in different pH buffer of 0.1N HCL , pH 7.4 and pH 6.8 in order to mimic GIT condition. All the parameters were found to be within the limits. Formulation F4 showed 85.46% at the end of 12 hrs and emerged as best formulation.

14. **Rajeswari P. *et al.*, (2016)[48]** Developed colon targeted drug delivery system by using Chitosan as a carrier for Mesalamine. Matrix tablets containing various excipients and Chitosan were prepared by wet granulation technique using different binder systems. The prepared tablets were evaluated for Hardness, Weight variation, Drug uniformity, Friability and *In-vitro* Drug release study. All the parameters were found to be within the limits. The final product is expected to have the advantage of being biodegradable and pH dependant. The matrix tablet containing Chitosan as a carrier and xanthum gum as binder was found to be suitable for targeting mesalamine for local action in the colon as

compare to other matrix tablets containing different binders. Matrix tablets containing Chitosan released 99.99% of mesalamine in simulated colonic fluid. The stability study for prepared tablets at 40°C/75% relative humidity for three months showed no significant change in *In-vitro* drug release pattern. The results of *in-vitro* study indicate that matrix tablets containing Chitosan as carrier and xanthum gum as binder are most suitable to deliver the drug specifically in colonic region. The final formulation of mesalamine for colon-specific drug delivery gives pH, time and enzyme controlled release. Formulation F6 showed 99.29% at the end of 24 hrs and emerged as best formulation.

15. Prashanthi. R. *et al., (*2014)[49] Developed the controlled release matrix tablets of Flurbiprofen by selecting different polymers like HPMC K100, Sodium Carboxy Methyl Cellulose, Xanthan gum and Guar gum. All the formulations were prepared by direct compression method using 12mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were showed good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F12 formulation that is with Guar Gum showed maximum percentage drug release 99.18 % in 12 hours. Hence it is considered as optimized formulation. The retardation in the release of the drug from optimized formulation is may be due to the increase in the concentration of the polymer.

16. Prasanta kumar choudhury *et al.*, (2012)[50] Developed the matrix tablets of Ornidazole were prepared by wet granulation method using matrix forming natural polymers like Guar gum and Xanthan gum in combination with different proportions. The further effect of enteric coat on the matrix tablets for colon specific drug release was investigated. The Ornidazole optimized matrix formulation OM1 showed drug release around 32.37±0.33% in 2 hrs. So it was further enteric coated with 5% Eudragit S100 and coded as OME1 which showed 44.09±0.16% of drug release after 12 hrs. All formulations were subjected to Hardness test, Friability test, determination of uniform diameter and thickness, drug content for optimization and further evaluation. *In-vitro*

dissolution studies indicated that the drug release in upper part of GIT from matrix tablets of Ornidazole can be prevented by enteric coating with pH sensitive polymer (Eudragit®S100), which releases the drug specifically in colonic region to achieve target delivery. All the parameters were found to be within the limits. Formulation OME1 showed 44.09% of drug release at the end of 12 hrs and emerged as best formulation.

17. Basavaraja *et al.*, (2015)[51] Formulated and evaluated the sustained release matrix tablets of Flurbiprofen. By using the natural and synthetic polymers. Flurbiprofen is NSAID drug used extensively in the treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, Ankylosing Spondylitis, acute musculoskeletal disorders, low back pain and allied conditions. The natural polymers are Xanthan gum, Karaya gum, and synthetic polymers like HPMC K-100, Ethyl cellulose were utilized in the formulation of matrix tablets containing Flurbiprofen by wet granulation technique and evaluated for its *in-vitro* drug release. Natural polymer is hydrophilic in nature and rate controlling polymers. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, showed satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), *in-vitro* drug release and stability studies. All the formulations showed compliance with Pharmacopeial standards. The *in-vitro* release study of matrix tablets were carried out in pH 1.2 HCl for 2 hours and pH 7.4 phosphate buffer for the remaining 10 hours as dissolution medium. Among all the formulation, F12 showed 97.23% of drug which was better controlled release at the end of 12 hrs. It has been found that the optimized formulation F-12 containing 500 mg of ethyl cellulose better sustained effect for 12 hrs and emerged as best formulation.

18. Manjula B. *et al.*, (2016) [52] Formulated and evaluated the colon specific tablets of Ornidazole tablets were successfully prepared using enteric coated polymers eudragit, guar gum and HPMC k15m study of the preformulation charcteristics and FTIR studies indicates that there was no interaction between ornidazole and excipients used in the formulation. *In-vitro* release profiles of optimized form of F7 were found to showed delayed release pattern in a very customized manner which was very much required for

the colon specific drug delivery. *In-vitro* release profiles of optimized formulation of ornidazole controlled release tablets (F-7) were found to be improvised and followed zero-order kinetics, hence the release of the drug from the dosage form was independent of concentration and followed Higuchi model, and hence release of drug from press coated tablet was by diffusion mechanism. The drug delivery system was designed to deliver the drug at such a time when it was needed nocturnal time. Formulation F7 showed 75.98% of drug release at the end of 10 hrs and emerged as best formulation.

19. **Matsyagiri L. *et al.*, (2014)[53]** Formulated and evaluated the colon specific drug release of Albendazole with the purpose of developing a release of drug at colon region for local action, which is very convenient for administration, without the problem of enzymatic degradation and effect of pH of upper part of GIT like stomach and small intestine. Colon specific matrix tablets of Albendazole were prepared using guar gum, xanthene gum and HPMC polymers as matrix. FTIR showed that there is no interaction between drug and excipients. *In-vitro* dissolution of prepared matrix tablets of Albendazole performed by using USP type II apparatus in pH 0.1N first 2 hrs and remaining three hours in phosphate buffer pH 7.4 phosphate buffer solutions. The tablets were evaluated for various parameters like thickness, drug content uniformity, weight variation, hardness, friability and *in-vitro* drug release, all were showed satisfactory results. It is concluded that colon specific drug release of Albendazole give all satisfactory results for formulation F1-F9. Formulation F7 showed 87.02% of drug release at the end of 12 hrs and emerged as best formulation.

20. **Patel Jayvadan K *et al.*, (2009)54** Developed the colon targeted drug delivery system by using Chitosan as a carrier for Mesalamine. Matrix tablets containing various excipients and Chitosan were prepared by wet granulation technique using different binder systems. The prepared tablets were evaluated for Hardness, Weight variation, Drug uniformity, Friability and *In-vitro* Drug release study. The surface of the device of best formulation was coated with Eudragit S100 to ensure that the device was more pH dependent and trigger the drug release only at higher pH. The final product is expected to have the advantage of being biodegradable and pH dependant. The matrix tablet

containing Chitosan as a carrier and Hydroxypropyl methyl cellulose as binder was found to be suitable for targeting mesalamine for local action in the colon as compare to other matrix tablets containing different binders. Matrix tablets containing Chitosan released 97- 99% of mesalamine in simulated colonic fluid. The stability study for prepared tablets at 40oC/75% relative humidity for three months showed no significant change in *In-vitro* drug release pattern. The results of *in-vitro* study indicate that matrix tablets containing Chitosan as carrier and Hydroxypropyl methyl cellulose as binder are most suitable to deliver the drug specifically in colonic region. The final formulation of mesalamine for colonspecific drug delivery gives pH, time and enzyme controlled release. All the parameters were found to be within the limits. Formulation F9 showed 90.25% at the end of 12 hrs and emerged as best formulation.

21. **Sam T Mathew *et al.*, (2016)[55]** Formulated and evaluated the matrix tablets of albendazole containing various proportions (20%, 25%, 30% and 35%) of guar gum, xanthum gum and dextrin were prepared by direct compression technique using 10 mm concave punch. The prepared tablets were evaluated for hardness, friability, weightvariation, drug content uniformity and were subjected to *in-vitro* drug release with and without rat caecal content (4% w / v). All formulations (F1 - F12) which shows restricted drug release in stomach and small intestine and which shows more release in colonic environment. The drug release was independent of its concentration and the mechanism of drug release followed by super case-II transport. The accelerated stability studies revealed that there was no significant change in the colour, shape and drug content. The formulation (F9) is most suitable to target colon without being released significantly in the stomach and small intestine, and also it may avoid systemic side effects in the gastrointestinal tract. All the parameters were found to be within the limits. Formulation F9 showed 94.25% at the end of 12 hrs and emerged as best formulation.

22. **Ramesh Reddy K. *et al.*, (2015)[56]** Formulated the Prednisolone matrix tablets for colon targeting drug delivery system by using pectin and chitosan polymers. Prednisolon**e** is synthetic Glucocorticoids, a derivative of cortisol, which is used to treat a variety of inflammatory and auto-immune conditions. Colon targeted drug delivery is an active area

of research for local diseases affecting the colon, as it improves the efficacy of therapeutics and enables localized treatment, which reduces systemic toxicity. Targeted delivery of therapeutics to the colon is particularly advantageous for the treatment of inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease. Prednisolone matrix tablets were prepared by wet granulation technique by using different polymers such as chitosan and pectin are sustained release polymers. Starch mucilage is a granulating agent .The matrix tablets were evaluated their compatibility studies by using FT-IR, micromeritics properties, post formulation characters, stability and *in-vitro* dissolution studies. The batch F2 showed maximum prolonged drug release 96.79% at the end of 12 hrs and emerged as best formulation.

23. Magdum Sonali Vijaykumar *et al*., (2016)[57] Formulated and evaluated the colon targeted tablet by using various proportion of guar gum. Budesonide drug was selected for this research work. The Budesonide which is used for treating colonic diseases. The tablet was formulated by using Guar gum, Lactose Starch, Talc and Magnesium Strearate.The tablets were evaluated for thickness, hardness and friability and all this was found to be in within range. The *in-vitro* dissolution study was carried out by using different PH of phosphate buffer solution as 250 ml HCL buffer PH 1.2 for 2 hr., 250 ml phosphate buffer PH 6.8 for another 3hr.and finally250 ml PBS PH7.4 till the end of 12hr.The drug release of all the formulation was found to be within range of 92.23 to 98.38%.tablet was capable to release drug at colon and protect the tablet from acidic PH. The batch F3 showed maximum prolonged drug release 98.38% upto 24 hrs and emerged as best formulation.

24. Satyanarayana. T. *et al*., (2017)[58] Formulated and Evaluated the Mesalazine colon targeted matrix tablets was done by using various polymers. To achieve pH independent drug release of Mesalazine, pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The pre-compression blend of all formulations was subjected to various flow property tests and all the

formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F7 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 97.87% drug release. It followed first order kinetics mechanism. Stability studies was Performed no chemical changes was occurred.

25. Nikhil Biswas *et al.*,[59] developed Pulse release of Doxazosin from Hydroxyethylcellulose Compression Coated Tablet. The Core Tablets were prepared by direct compression method. The influence of disintegrants CCS, l-Hydroxypropylcellulose (l-HPC), gellan gum on drug release and *in-vivo* performance were investigated. The compression coating is done by using Ethyl cellulose and PEG 6000. *In-vitro* optimized Croscarmellose sodium–HEC matrix showed significantly faster ($p < 0.05$) drug release (t90%= 46 min) after an initial lag of 243 min. Disintegrant –HEC blended matrices were found significantly superior ($p < 0.05$) in terms of *in-vitro* release and bioavailability in comparison to plain HEC matrices.

26. Sateesh Kumar Vemula *et al.*,[60] formulated and evaluated Colon-specific double Compression Coated Mini-Tablets of Ketorolac tromethamine. Double Compression Coated Tablets were prepared based on Time-controlled Hydroxypropyl methylcellulose K100M inner compression coat and pH-sensitive Eudragit S-100 outer compression coat. 6 formulations were done. From the *in-vitro* drug release studies, F6 Tablets was considered as the optimized formulation, which retarded the drug release in stomach and small intestine (3.51 + 0.15% in 5 h) and progressively released to colon (99.82 + 0.69% in 24 h). The release process followed supercase-II transport with zero order release kinetics. From the pharmacokinetic evaluation, the Immediate-release Core Mini-Tablets reached peak plasma concentration (C-max of 4532.68 + 28.14 ng/ml) at 2 h T-max and Colon targeted Tablets showed C-max of 3782.29 + 17.83 ng/ml at 12 h T-max. The area under the curve and mean resident time of Core Mini-Tablets were found to be 11,278.26 + 132.67 ng.h/ml and 3.68 h respectively while 17,324.48 + 56.32 ng.h/ml and 10.39 h for Compression Coated Tablets.

27. Patel Rushikesh Chandubhai *et al.*, [61] formulated and evaluated an oral Time-controlled Drug Delivery System of Flurbiprofen, based on chronotherapeutic approach for the treatment of Rheumatoid arthritis (RA). In this study, Flurbiprofen CCT were prepared by compression coating the Core Tablet with different polymers like HPMC K4M, HPMC K15M and HPC in various proportions. Different ratios of polymers were selected to achieve suitable lag time for the treatment of RA. The CCT were evaluated for their hardness, thickness, friability, weight variation, drug content uniformity and core erosion ratio. The *in-vitro* drug release profile of the formulations was performed in simulated gastric and intestinal pH conditions up to 8 h. The desired lag time of 6 h was obtained for selected formulations and burst release was obtained after the lag time, which was consistent with the demands of chronotherapeutic drug delivery.

28. Khadabadi S.S. *et al.*, [62] formulated and evaluated the Press Coated Tablet of Ketoprofen. The PCT containing Ketoprofen in the inner core were formulated by direct compression method. SSG is used as a super disintegrant in Core Tablet. The HPMC K4M is used as a coating material to modify the release in outer coat. Totally 9 formulations were made by varying amounts of SSG and HPMC K4M. Evaluations were done. The release profile of PCT exhibited a lag time depending upon the amount of HPMC K4M in compression coating, followed by burst release. Optimization was done using 32 factorial design considering two independent factors at three levels. The optimized batch F6 gave a lag time of 6 h and drug release of 95.74% which consisted of 40% HPMC K4M and 2% SSG.

29. Pruthviraj S Pawar *et al.*, [63] formulated and evaluated the oral Colon targeted Compression Coated Tablet of budesonide. Colon targeted Tablets of budesonide were prepared using pectin, guar gum as enzyme dependent polymers along with HPMC, HEC as time dependent polymers followed by pH-dependent polymers like Eudragit S100 and Cellulose acetate phthalate. Fast dissolving core tablet of Budesonide was prepared by using CCS as a superdisintegrant by direct compression method which showed rapid release within 2 min. The compression coating was done over the Core Tablets by using

pectin, guar gum, HPMC and HEC in different ratios by direct compression method. The enteric coating was done on the CCT using ED S-100 and CAP in different ratios by dip coating method. The evaluations were done for all the formulations. *In-vitro* swelling and *in-vitro* drug release studies were carried out at different pH (1.2, 6.8 and 7.4). The compression coated formulation C1 (pectin: guar gum 1:2), C2 (HPMC: HEC 1:2) and C3 (HPMC, HEC: pectin, guar gum 2:1) showed good swelling (493.42%, 411.08% and 393.61%) up to 18, 20 and 21 h respectively. pH dependent polymers ED S-100: CAP in the ratio 2:1 as an enteric coating material applied over CCT was capable of protecting the drug from being released in physiological environment of stomach and small intestine. This study proved that Budesonide CCT, enteric coated with ED S-100: CAP in the ratio 2:1 may be beneficial in the treatment of IBS and Nocturnal Asthma.

30. **Krishnaveni. G *et al.*,** [64] Developed and Evaluated of Pulsatile Drug Delivery System containing Montelukast Sodium by Press Coated Tablet using Natural Polysaccharides. Totally 9 different Montelukast sodium Core Tablet formulations were prepared by direct compression method using different concentrations of SSG, CCS, Crospovidone. Then the optimized F3 formulation was coated with a natural polymers such xanthan gum, guar gum and mixture of it respectively. The evaluations were done. Formulation P5-F3 shows great ideal in pulsatile drug delivery. The release data from the formulation was found to fit in peppas model with r2 of 0.983. Stability studies also performed for 3 months at 40ºC and 55ºC at 75% RH as per ICH guidelines for optimized formulation and it was found to be stable.

31. Krishna K. V. *et al.*,[65] designed and evaluated the Extended-release Tablet of Venlafaxine hydrochloride using Compression coating technology. Venlafaxine HCl pellets were prepared. The compression coating of the pellets are done by both direct compression method and wet granulation method. As per USP Dissolution profiles for Compression Coated Tablets formulated by direct compression method and Compression Coated Tablets formulated by wet granulation method are performed in 0.1 N HCl.

32. **Pavani D. *et al.*,** [66] developed and evaluated the Metoprolol Tartrate Compression Coated Tablets for Chronotherapeutic drug delivery system. The Core Tablets of Metoprolol Tartrate was prepared by direct compression method using various concentrations of super disintegrants. Three different formulations of Core Tablets were formulated. From this F1 shows faster drug release. Then the coating is done by using Ethyl cellulose N 50 and Methocel K100M. All the Core and Press Coated Tablet formulations were subjected to various physical and chemical evaluation tests for Core and Press Coated Tablets. Ten formulations of Compression Coated Tablets were made. From this C1, C2 and C3 produces maximum drug release after 3 hours, C5 and C9 produces maximum drug release after 8 hours. Time-dependent Pulsatile Drug Delivery System has been achieved from Tablet of formulation C5 and C9 with 98.37% and 99.9%.

33. Dahal Amit *et al.*, [67] designed and evaluated the Compression Coated Tablets of Nifedipine. In this study, Core Tablets are prepared using solid dispersion of Nifedipine. Solid dispersion contains Nifedipine : Mannitol (1:2), prepared by hot melt method. The coat layer consists polymers such as PEG 6000, HPMC K4M, HPMC K15M and HPMC K100M in different ratios. Totally 12 formulations were done. All the evaluation parameters are checked out for both Core and Compression Coated Tablets. The mechanism of drug release was Higuchi's model release kinetics with r2 value between 0.983-0.997. Hence, Compression Coated Tablets of Nifedipine prepared with hydrophilic polymers showed promising results to be chosen for chrono therapeutic treatment of Hypertension.

34. **Kommineni veditha *et al.***,[68] designed and developed the Pulsin cap and Press Coated Tablets of Salbutamol sulphate. Press coated systems were prepared with different ratios of swelling and rupturable polymers [HPMC: Eudragit]. The lag time was dependent on composition of these polymers and the desired lag time was observed form the formulation containing only Eudragit. Modified Pulsin cap is based on cross linked hard gelatin capsules with formaldehyde and filled with Hydrogel plug. The Hydrogel plug plug was prepared with different ratios of swellable polymer HPMC and diluent

Dicalcium phosphate. The lag time was dependent on the polymer and diluent ratio. The desired lag time was observed form the formulation containing HPMC: DCP (3:1) ratio. Pulsin cap technique was found to be more suitable to achieve prolonged lag time when compared with the Compression Coated Tablets.

35. Mohd abdul hadi *et al.,* [69] formulated and evaluated of Compression Coated Tablets of Lornoxicam for targeting early morning peak symptoms of Rheumatoid Arthritis. The Core Tablets of Lornoxicam were prepared by direct compression technique using different concentration of Crospovidone. From this, the optimized formulation is compression coated with combination of different concentrations of polymers such as HPMC K4M, L-HPC, Na-CMC and EC (18-22 cps). Pre and post compression parameters were studied. The F5 formulation was chosen as better one as it releases 9.13 + 0.79% and 99.81 + 0.81% at the end of 5.5 and 8 hours respectively.

36. Renu dinkar *et al.,* [70] developed and evaluated the Nifedipine loaded Tablet formulation for Colonic delivery. The objective of present study was to develop a Pulsatile Compression Coated Tablet. The Core Tablets of Nifedipine were prepared by wet granulation method. Then the Core Tablets are coated with different ratios of Ethyl cellulose and Eudragit L-100. Six formulations were made by varying coating level (%w/w of core) and weight ratio of Ethyl cellulose to Eudragit L-100. The drug release study is carried out in 0.1 N HCl for 2 hours and in Phosphate buffer pH-6.8 for 10 hours. The formulation having coating level of 50 % w/w of core and weight ratio of Ethyl cellulose to Eudragit L-100 (20%) produces the lesser release profile when compared to other formulations.

37. Sayantan mukhopadhyay *et al.*, [71] formulated and evaluated the Pulsatile Drug Delivery System for sequential release of Atorvastatin. The Core Tablets of Atorvastatin were prepared by direct compression technique using SSG as super disintegrants. Then the Core Tablets are coated with the different concentrations of polymers such as Eudragit RS-100, Eudragit S-100, Ethyl cellulose, CAP, HPC. All prepared Multilayered Tablets were subjected for evaluation parameters. *In-vitro* drug release profiles of the

prepared tablets were suggested that, the release of drug from Compression Coated Tablets match with chrono biological requirement of disease.

38. Kamat Akshay Ramesh *et al.,*[72] formulated and evaluated the Indomethacin Compression Coated Tablets using Natural polymers for Pulsatile Drug Delivery for the treatment of Rheumatoid Arthritis. The Immediate-release Core Tablets of Indomethacin is formulated by direct compression method. Plantago ovata mucilage and Modified agar is utilized in the Core Tablet formulation as super disintegrants. The external coat is formulated using the Natural polymers such as Dammar gum, Chitosan, Xanthan gum and Guar gum by both direct compression and wet granulation method. The formulated Tablets were evaluated for various pre and post compression parameters. Formulation prepared by wet granulation method containing Xanthum gum and Dammar gum in the ratio of 2:1 having maximum lag time of 7 hours 15 minutes.

39. Sateesh Kumar Vemula *et al.*,[73] formulated and evaluated the Flurbiprofen CCT. Direct compression method was used to prepare flurbiprofen Core Tablets using CP as super disintegrants. Then the Core Tablets were compression coated with different concentrations of Guar gum. Then all the formulated Tablets were evaluated and optimized based on dissolution profiles. The optimized formulation provide the complete drug release in the Colon (99.86%) within 24 hours, drug loss in the initial period of 5 hours is only about 6.84%.

40. **Halba PD *et al.,*[74]** formulated and evaluated the Enteric Coated Delayed-release Tablets of Omeprazole for Duodenal Ulcer. The Core Tablets were prepared by direct compression method using different concentration of CP as super disintegrant. Then the Core Tablets were subcoated with the HPMC 15 cps upto 3% weight gain followed by enteric coating with Eudragit L-100, Eudragit L 100-55 and Cellulose Acetate Pthalate. Pre and post compression evaluations were studied. *In-vitro* drug release studies were carried out in 0.1 N HCl and phosphate buffer pH-6.8.

3.AIM & OBJECTIVE

Aim:

The aim of this research is to design and evaluate novel Colon Specific Release System of Aceclofenac using pH dependent polymer and microbially degradable polymer. When the drug is administered as the conventional formulation, it causes gastro intestinal complications including irritation, ulcer, bleeding and perforation. Site-specific delivery of drugs to the site of action has the potential to reduce side effects and to increase pharmacological response. Incorporation of pH dependent polymer and microbially degradable polymer in the tablet minimizes all these complications which makes it suitable candidate for administration by oral route. The purpose of this colon targeted delivery system enables the drug to be released in a delayed manner. So, the anti-Inflammatory drugs for the treatment of rheumatoid arthritis get released after reaching the target site of colon. By colon targeting prevents those side effects of conventional dosage form.

Objective:

- To develop pH dependent aceclofenac tablets with a view of minimizing the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of colon with an improved patient compliance. Incorporating Eudragit S 100 & L100 as a pH dependent polymer in the tablet.
- NSAID'S & Anti-Inflammatory's are used for treating ulcerative colitis, rheumatoid arthritis & osteoarthritis, which had apparent circadian rhythms and peak symptoms in the early morning.
- When they are administered orally as a conventional formulation, it is difficult to achieve the desired clinical effect, because it elicits patient's non-compliance of administration in the early morning to co-ordinate the rhythm of rheumatoid arthritis & osteoarthritis, due to rapid absorption of conventional formulation.
- To study release profile of colon specific dosage form for 12 hrs.

4. PLAN OF WORK

PREFORMULATION STUDIES:

1. Fourier Transform Infrared Spectroscopy (FTIR)
2. Bulk Density
3. Tapped Density
4. Hausner's Ratio
5. Carr's Index
6. Angle of Repose
7. Wavelength Analysis
8. Calibration Curve

Evaluation of Tablets:

1. Hardness
2. Thickness
3. Friability
4. Weight Variation
5. Content Uniformity test
6. Disintegration test
7. Invtro drug release.

5. DRUG PROFILE

Aceclofenac [75,76]

Aceclofenac is a potent non-steroidal anti-inflammatory drug. Due to its preferential cox-2 blockade it has better safety than conventional NSAIDs with respect to adverse effects on gastro intestinal and cardiovascular system.

IUPAC Name

2-[(2, 6-Dichlorophenylamino) phenyl] acetoxy acetic acid.

Description

A white to almost white crystalline powder.

Molecular formula

C16H13Cl2NO4

Molecular weight

354.2

structure

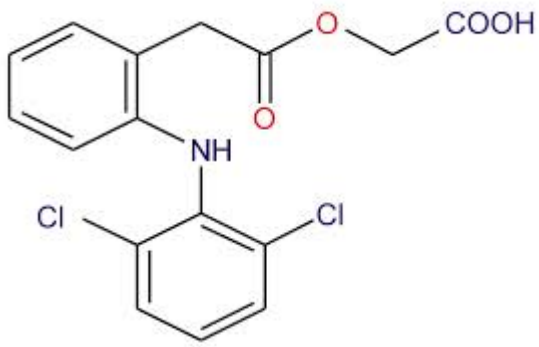


Fig.7 Structure of Aceclofenac

Category

Non-steroidal anti inflammatory drug.

Solubility

It is practically insoluble in water; soluble in alcohol and methyl alcohol; freely soluble in acetone and dimethyl formamide.

Melting point

149 - 150ºC

Pharmacology

The mode of action of aceclofenac is largely based on the inhibition of the prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins.

The drug inhibits synthesis of the inflammatory cytokines, interleukin (IL)-1 and tumor necrosis factor and prostaglandin (PGE2) production. Effects on cell adhesion molecular from neurophils have also been noted. *In vivo* data indicate inhibition of cyclooxygenase (Cox)-1 and 2 by aceclofenac in whole blood says, with selectivity for Cox-2 being evident.

Aceclofenac has shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1 activity. *In vitro* data indicate stimulation by the drug of synthesis of glycosaminoglycan in osteoarthritic cartilage. There is also evidence that aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli and that 4'-hydroxyacelofenac has chondroprotective properties attributable to aceclofenac in patients with ankylosing spondylitis.

Pharmacokinetics

Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentration is reached 1 to 3 hours after an oral dose. The drug is highly protein bound. The presence of food does not alter the extent of absorption of aceclofenac but the absorption rate is reduced. It is metabolized to a major metabolite 4'-hydroxyaceclofenac and to a number of other metabolites including 5-hydroxy aceclofenac, 4'-hyrodxydiclofenac, diclofenac and 5-hydroxydiclofenac. Renal excretion is the main route of elimination of aceclofenac with 70 to 80 % of an administered dose found in the urine, mainly as the glucuronides of aceclofenac and its metabolites of each dose of aceclofenac, 20% is excreted in the faeces. The plasma elimination half life of the drug is approximately 4 hours.

Drug interactions

Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate, increase the activity of anticoagulant, inhibits the activity of diuretics, enhance cyclosporine nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics. Furthermore, hypo or hyperglycemia may result from the Concomitant administration of aceclofenac and anti-diabetic drugs, although this is rare. The co-administration of aceclofenac with other NSAIDs results in increased frequency of adverse event.

Adverse drug interactions

Aceclofenac is well tolerated with, most adverse events being minor and reversible and affecting mainly the G.I system. Most common events include dyspepsia (7.5%), abdominal pain (6.2%), nausea (1.5%), diarrohoea (1.5%), flatulance ((0.8%), gastritis (0.6%), constipation (0.5%), vomiting (0.5%), pancreatitis (0.1%). Other adverse effect, which is not common such as dizziness (1%), vertigo (0.3%), and rare cases paraesthesia and tremor.

Dosage and administration

The usual dose of aceclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening.

Storage

In an air tight container, protected from light.

Uses

Aceclofenac is used in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, dental pain, post operative pain, dysmenorrhoea, acute lumbago, musculoskeletal trauma and gonalgia (knee pain).

POLYMER PROFILE

EUDRAGIT L 100[77]

Synonyms

Eudragit; Polymeric methacrylates.

Molecular Weight

≥100 000

Description

These polymers are readily soluble in neutral to weakly alkaline conditions (pH 6-7) and form salts with alkalis, thus affording film coats which are resistant to gastric media but soluble in intestinal fluid.

Solubility

Eudragit L 100 is soluble in acetone, alcohols, 1N NaoH & 1N HCl insoluble in Dichloromethane and water.

Incompatibilities

Incompatible with some oxidizing agent.

Functional Category

Film former; tablet binder; tablet diluent.

Applications in pharmaceutical formulation

Polymethacrylates are primarily used in oral capsule and tablet formulations as film coating agents.

Stability and storage conditions

Dry powder form polymers are stable at room temperature less than 30ºC. Dispersion is sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions therefore are stored at temperatures below 5-25ºC.

EUDRAGIT S100[78]

Synonyms

Polymeric methacrylate

Chemical name

Poly (methacrylic acid-co-methyl methacrylate) 1:2

Structural formula

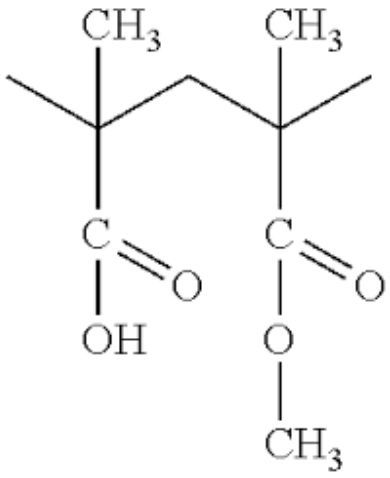


Fig.8 Structure of Eudragit S - 100

Molecular weight

approx. 125,000 g/mol

Melting point

1600C

Description

It occurs as a fine white free flowing powder

Solubility

Soluble in acetone and alcohols and 1N NaOH. EUDRAGIT S 100 is practically insoluble in ethyl acetate, methylene chloride, petroleum ether and water.

Functional category

Film former, Tablet binder, Tablet diluents

Application

Used as enteric coating agents because they are resistant to gastric fluid

Stability

Dry powder polymer forms are stable at temperature less than 300C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substances and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 300C.

Incompatibilities

Incompatibilities occur with certain poly methacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent.

GUAR GUM [79-81]

Synonyms

Galactosol, gaurflour, jaguar gum, meprogat, meyprodor.

Chemical name

Galactomannan polysaccharide

Empirical formula

$(C_6H_{12}O_6)_n$

Molecular weight

≈ 220 000

Structural formula

Gaur gum consists of linear chains of (1→4)-β-D-manno-pyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkages. The ratio of D-galactose to D- mannose is 1: 1.4 to 1:2.

Description

The USPNF 20 describes guar gum as a gum obtained from the ground endosperms of cyamopsis tetragonolobus (Fam: Leguminosae).

Colour

white to yellowish white

Odour

odorless or nearly odorless

Taste

blunt taste

Texture

powder

Acidity / Alkalinity

pH 5.0 to 7.0 (1% w/v aqueous dispersion)

V**iscosity**

4.86 Pas for 1% w/v dispersion

Solubility

In organic solvents disperses and swells immediately in cold or hot water to form a highly viscous and thixotropic solution.

Functional category:

Suspending agent, Tablet binder, Tablet disintegrant **,** Viscosity increasing agent.

Applications in pharmaceutical technology

- Used in solid dosage forms as a binder (up to 10%) and disintegrant
- Used in oral and topical products as a suspending, thickening (up to 2.5%) and stabilizing agent (1%)
- Used in colon targeted drug delivery systems
- Used as an appetite suppressant
- Also, used in cosmetic and food products

Storage

Guar gum should be stored in a well closed container and kept in a cool and dry place.

Incompatibilities

It is incompatible with acetone, alcohol, tannins, strong acids and alkalis. Presence of borate ions in distilled water, will prevents the hydration of guar gum.

Magnesium stearate

Synonyms

Dibasic magnesium stearate, Magnesium distearate, Magnesiistearas, Magnesium octadecanoate, Octadecanoic acid, Magnesium salt, Stearic acid, Synpro 90

Chemical name

Octadecanoic acid magnesium salt

CAS Number

[557-04-0]

Molecular formula

[CH3(CH2)16COO]2Mg

Molecular weight

591.24

Structure

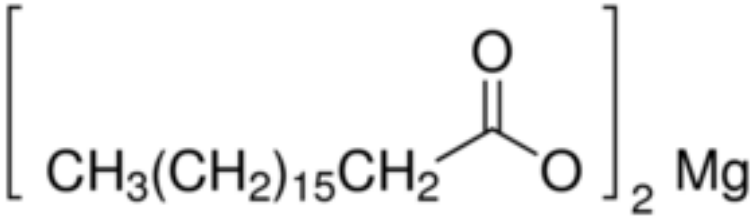


Fig.9 Structure of Magnesium Stearate

Functions

Tablet and capsule lubricant

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste.The powder is greasy to the touch and readily adheres to the skin.

Application

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0%w/w. It is also used in barrier creams.

Density

Bulk:0.159g/cm3

Tapped:0.286g/cm3

True:1.092g/cm3

Flowability

Poorly flowing, Cohesive powder

Melting point

117-150˚C

Solubility

Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%)

Specific surface area

1.6-14.8m2/g

Stability

It is stable

Storage

It should be stored in a well-closed container in a cool, dry place.

Related Compounds

Calcium stearate, magnesium aluminium silicate, stearic acid, zincs stearate.

Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Method of manufacture

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

Handling precautions

Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magneisum stearate should be handled in a well-ventilated environment.

Talc

Synonyms

Altalc, Hydrous magnesium calcium silicate, Hydrous magnesium silicate, Imperial, Magnesium hydrogen metasilicate, Magsil Star, Powdered talc, Purified French chalk, Purtalc, Soapstone, Steatite

Chemical name

Talc

CAS number

[14807-96-6]

Molecular formula

$Mg_6(Si_2O_5)_4(OH)_4$

Molecular weight

It may contain small, variable amounts of aluminium silicate and iron.

Functions

Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

Description

Talc is a very fine, white to greyish-white, odorless, impalpable, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Application

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent.

Acidity/Alkalinity

pH=7-10 for a 20%w/v aqueous dispersion.

Moisture content

Talc absorbs insignificant amounts of water at 25˚C and relative humidities up tp about 90%.

Particle size distribution

Varies with the source and grade of material. Two typical grades are ≥99% through a 74μm (#200 mesh) or ≥99% through a 44μm (#325mesh).

Refractive index

1.54-1.59

Solubility

Practically insoluble in dilute acids and alkalis, organic solvents and water.

Specific gravity

2.7-2.8

Specific surface area

2.41-2.42m2/g

Stability

Talc is a stable material and may be sterilized by heating at 160˚C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation

Storage

Talc should be stored in a well-closed container in a cool, dry place.

Incmpatibilities

Incompatible with quaternary ammonium compounds.

Related substances

Bectonite, Magnesium aluminum silicate, Magnesium silicate, Magnesium trisilicate.

Method of manufacture

Talc is a naturally occurring hydro poly silicate mineral. It is pulverized before being subjected to flotation processes to remove various impurities such as asbestos; carbon; dolomite; iron oxide; and various other magnesium and carbonate minerals. Following this process, talc is finely powdered, treated with dilute hydrochloric acid, washed with water, and then dried.

Handling precautions

Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. Eye protection, gloves and a respirator are recommended.

6. LIST OF INGREDIENTS

Table.1 List of ingredients

Sl.no.	Name of Ingredient's	Manufacturer's
1.	Aceclofenac	Madras Pharma
2.	Eudragit L-100	Blue Fish Pharmaceuticals
3.	Eudragit S-100	Blue Fish Pharmaceuticals
4.	Guargum	Fourrts India
5.	Micro crystalline cellulose	Madras Pharma
6.	Starch	Madras Pharma
7.	Magnesium stearate	Madras Pharma
8.	Talc	Madras Pharma
9.	Potassium chloride	Central Drug House(P) Ltd.

10.	Potassium Dihydrogen OrthoPhophate	Nice Chemicals (P) Ltd.
11.	Sodium hydroxide	Avantor Performance Materials Ltd.
12.	Acetone	Avantor Performance Materials Ltd
13.	Hydrochloric acid	Central Drug House(P) Ltd.

LIST OF EQUIPMENTS

Table .2 List of Equipment's

Sl.no.	Name of Equipment's	Manufacturer's
1.	Electronic balance	WENSAR^{TM}
2.	pH – Meter	MC Dalal, Chennai.
3.	UV Spectrophotometer	UV – 1700 Pharmaspec, Shimadzu, Japan.
4.	Rotary Punching Machine	Accura, 12station Compression Machine
5.	Hardness tester	Praveen Enterprises, Bangalore.
6.	Roche Friabilator	Indian Equipment Corporation.
7.	Disintegration apparatus	Electro lab
8.	Tapped density apparatus	DBK Instruments
9.	USP dissolution apparatus	Lab India, D5 8000

EXPERIMENTAL PROTOCOL

7. PRE FORMULATION STUDY

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

The Fourier transform infra-red (FTIR) analysis was conducted for the structure characterization. FTIR of pure drug, polymers, and their physical mixtures were recorded. Samples were taken in a KBr pellet using BOMEN MB SERIES FTIR instrument. Approximately 5 mg of spectroscopic grade KBr and samples were scanned in the IR range from 500 to 3500 cm^{-1} with a resolution of 4 cm^{-1}.

Density[82]

Powder flow, compressibility, dissolution and other properties may dependent on density.

Bulk density

The term bulk density refers to a measure used to describe a packing of particles. It is (gm/ml) and was determine using a balance and measuring cylinder. Initially the weight of the measuring cylinder was tarred. Then, 4gm pre-sieved (40#) bulk drug were poured into the measuring cylinder using a funnel. Then volume of the powder was taken. Bulk density of the granules was calculated using following formula.

Bulk density = Weight of powder / Volume of powder

Tapped density

Tapped density is determined by placing a graduated cylinder containing same mass of powder used for B.D. on a mechanical tapper apparatus which is operated for a fixed number of taps until powder bed volume has reached a minimum.

Tapped density = Weight of powder / min. volume of powder

Carr's Index (CI)

Tapped and bulk density measurements can be used to estimate the carr's index of a material. Carr's index was determined by,

Carr's index (%) = [(Tapped density – Bulk density)/Tapped density]*100

Table 3: Standards for Carr's index

Carr's Index	Flow
5 – 15	Excellent
12 - 16	Good
18 – 21	Fair
23 – 35	Poor
35 – 38	Very poor
More than 40	Extremely poor

Hausner's ratio (HR):

It is stated by Hausner's. It was calculated as follow:

Hausner's ratio = Tapped density / Bulk density

Table 4: Standards for Hausner ratio

Hausner ratio	Flow
1.0 –1.11	Excellent
1.12 – 1.18	Good
1.19 – 1.25	Fair
1.26 – 1.34	Passable
1.35 – 1.45	Poor
1.46 - 1.59	Very poor

Angle of repose (Tan θ):

Angle of repose is the tan inverse of angle between height (h) of pile of powder and the radius (r) of the base of conical pile. It can be obtained between the freestanding surface of the powder heap and the horizontal plane. The fixed funnel that is secured with its tip at a given height h, above graph paper, placed on the flat horizontal surface. Powder is carefully poured through funnel until the apex of conical pile just touches the tip of funnel.

Table 5: Standards for Angle of Repose

Angle of Repose	Flow
25 – 30	Excellent
30 – 35	Good
35 – 40	Fair
40 – 45	Poor
45 – 50	Very poor

Determination of Lambda Max:

Weighed 100 mg of Aceclofenac and dissolved in 100 ml of buffer solution (1000µg/ml). From this solution 1ml was taken and diluted to 10ml with buffer solution to get a solution containing 100µg/ml. From this 1ml was diluted to 10ml to get working standard solutions of 10µg/ml. This solution was scanned between 200-400 nm and an absorption maximum was determined and compared with literature value.

Preparation of calibration curve in phosphate buffer :

Weighed 100 mg of Aceclofenac and dissolved in 100 ml of buffer solution (1000µg/ml). From this solution 0.5 ml, 1ml, 2ml, 3ml, 4 ml was taken and diluted up to 100ml using phosphate buffer solution to obtain a working standard solution of 5- 40 µg/ml. The prepared concentrations were analyzed in UV-Visible spectroscopy at 266.5nm for acid buffer, 276nm for phosphate buffer pH 7.4 and 268nm for phosphate buffer pH6.8.

Linearity and Calibration:

The linearity of the calibration curve was estimated by plotting the graph in between absorbance (nm) (y) versus concentration (µg/ml) (x) of Aceclofenac in the concentration range 5-50 µg/ml. A calibration curve was prepared by measure the absorbance at 266.5 nm, 276 nm, 268 nm. The Statistical evaluation parameter like as the slope, intercept, regression coefficient, standard deviation (R^2), and relative standard deviation were determined.

8. PREPARATION OF TABLET

The Tablet was prepared by using a Direct Compression method. In this method all the ingredients of core tablet were accurately weighed and uniformly triturated and mixed through mortor and pestle and the powdered ingredients were weighed accurately as 200mg of each for compression. Then the powders were compressed in a 8mm punch setting on 12station compression machine. The same way coating ingredients were accurately weighed and triturated in a mortor and pestle. The coating of core tablet was done by 11mm punch settings on a 12 station compression machine. The coating ingredients were evenly divided into two halves as upper layer and bottom layer in between that the core tablet pre-punched was placed.

Table.6: Preparation of aceclofenac with Guar Gum

Sl.no.	Ingredients	Quantity (mg) present in each tablet			
		F_1	**F_2**	**F_3**	**F_4**
1.	Aceclofenac	100	100	100	100
2.	Guar Gum	20	40	60	80
3.	Micro Crystalline Cellulose	78	58	38	18
4.	Magnesium Stearate	1	1	1	1
5.	Talc	1	1	1	1

F_1 – F_4 – Aceclofenac + Guar Gum Formulation

Table.7 Preparation of Aceclofenac with Eudragit L100

Sl.no.	Ingredients	Quantity (mg) present in each tablet			
		F_5	**F_6**	**F_7**	**F_8**
1.	Aceclofenac	100	100	100	100
2.	Guar Gum	20	40	60	80
3.	Micro Crystalline Cellulose	78	58	38	18
4.	Magnesium Stearate	1	1	1	1
5.	Talc	1	1	1	1

F_6 – F_8 – Aceclofenac + Eudragit L100 Formulation

Table.8: Preparation of Aceclofenac with Eudragit S100

Sl.no.	Ingredients	Quantity (mg) present in each tablet			
		F_9	**F_{10}**	**F_{11}**	**F_{12}**
1.	Aceclofenac	100	100	100	100
2.	Guar Gum	20	40	60	80
3.	Micro Crystalline Cellulose	78	58	38	18
4.	Magnesium Stearate	1	1	1	1
5.	Talc	1	1	1	1

F_9 –F_{12} – Aceclofenac + Eudragit S100 Formulation

Table.9: Composition of Compression Coating

Sl.No.	Ingredients	Quantity (mg) Present in Each Tablet
1.	Guar Gum	220
2.	Micro Crystalline Cellulose	128
3.	Starch	40
4.	Talc	8
5.	Magnesium stearate	4

9. EVALUATION OF POST-COMPRESSION PARAMETERS

The compressed tablets were evaluated for the following parameters.

General appearance

The tablets should be free from cracks, depression, pinholes etc. the color and polish of the tablets should be uniform on whole surface. The surface of the tablets should be smooth.

Hardness:

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging, and shipping. Tablet hardness has been defined as, the force required to break a tablet in a diametric compression test[81].Tablet hardness of all the formulations was measured using a Monsanto hardness tester.

Thickness

The thickness of tablets was determined using a Digimatic vernier caliper (Mitutoya, Japan). Three tablets from each batch were used, and average values were calculated. The results are shown in Table.

Friability test

The friability of tablets was determined using Roche Friabilator. It is express in percentage (%). Ten tablets were initially weighed and revolved at 25 rpm for 4 min. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated. The % friability was then calculated by,

$$F = W_{initial} - W_{fiinal} \times 100 / W_{initial}$$

Acceptance criteria for percentage friability (percentage weight loss) should be less than 1%. The results are shown in Table.

Weight Variation Test

Twenty tablets were selected randomly from each batch and weighed individually on electronic balance. The individual weighed is then compared with average weight for the weight variations. The following percentage deviation in weight variation is allowed. The results are shown in Table.

Table.10: Percentage weight deviations

Sl.No.	Average Weight	% Deviation
1.	130 mg or less	10
2.	130 – 324 mg	7.5
3.	324 mg and greater	5

Drug Content

Two tablets were weighed individually and powdered. The powder equivalent to 100mg of Aceclofenac was weighed and dissolved in 100mL of Saline Phosphate buffer (pH 6.8). The solution was then filtered and from this solution 1 mL was taken and makes up with Saline Phosphate buffer (pH 6.8) in 100 mL standard volumetric flask. The amount of drug present in each tablet was determined spectrophotometrically at 268 nm using UV– spectrophotometer. The percentage content was determined using standard graph**.**

Invitro drug release studies

The invitro release of aceclofenac was carried out by using USP apparatus I (Paddle) method.200mg of tablets (f1 – f12) were placed separately in to the paddle and introduced in to the vessels of the dissolution test (Lab India, Disso 8000). The continuous dissolution method was used for simulating pH conditions of the GI tract (Huyghebaert et al., 2005). Initially, tablets were added in 700ml of 0.1N HCL (pH 1.2) for 2 h. At the end of 2h, 200ml of 0.2M tribasic sodium phosphate solution was added to

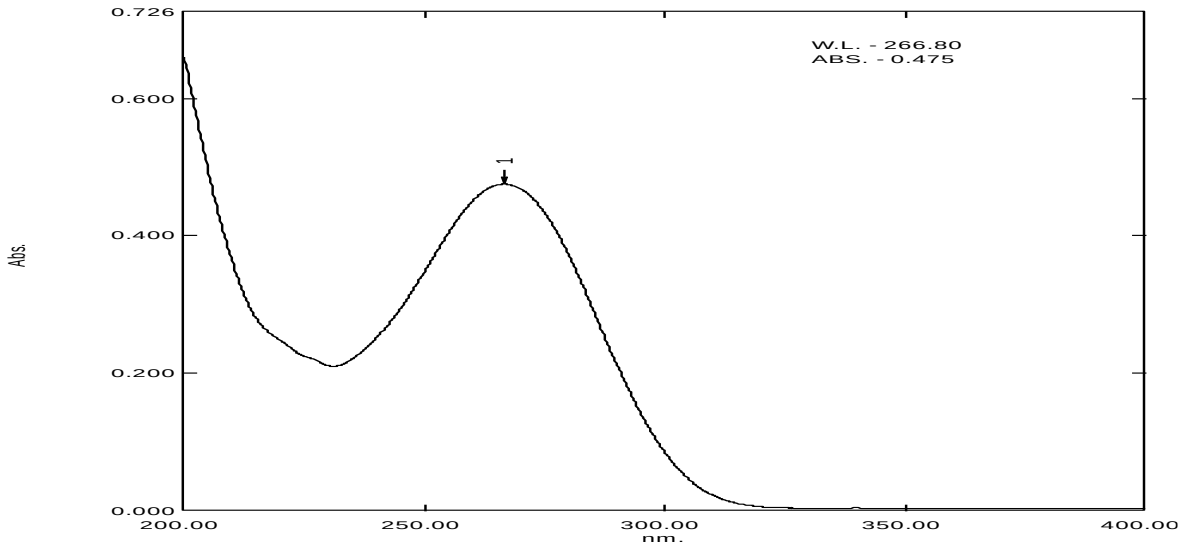
all the dissolution vessels and the pH was adjusted to 7.4 by using 2M NaOH. At the end of 5h, 2M HCL was added to all the dissolution vessels and the pH was adjusted to 6.8. 5ml samples withdrawn every hour and analysed in a UV spectrophotometer at 266.5nm for first two hours samples for acid buffer, after 2 hours analysed at 274nm and the remaining hour samples were analysed at 268nm. The percent drug released was recorded and graph was constructed by plotting % drug release versus time.

Determination of Lambda Max:

The lambda max of aceclofenac at different pH buffer solutions were determined by using a suitable UV-Spectrophotometry.

Fig.10: Lambda max of Acid buffer

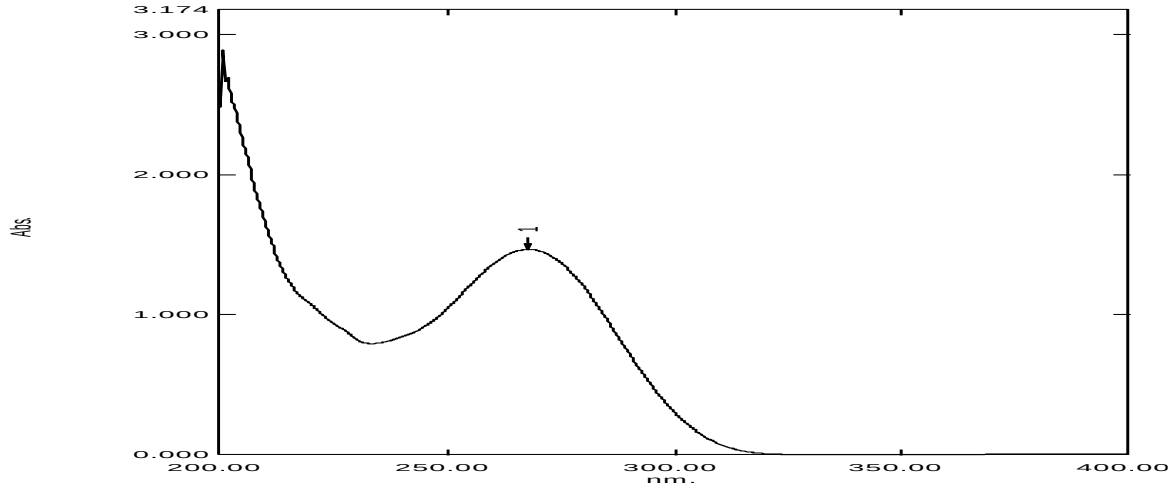
1. Aceclofenac 10 Mcg Acid buffer pH(1.2)



W.L.- 266.8 ABS.- 0.475

Fig.11: Lambda max of phosphate buffer pH(7.4)

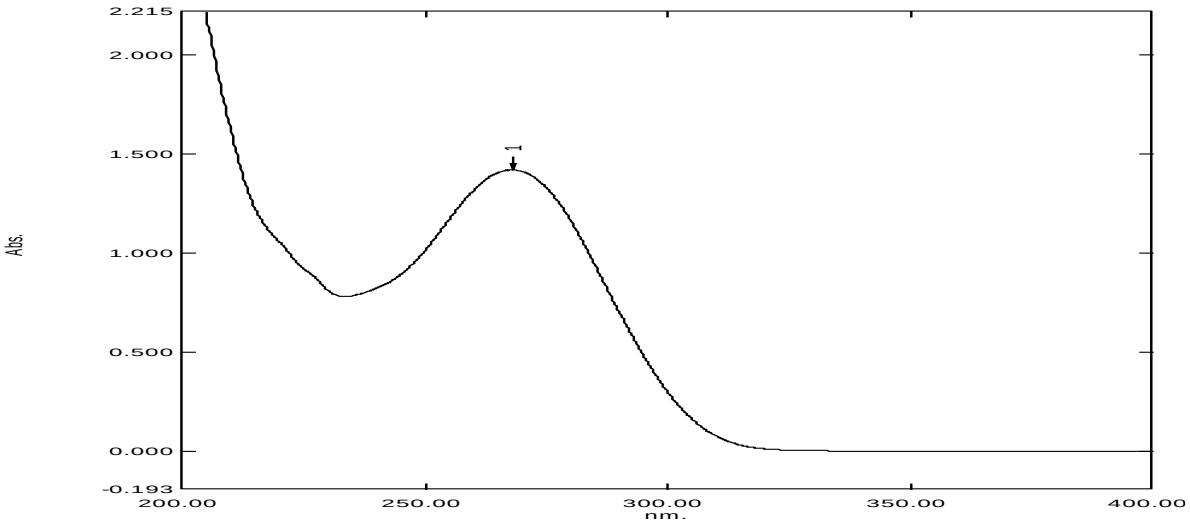
2. Aceclofenac 10Mcg Phosphate Buffer PH(7.4)



W.L.- 274.0 ABS.- 1.257

Fig.12: Lambda max of phosphate buffer pH(6.8)

3. Aceclofenac 10Mcg Phosphate Buffer PH(6.8)



W.L,- 267 ABS.- 1.061

Linearity and Calibration:

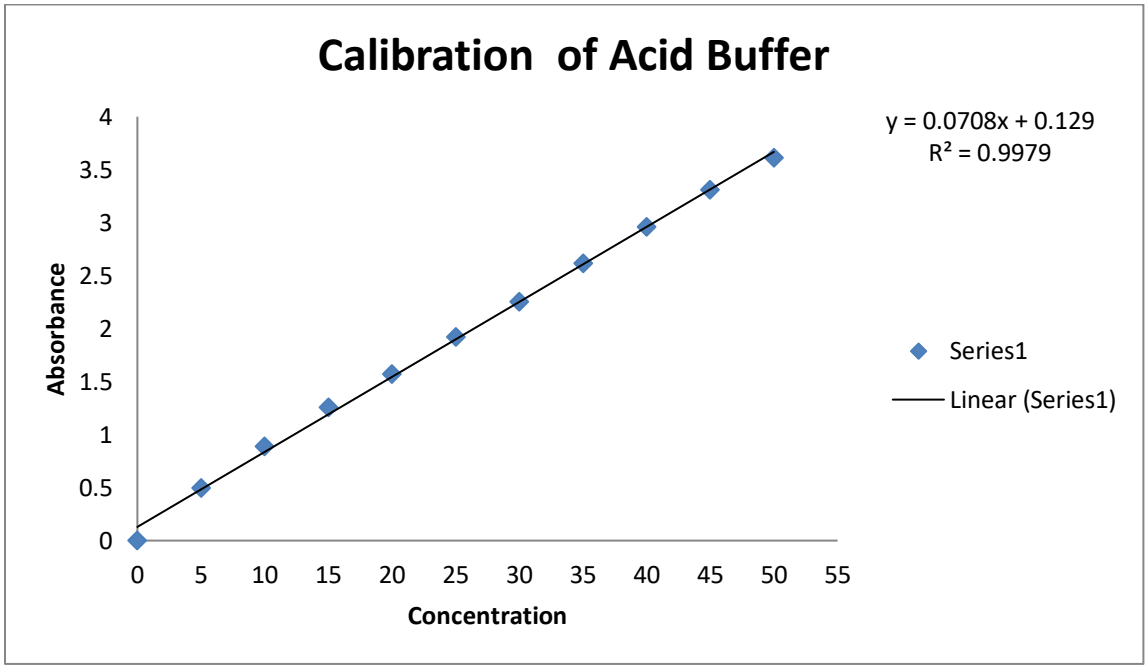
The linearity of the calibration curve was estimated by plotting the graph in between absorbance (nm) (y) versus concentration (µg/ml) (x) of Aceclofenac in the concentration range 5-50 µg/ml. A calibration curve was prepared by measure the absorbance at 266.5 nm, 276 nm, 268 nm.

Calibration of acid buffer pH(1.2):

Table.11: Calibration of acid buffer

CONC.	ABS.
0	0
5	0.495
10	0.889
15	1.258
20	1.571
25	1.922
30	2.251
35	2.613
40	2.959
45	3.311
50	3.612

Fig.13: Calibration of acid buffer

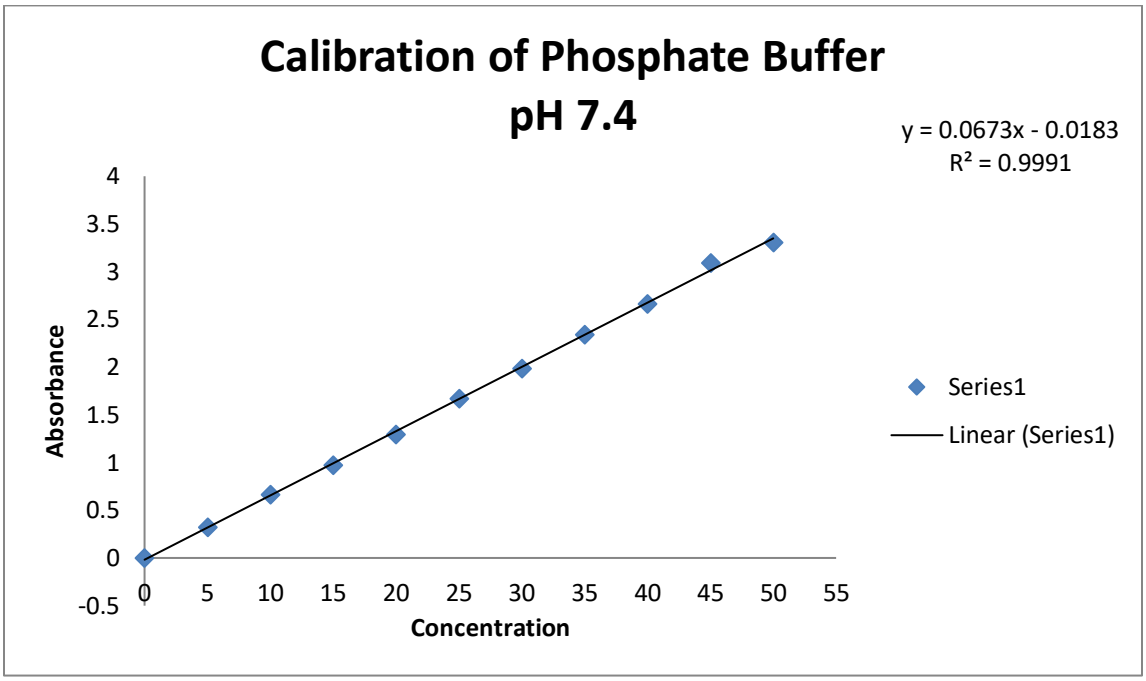


Calibration of Phosphate Buffer pH(7.4):

Table.12: Calibration of Phosphate Buffer pH(7.4)

CONC.	ABS.
0	0
5	0.322
10	0.666
15	0.974
20	1.294
25	1.671
30	1.987
35	2.342
40	2.661
45	3.093
50	3.308

Fig.14: Calibration of Phosphate Buffer pH(7.4)

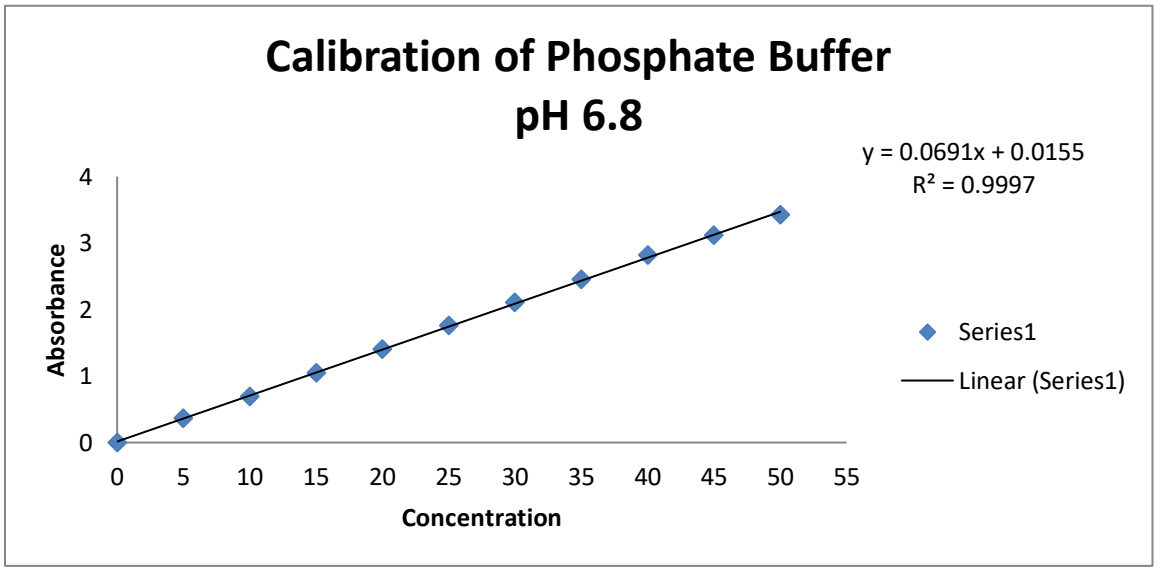


Calibration of Phosphate Buffer pH(6.8):

Table.13: Calibration of Phosphate Buffer pH(6.8)

CONC.	ABS.
0	0
5	0.362
10	0.694
15	1.049
20	1.406
25	1.754
30	2.104
35	2.448
40	2.812
45	3.117
50	3.427

Fig.15: Calibration of Phosphate Buffer pH(6.8)



Bulk density

The term bulk density refers to a measure used to describe a packing of particles. It is (gm/ml) and was determine using a balance and measuring cylinder. The results were given on the table.

TABLE.14: Bulk Density (F_1-F_6)

	BULK DENSITY			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	0.58	0.49	0.55	0.54	0.046	0.54 ± 0.046
F2	0.5	0.47	0.52	0.50	0.025	0.50 ± 0.025
F3	0.6	0.57	0.59	0.59	0.015	0.59 ± 0.015
F4	0.5	0.45	0.48	0.48	0.025	0.48 ± 0.025
F5	0.44	0.46	0.46	0.45	0.012	0.45 ± 0.012
F6	0.42	0.44	0.42	0.43	0.012	0.43 ± 0.012

TABLE.15: Bulk Density (F_7-F_{12})

	BULK DENSITY			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	0.44	0.47	0.43	0.45	0.021	0.45 ± 0.021
F8	0.45	0.48	0.41	0.45	0.035	0.45 ± 0.035
F9	0.44	0.47	0.41	0.44	0.030	0.44 ± 0.030
F10	0.42	0.44	0.47	0.44	0.025	0.44 ± 0.025
F11	0.41	0.4	0.45	0.42	0.026	0.42 ± 0.026
F12	0.46	0.49	0.42	0.46	0.035	0.46 ± 0.035

Tapped density

Tapped density is determined by placing a graduated cylinder containing same mass of powder used for B.D. on a mechanical tapper apparatus which is operated for a fixed number of taps until powder bed volume has reached a minimum. The results were given on the table.

Table.16: Tapped density (F_1-F_6)

	TAPPED DENSITY			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	0.58	0.51	0.62	0.57	0.056	0.57 ± 0.056
F2	0.57	0.47	0.52	0.52	0.050	0.52 ± 0.050
F3	0.71	0.57	0.59	0.62	0.076	0.62 ± 0.076
F4	0.56	0.45	0.48	0.50	0.057	0.50 ± 0.057
F5	0.5	0.46	0.46	0.47	0.023	0.47 ± 0.023
F6	0.6	0.44	0.42	0.49	0.099	0.49 ± 0.012

Table.17: Tapped density (F_7-F_{12})

	TAPPED DENSITY			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	0.49	0.47	0.43	0.46	0.031	0.46 ± 0.031
F8	0.52	0.48	0.49	0.50	0.021	0.50 ± 0.021
F9	0.5	0.47	0.52	0.50	0.025	0.50 ± 0.025
F10	0.5	0.44	0.55	0.50	0.055	0.50 ± 0.055
F11	0.46	0.4	0.49	0.45	0.046	0.45 ± 0.046
F12	0.5	0.49	0.52	0.50	0.015	0.50 ± 0.015

Carr's Index (CI):

Tapped and bulk density measurements can be used to estimate the carr's index of a material. The results were given on the table.

Table.18: Carr's Index (F_1-F_6)

	CARR'S INDEX			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	12.41	11.57	12.21	12.06	0.439	12.06% ± 0.439
F2	12.28	12.67	11.87	12.27	0.400	12.27% ± 0.400
F3	15.59	14.73	15.12	15.15	0.431	15.15% ± 0.431
F4	11.66	12.98	12.32	12.32	0.660	12.32% ± 0.660
F5	13.3	13.02	12.65	12.99	0.326	12.99% ± 0.326
F6	12	12.59	12.88	12.49	0.448	12.49% ± 0.448

Table.19: Carr's Index (F_7-F_{12})

	CARR'S INDEX			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	10.2	10.7	9.98	10.29	0.369	10.29% ± 0.369
F8	13.68	13.42	12.87	13.32	0.414	13.32% ± 0.414
F9	12.7	12.21	12.95	12.62	0.376	12.62% ± 0.376
F10	17.32	17.11	17.78	17.40	0.343	17.40% ± 0.343
F11	11.06	11.54	11.76	11.45	0.358	11.45% ± 0.358
F12	9.44	9.89	9.21	9.51	0.346	9.51% ± 0.346

Hausner's ratio (HR):

The results are given in the table.

Table.20: Hausner's ratio (F_1-F_6)

	HAUSNER'S RATIO			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	1.14	1.19	1.11	1.15	0.040	1.15 ± 0.040
F2	1.14	1.13	1.12	1.13	0.010	1.13 ± 0.010
F3	1.18	1.16	1.19	1.18	0.015	1.18 ± 0.015
F4	1.13	1.12	1.16	1.14	0.021	1.14 ± 0.021
F5	1.15	1.14	1.17	1.15	0.015	1.15 ± 0.015
F6	1.19	1.18	1.14	1.17	0.026	1.17 ± 0.026

Table.21: Hausner's ratio (F_7-F_{12})

	HAUSNER'S RATIO			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	1.11	1.14	1.17	1.14	0.030	1.14 ± 0.030
F8	1.15	1.16	1.19	1.17	0.021	1.17 ± 0.021
F9	1.13	1.11	1.17	1.14	0.031	1.14 ± 0.031
F10	1.2	1.19	1.14	1.18	0.032	1.18 ± 0.032
F11	1.12	1.15	1.16	1.14	0.021	1.14 ± 0.021
F12	1.1	1.14	1.16	1.13	0.031	1.13 ± 0.031

Angle of repose (Tan θ):

Angle of repose is the tan inverse of angle between height (h) of pile of powder and the radius (r) of the base of conical pile. Powder is carefully poured through funnel until the apex of conical pile just touches the tip of funnel. The results were given on the table.

Table.22: Angle of repose (F_1-F_6)

	ANGLE OF REPOSE (Ɵ)			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	29.28	30.14	29.28	29.57	0.497	29°57′ ± 0.497
F2	31.04	30.14	31.04	30.74	0.520	30°74′ ± 0.520
F3	29.28	28.07	28.07	28.47	0.699	28°47′ ± 0.699
F4	28.37	28.37	29.13	28.62	0.439	28°62′ ± 0.439
F5	29.05	28.17	29.05	28.76	0.508	28°76′ ± 0.508
F6	29.13	29.13	29.53	29.26	0.231	29°26′ ± 0.231

Table.23: Angle of repose (F_7-F_{12})

	ANGLE OF REPOSE (Ɵ)			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	29.53	29.13	29.53	29.40	0.231	29°40′ ± 0.231
F8	28.17	28.17	27.34	27.89	0.479	27°89′ ± 0.479
F9	30.38	30.38	29.53	30.10	0.491	30°10′ ± 0.491
F10	27.29	28.07	27.29	27.55	0.450	27°55′ ± 0.450
F11	29.05	29.05	28.17	28.76	0.508	28°76′ ± 0.508
F12	28.07	28.07	27.29	27.81	0.450	27°81′ ± 0.450

Hardness:

Tablet hardness has been defined as, the force required to break a tablet in a diametric compression test[81].Tablet hardness of all the formulations was measured using a Monsanto hardness tester. The results were given on the table.

Table.24: Hardness (F_1-F_6)

	Hardness			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	2.5	2	2.5	2.33	0.289	2.33 ± 0.289
F2	2	2.5	2.5	2.33	0.289	2.33 ± 0.289
F3	2.5	2.5	2	2.33	0.289	2.33 ± 0.289
F4	2	2	2.5	2.17	0.289	2.17 ± 0.289
F5	2	2.5	2	2.17	0.289	2.17 ± 0.289
F6	2.5	2	2	2.17	0.289	2.17 ± 0.289

Table.25: Hardness (F_7-F_{12})

	Hardness			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	2.5	2.5	2	2.33	0.289	2.33 ± 0.289
F8	2	2.5	2.5	2.33	0.289	2.33 ± 0.289
F9	2	2	2.5	2.17	0.289	2.17 ± 0.289
F10	2.5	2.5	2	2.33	0.289	2.33 ± 0.289
F11	2.5	2	2.5	2.33	0.289	2.33 ± 0.289
F12	2	2	2.5	2.17	0.289	2.17 ± 0.289

Thickness

The thickness of tablets was determined using a Digimatic vernier caliper. The results are shown in Table. The results were given on the table.

Table.26: Thickness (F_1-F_6)

	THICKNESS			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	3.64	3.63	3.65	3.64	0.010	3.64 ± 0.010
F2	3.64	3.65	3.66	3.65	0.010	3.65 ± 0.010
F3	3.73	3.75	3.74	3.74	0.010	3.74 ± 0.010
F4	3.73	3.74	3.73	3.73	0.006	3.73 ± 0.006
F5	3.63	3.64	3.63	3.63	0.006	3.63 ± 0.006
F6	3.67	3.67	3.66	3.67	0.006	3.67 ± 0.006

Table.27: Thickness (F_7-F_{12})

	THICKNESS			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	3.74	3.75	3.75	3.75	0.006	3.75 ± 0.006
F8	3.77	3.76	3.78	3.77	0.010	3.77 ± 0.010
F9	3.63	3.64	3.64	3.64	0.006	3.64 ± 0.006
F10	3.65	3.65	3.66	3.65	0.006	3.65 ± 0.006
F11	3.7	3.69	3.69	3.69	0.006	3.69 ± 0.006
F12	3.8	3.81	3.8	3.80	0.006	3.80 ± 0.006

Friability test

The friability of tablets was determined using Roche Friabilator. It is express in percentage (%). The results were given on the table.

Table.28: Friability test (F_1-F_6)

	FRIABILITY			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	0.56	0.82	0.91	0.76	0.182	0.76 % ± 0.182
F2	0.67	0.49	0.77	0.64	0.142	0.64% ± 0.142
F3	0.96	0.87	0.65	0.83	0.159	0.83 % ± 0.159
F4	0.78	0.69	0.93	0.80	0.121	0.80 % ± 0.121
F5	0.54	0.83	0.62	0.66	0.150	0.66% ± 0.150
F6	0.59	0.74	0.95	0.76	0.181	0.76 % ± 0.181

Table.29: Friability test (F_7-F_{12})

	FRIABILITY			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	0.98	0.65	0.53	0.72	0.233	0.72% ± 0.233
F8	0.56	0.91	0.87	0.78	0.192	0.78 %± 0.192
F9	0.48	0.87	0.9	0.75	0.234	0.75 %± 0.234
F10	0.76	0.86	0.59	0.74	0.137	0.74 %± 0.137
F11	0.74	0.82	0.67	0.74	0.075	0.74 %± 0.075
F12	0.87	0.93	0.89	0.90	0.031	0.90 %± 0.031

Weight Variation Test:

Twenty tablets were selected randomly from each batch and weighed individually on electronic balance. The individual weighed is then compared with average weight for the weight variations. The results were given on the table.

Table.30: Weight Variation Test (F_1-F_6)

	WEIGHT VARIATION			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	192.8	192.1	193.1	192.67	0.513	192.67 ± 0.513
F2	196.5	197.1	195.9	196.50	0.600	196.50 ± 0.600
F3	196.2	195.7	196.6	196.17	0.451	196.17 ± 0.451
F4	195.7	196.1	195.3	195.70	0.400	195.70 ± 0.400
F5	199.05	199.2	198.9	199.05	0.150	199.05 ± 0.150
F6	200.2	199.8	200.5	200.17	0.351	200.15 ± 0.351

Table.31: Weight Variation Test (F_7-F_{12})

	WEIGHT VARIATION			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	198.05	198.55	197.83	198.14	0.369	198.14 ± 0.369
F8	199.9	199.1	200.6	199.87	0.751	199.87 ± 0.751
F9	198.65	199.83	197.1	198.53	1.369	198.53 ± 1.369
F10	197.7	196.8	198.9	197.80	1.054	197.80 ± 1.054
F11	198.2	197.8	198.8	198.27	0.503	198.27 ± 0.503
F12	196.45	197.1	196.02	196.52	0.544	196.52 ± 0.544

Drug Content:

Two tablets were weighed individually and powdered. . The amount of drug present in each tablet was determined spectrophotometrically at 268 nm using UV–spectrophotometer. The results were given on the table.

Table.32: Drug Content (F_1-F_6)

	DRUG CONTENT			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F1	96.78	94.87	96.38	96.01	1.007	96.01 ± 1.007
F2	94.53	96.55	98.37	96.48	1.921	96.48 ± 1.921
F3	98.36	96.56	99.53	98.15	1.496	98.15 ± 1.496
F4	97.52	98.46	95.27	97.08	1.639	97.08 ± 1.639
F5	96.66	97.78	94.67	96.37	1.575	96.37 ± 1.575
F6	99.02	95.38	98.53	97.64	1.975	97.64 ± 1.975

Table.33: Drug Content (F_7-F_{12})

	DRUG CONTENT			AVERAGE	STD DEV	MEAN DEVIATION
	T1	T2	T3			
F7	98.65	99.54	96.38	98.19	1.629	98.19 ± 1.629
F8	99.35	96.77	94.87	97.00	2.249	97.00 ± 2.249
F9	95.67	98.57	98.15	97.46	1.567	97.46 ± 1.567
F10	97.52	94.78	95.27	95.86	1.461	95.86 ± 1.461
F11	98.47	96.62	97.64	97.58	0.927	97.58 ± 0.927
F12	98.89	96.83	95.38	97.03	1.764	97.03 ± 1.764

Invitro Drug release studies of Core Tablets:

The Invitro release of aceclofenac was carried out by using USP apparatus I (Paddle) method. The results were given on the table.

Table.34: Invitro Drug release of Core Tablets (F_1-F_4)

TIME	F1	F2	F3	F4
0	0	0	0	0
1	0.9	3.05	2.9	3.53
2	2.7	4.2	4.1	4.52
3	38.6	17.6	15.7	17.5
4	39.9	34.8	25.5	26.01
5	44.3	38.7	28.12	30.31
6	53.03	42.9	33.18	35.8
8	56.03	45.6	34.9	42.01
10	59.02	56.5	37.7	47.3
12	74.58	62.4	46.68	60.62
24	94.01	82.47	64.54	84

Fig.16: Invitro Drug release of Core Tablets (F_1-F_4)

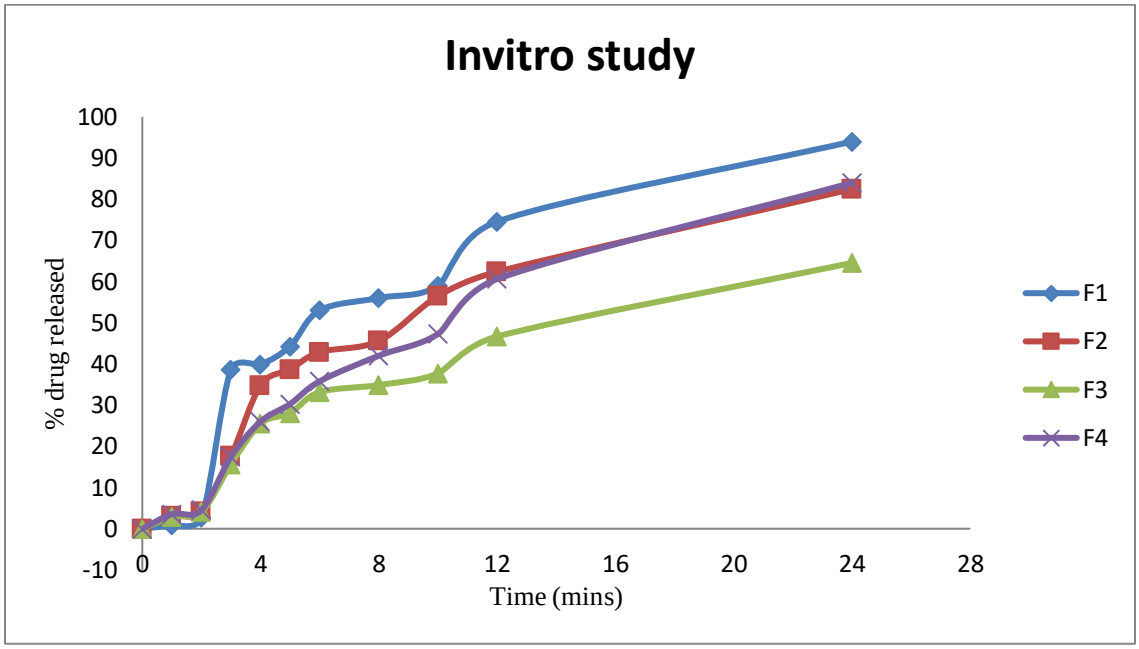


Table.35: Invitro Drug release of Core Tablets (F_5-F_8)

TIME	F5	F6	F7	F8
0	0	0	0	0
1	3.05	0.225	0.72	1.1
2	14.6	0.902	0.8	2.3
3	33	22.2	27.1	28.7
4	57.1	28.08	31.06	38.7
5	82.8	32.5	41.54	44.19
6	85	57.4	46.92	49.09
8	85.8	58.2	48.65	50.72
10	86.63	63.1	49.77	54.91
12	88.85	66.4	52.12	64.4
24	89.45	72.5	69.23	82.46

Fig.17: Invitro Drug release of Core Tablets (F_5-F_8)

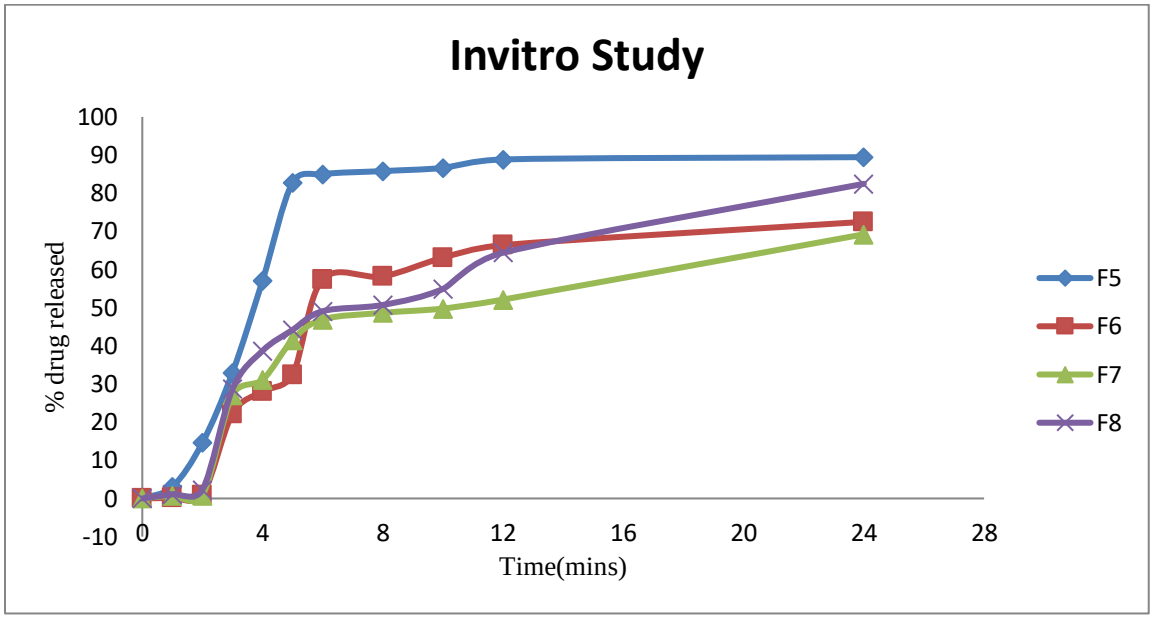
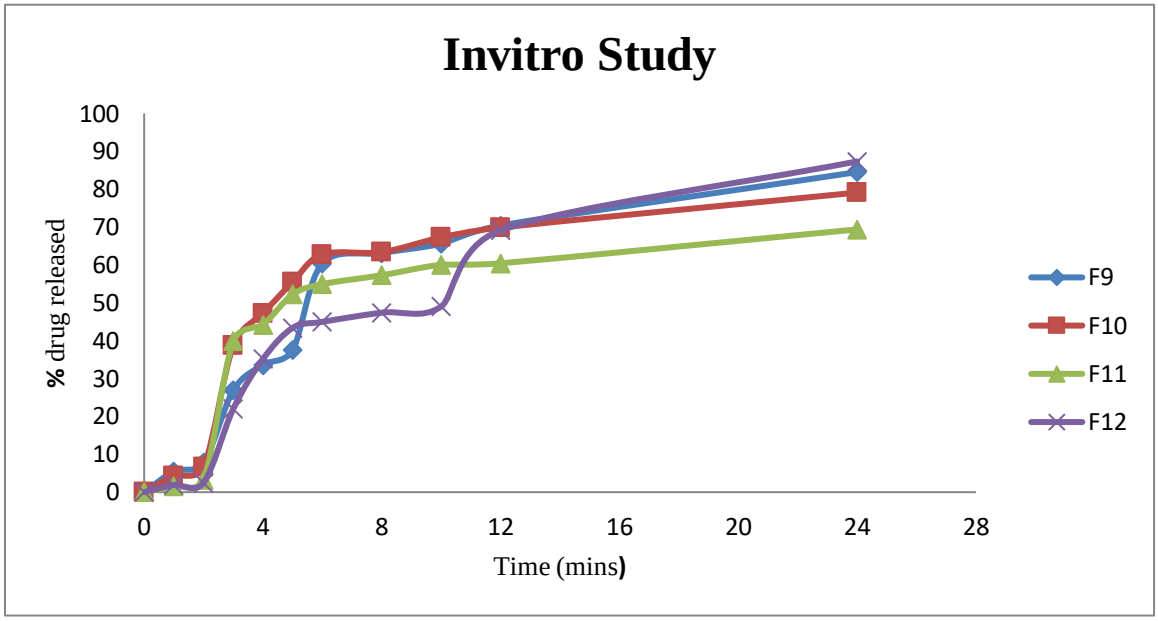


Table.36: Invitro Drug release of Core Tablets (F_9-F_{12})

TIME	F9	F10	F11	F12
0	0	0	0	0
1	5.5	4.25	1.6	1.9
2	7.9	6.64	3.3	2.5
3	26.9	38.71	39.9	22.01
4	33.63	47.24	44.24	35.2
5	37.62	55.49	52.23	43.4
6	60.42	62.8	54.94	44.99
8	63.18	63.4	57.3	47.42
10	65.63	67.3	60.05	49.05
12	70.44	69.89	60.45	69.14
24	84.53	79.12	69.4	87.36

Fig.18: Invitro Drug release of Core Tablets (F_9-F_{12})



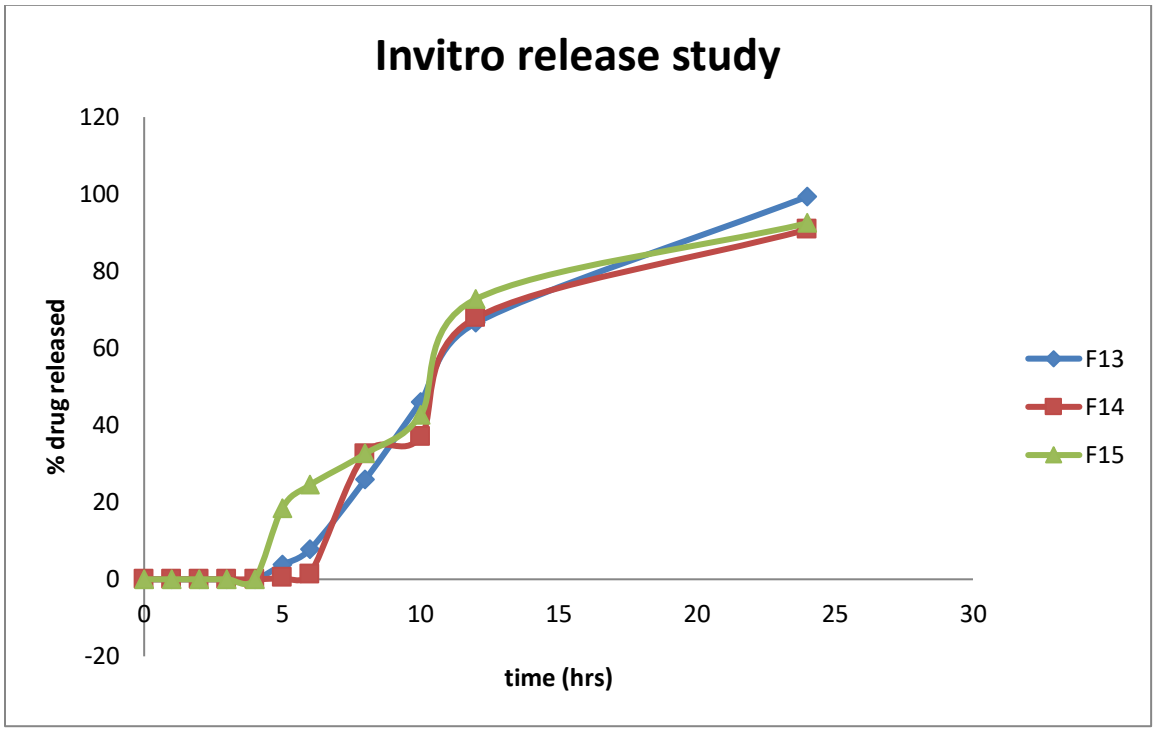
Invitro Drug release of Coated Tablets:

Based on Invitro release of core tablet the formulations of F_1, F_5 & F_9 were selected for a coating a core tablet**.** The release of coated tablet was showed on table36.

Table.36: Invitro Drug release of Coated Tablets (F_{13}-F_{15})

TIME	F13	F14	F15
0	0	0	0
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	3.78	0.36	18.43
6	7.76	1.33	24.47
8	25.83	32.57	32.59
10	45.96	36.91	42.58
12	66.51	67.87	72.72
24	99.34	90.8	92.42

Fig.19: Invitro Drug release of Coated Tablets (F_{13}-F_{15})



Release Kinetics study:

Fig.20: Release Kinetics of Formulation 1

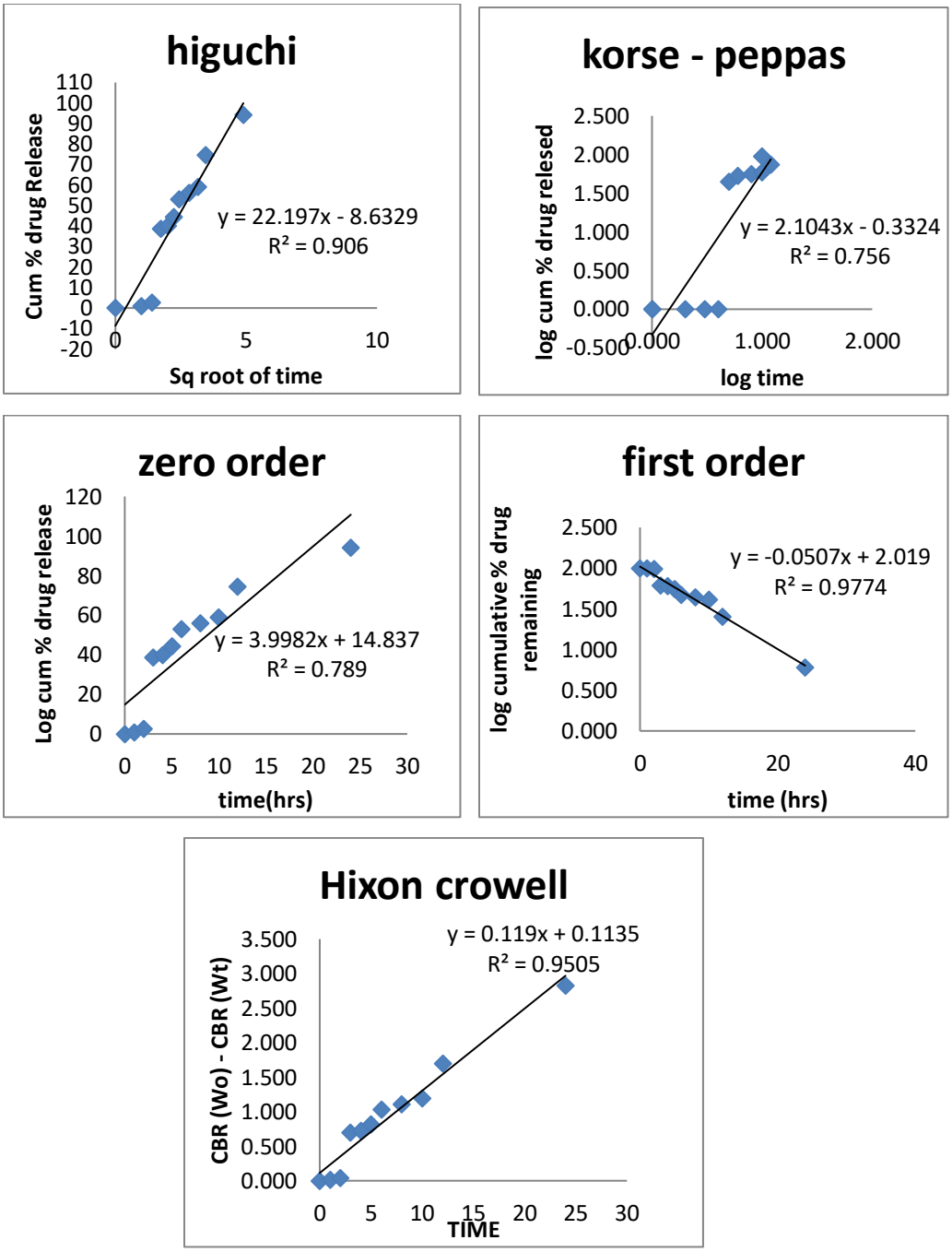


Fig.21: Release Kinetics of Formulation 2

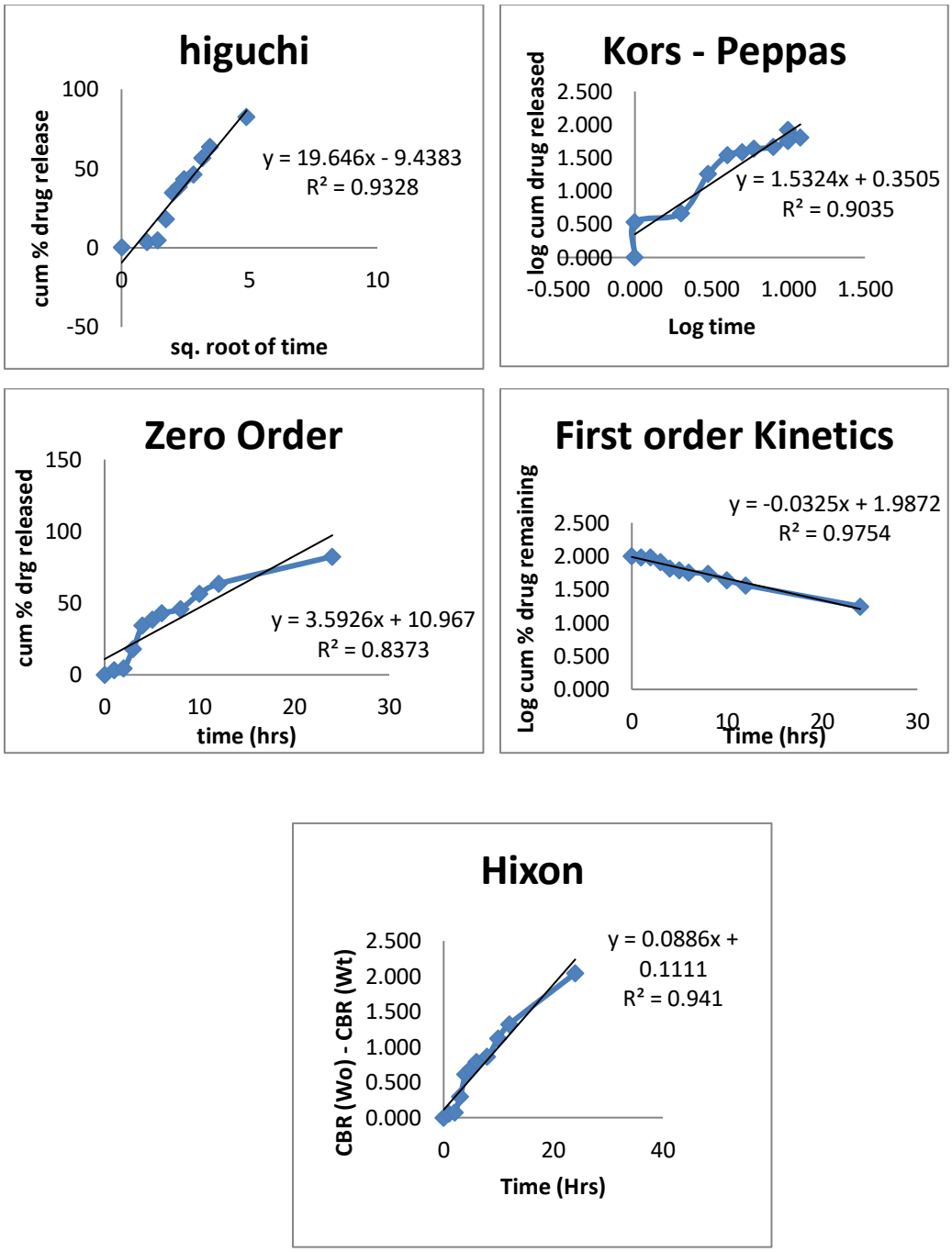


Fig.22: Release Kinetics of Formulation 3

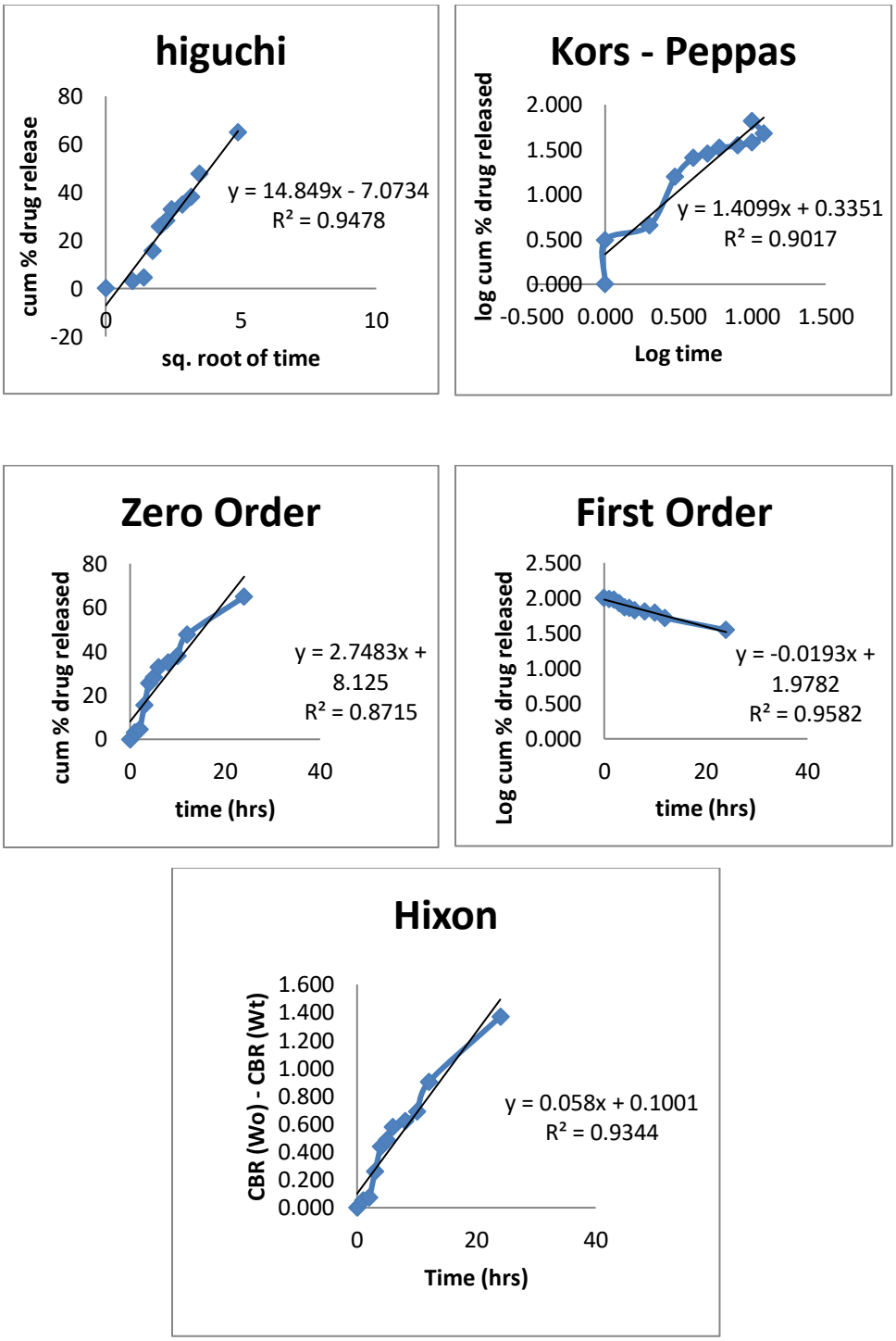


Fig.23: Release Kinetics of Formulation 4

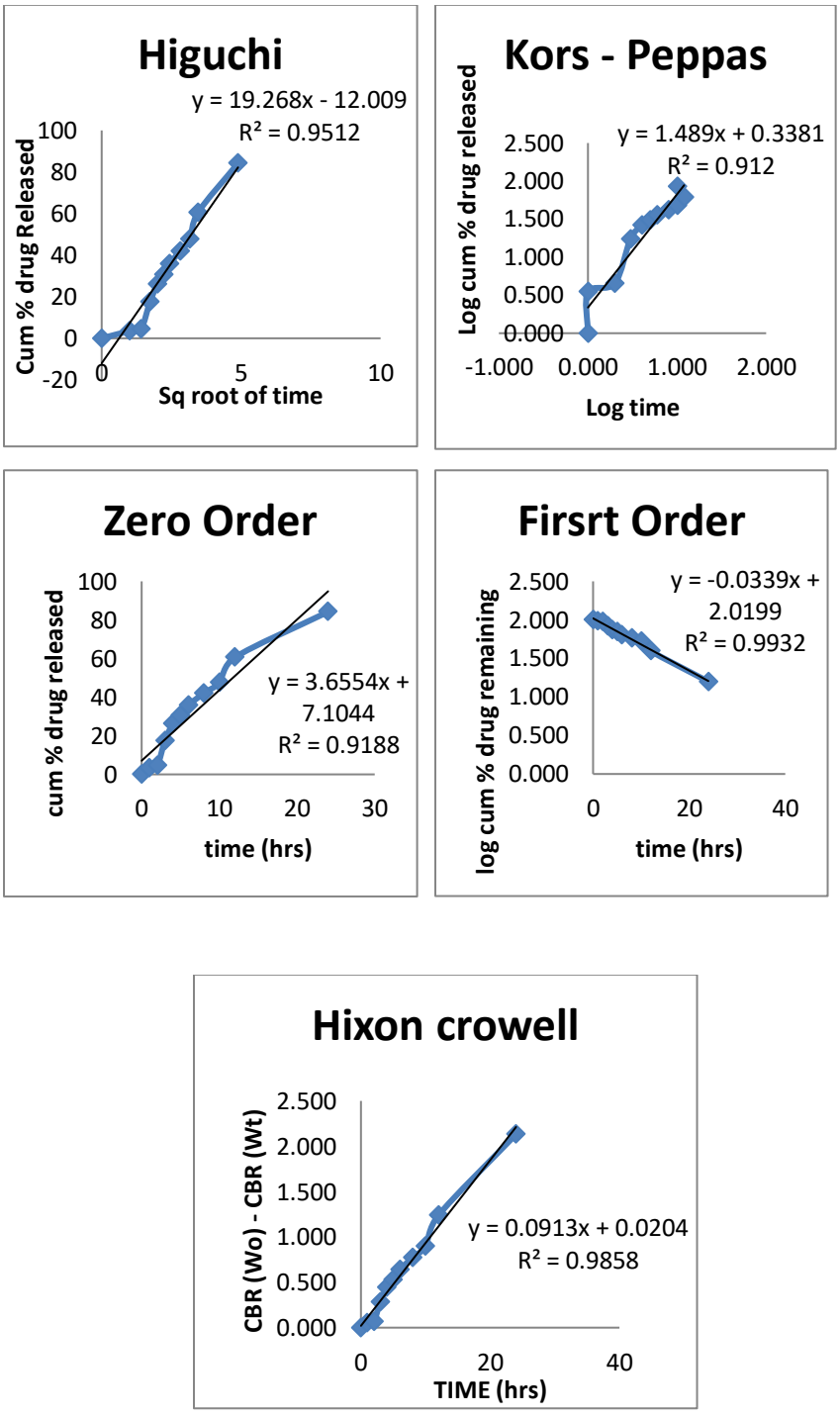
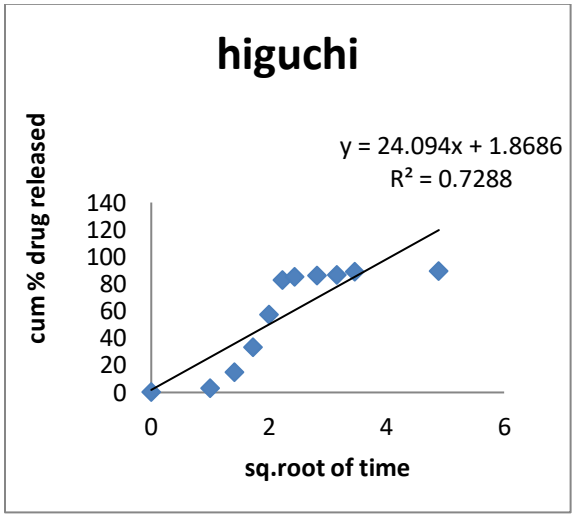
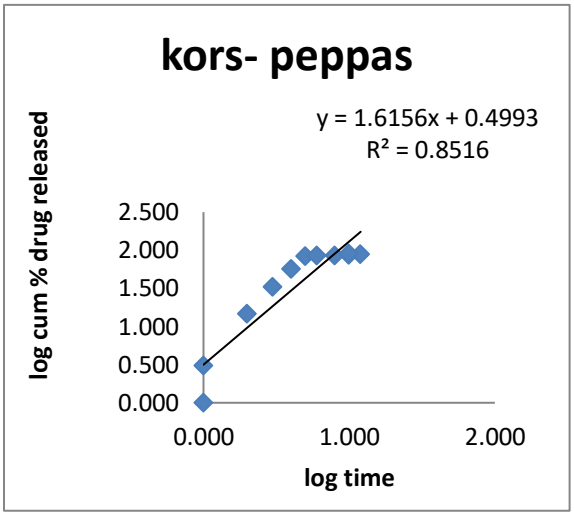
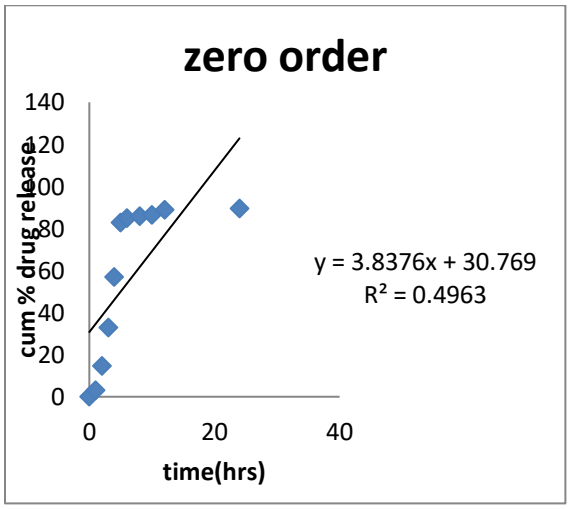
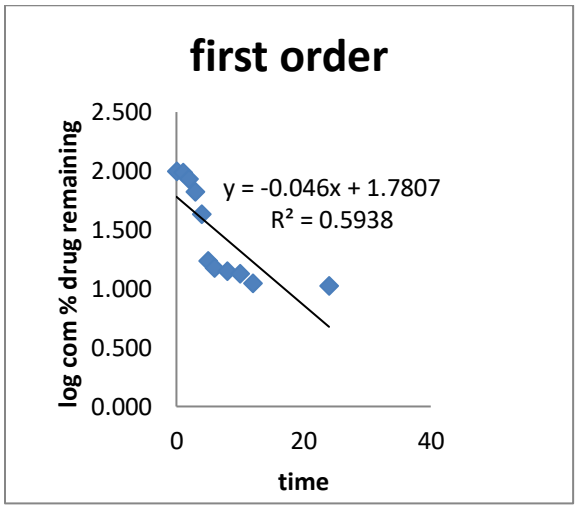


Fig.24: Release Kinetics of Formulation 5









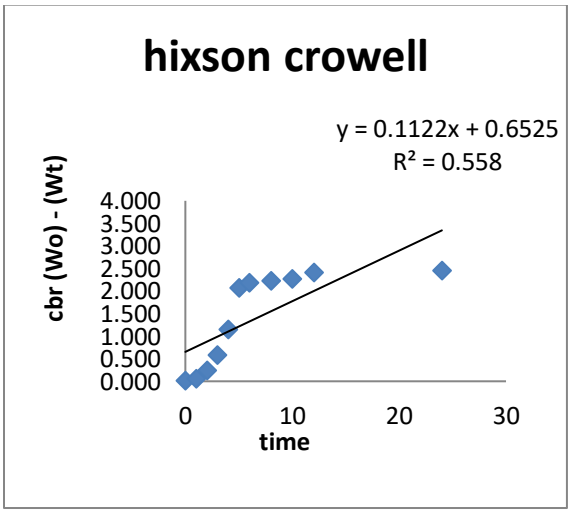
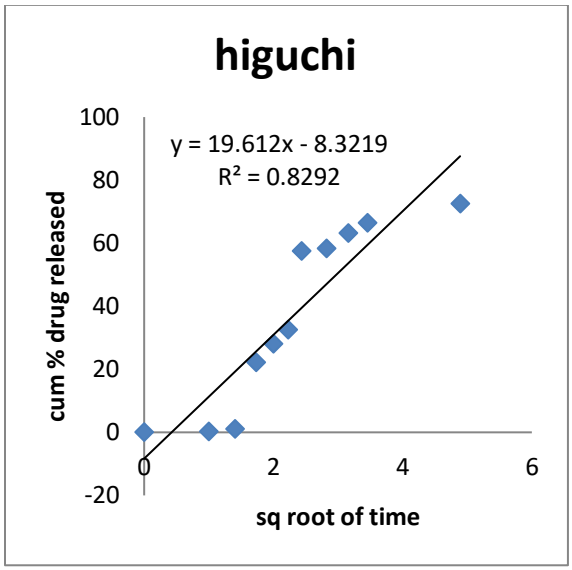
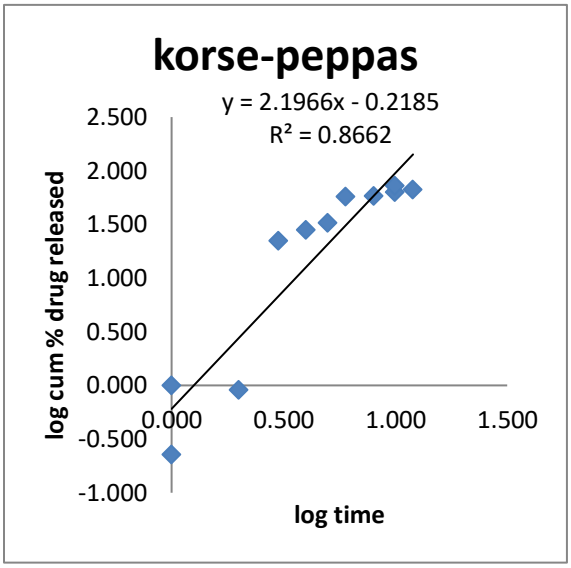
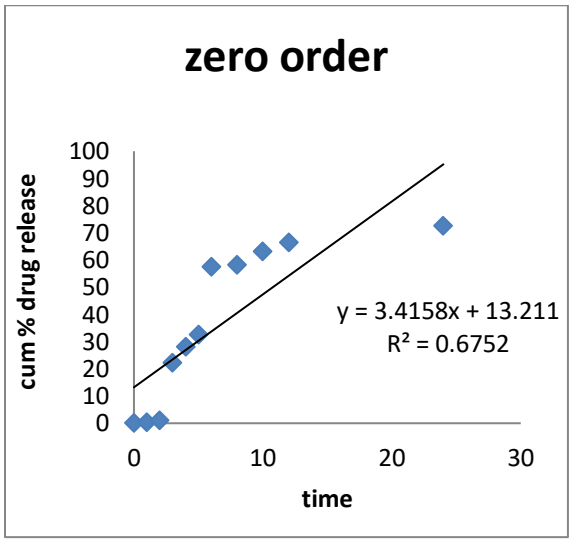
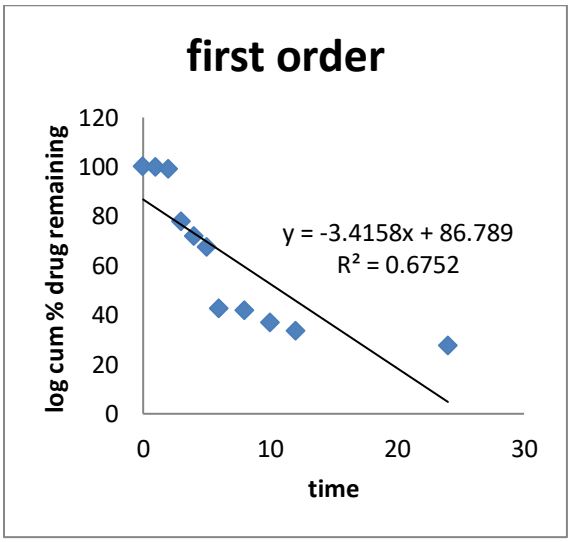


Fig.25: Release Kinetics of Formulation 6









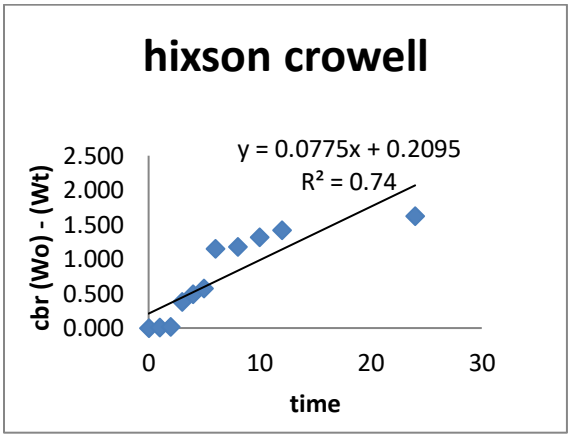


Fig.26: Release Kinetics of Formulation 7

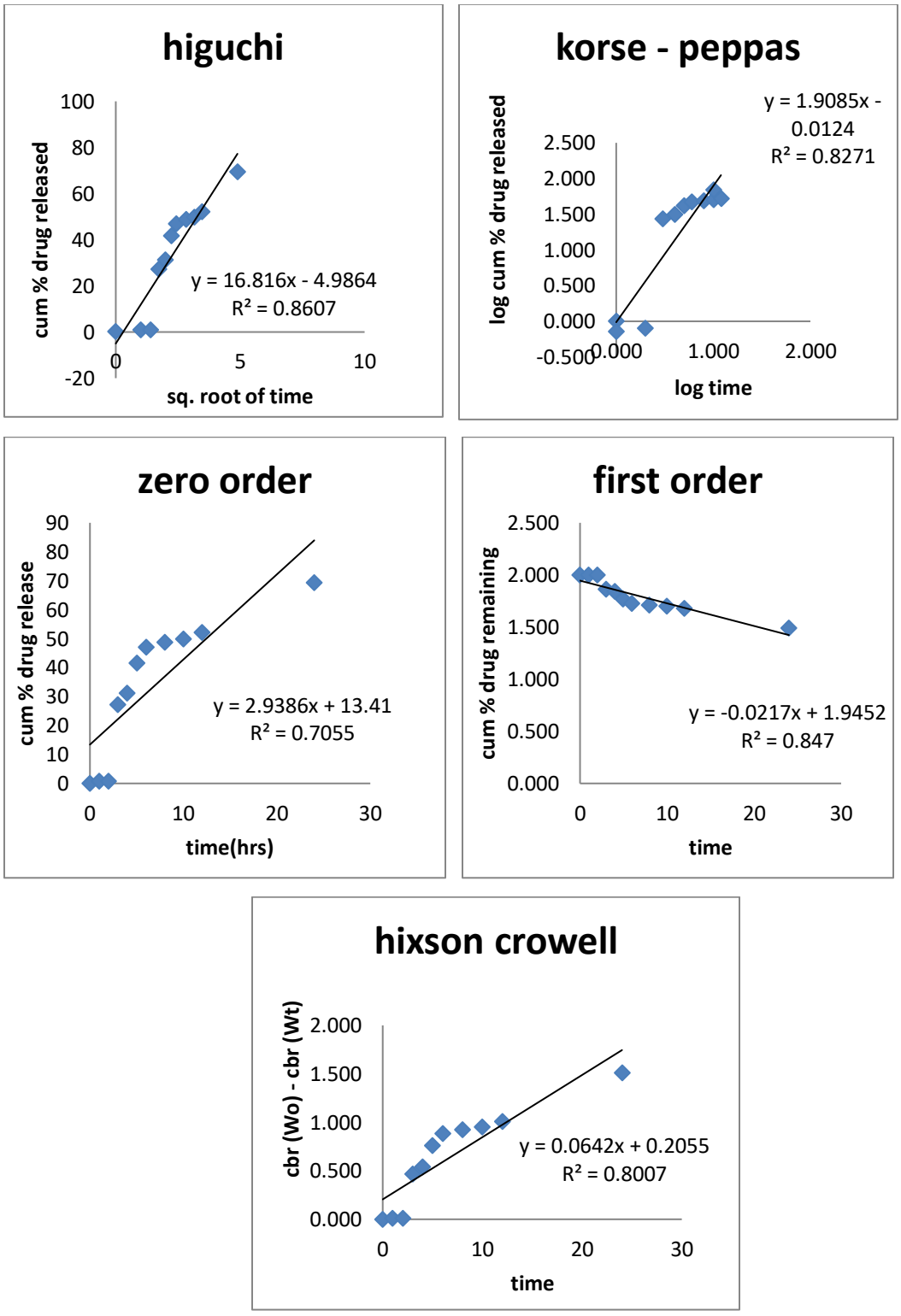


Fig.27: Release Kinetics of Formulation 8

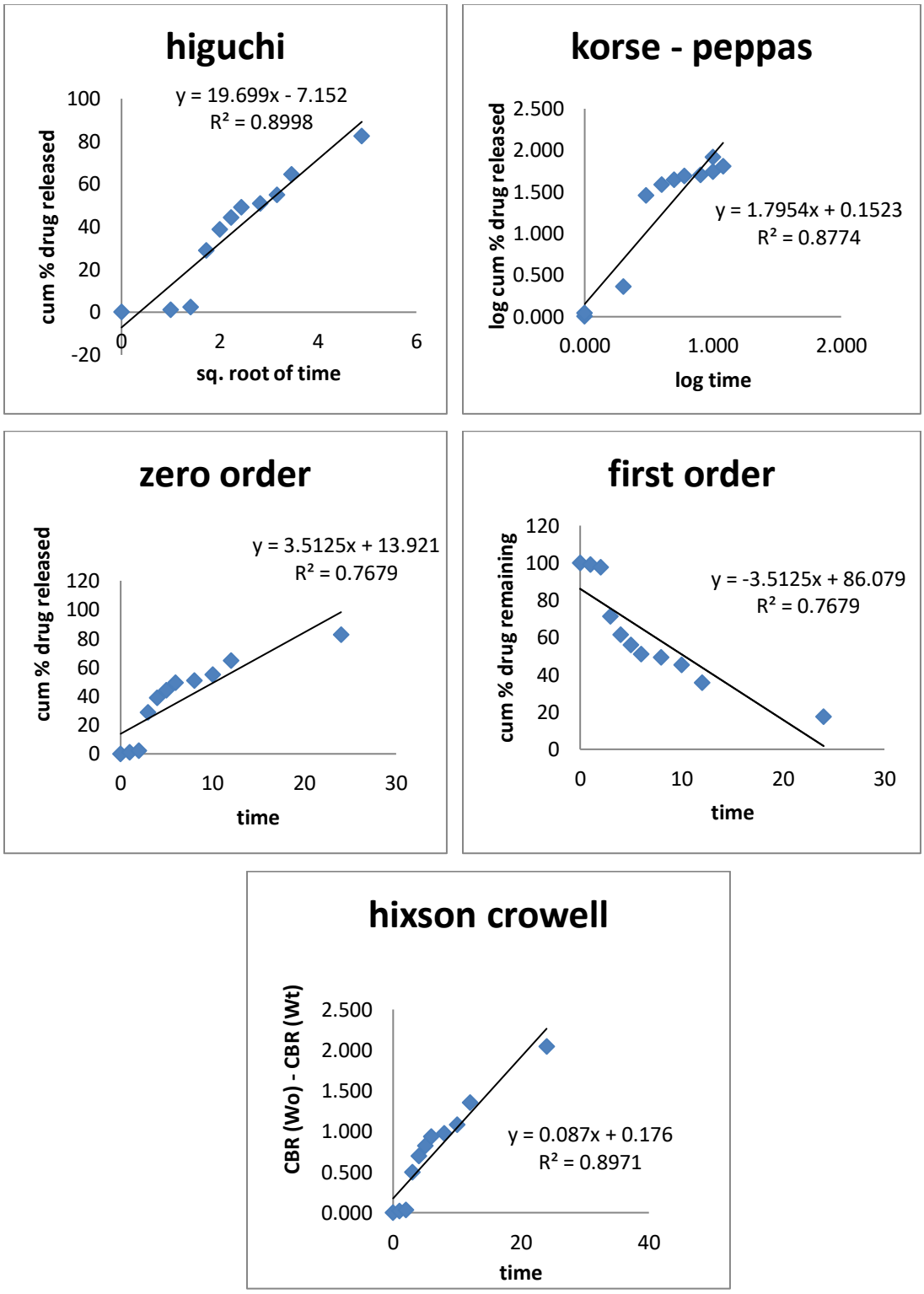
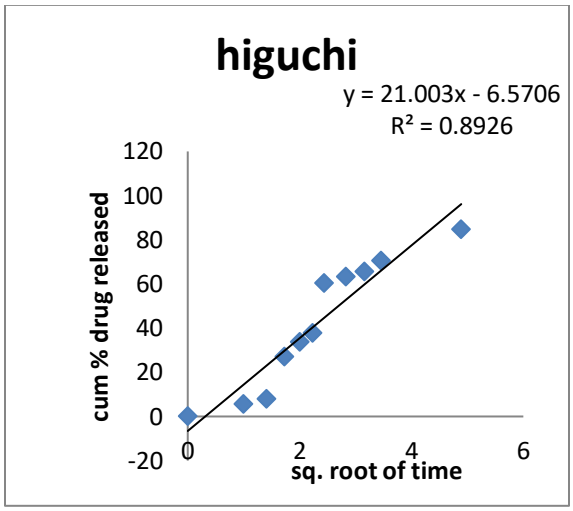
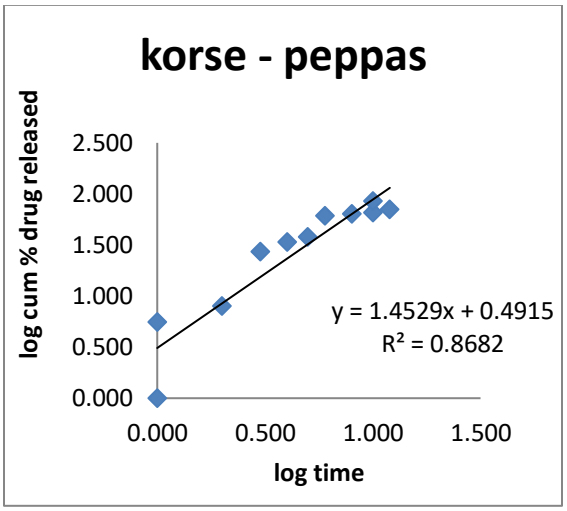
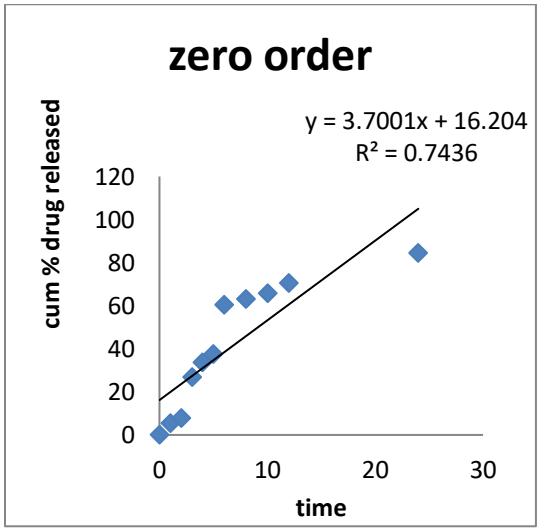
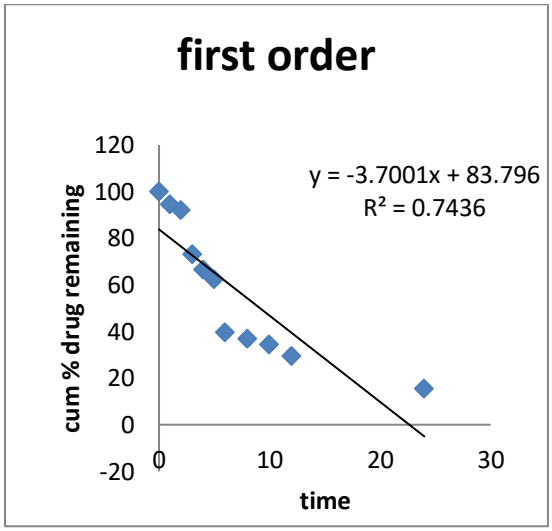


Fig.28: Release Kinetics of Formulation9









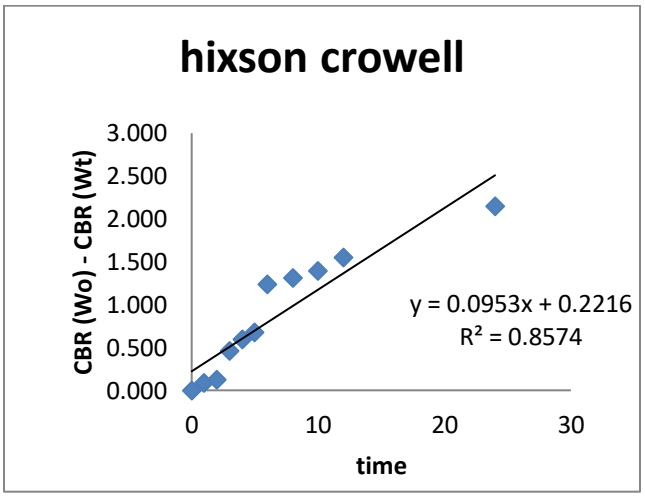
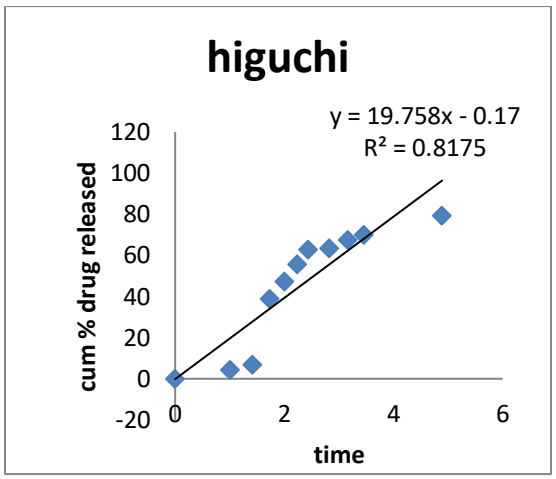
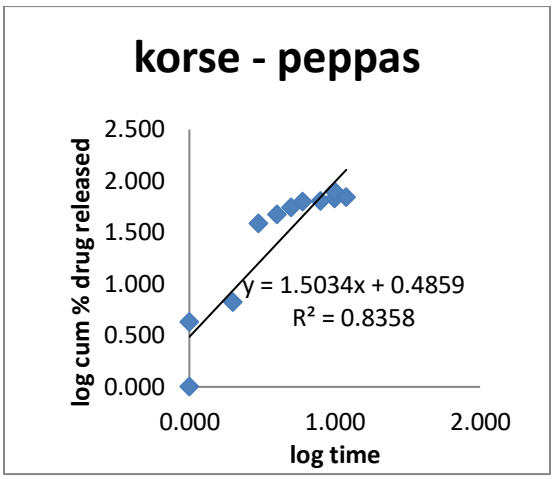
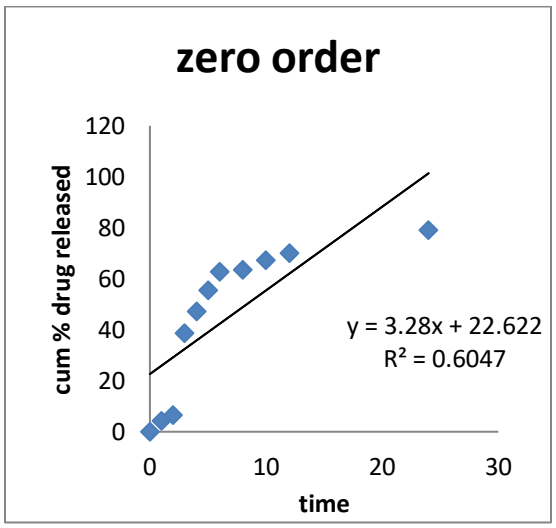
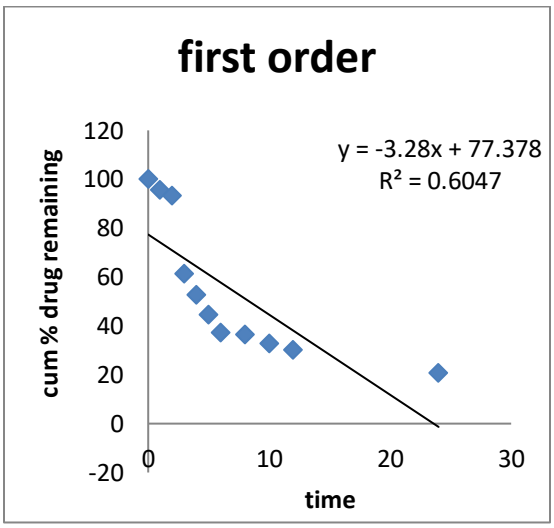


Fig.29: Release Kinetics of Formulation 10









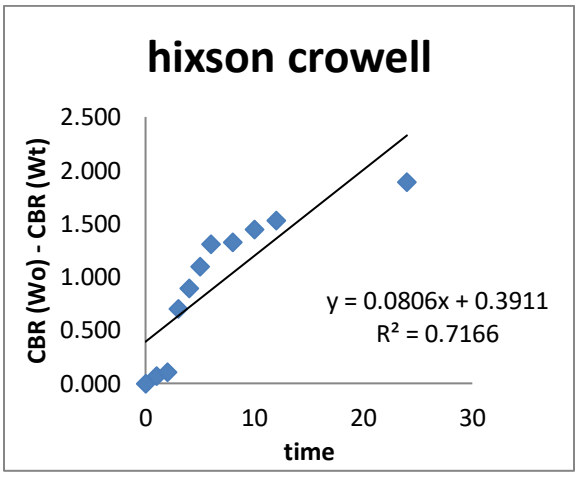
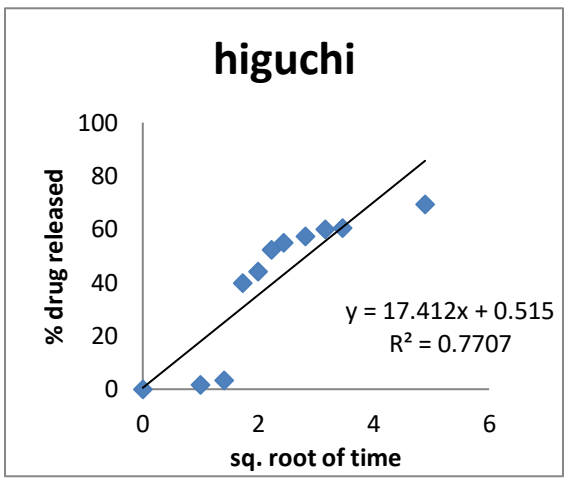
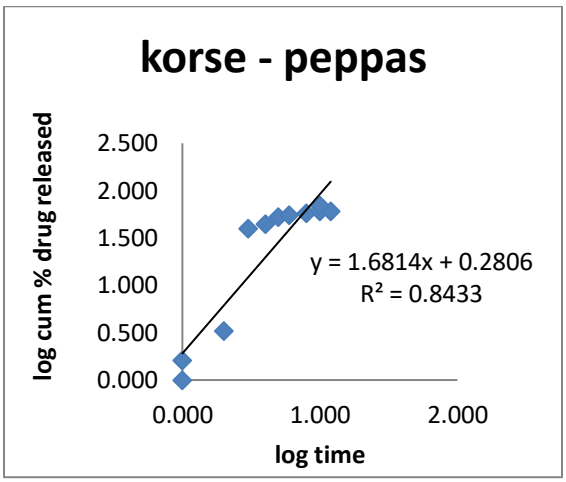
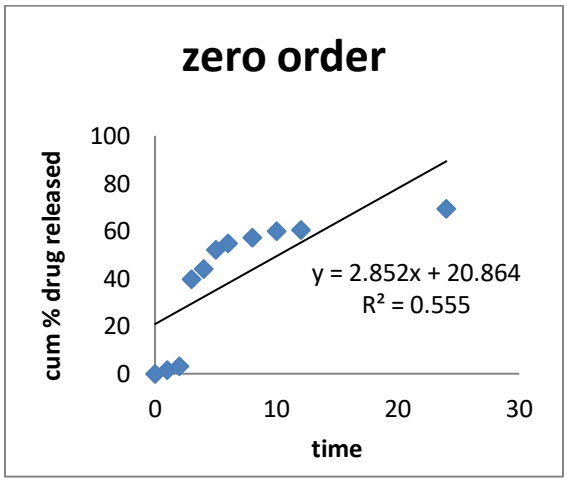
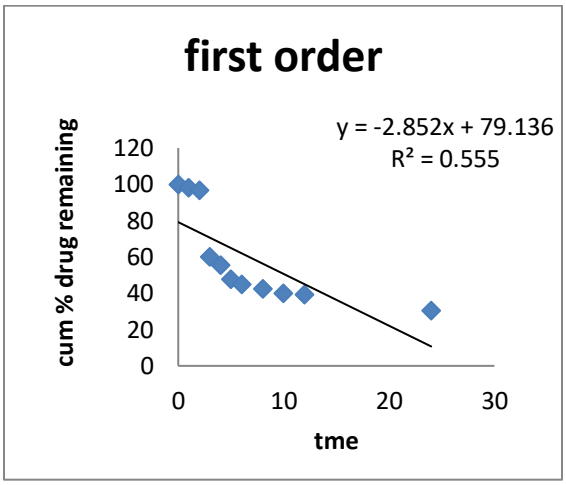


Fig.30: Release Kinetics of Formulation 11









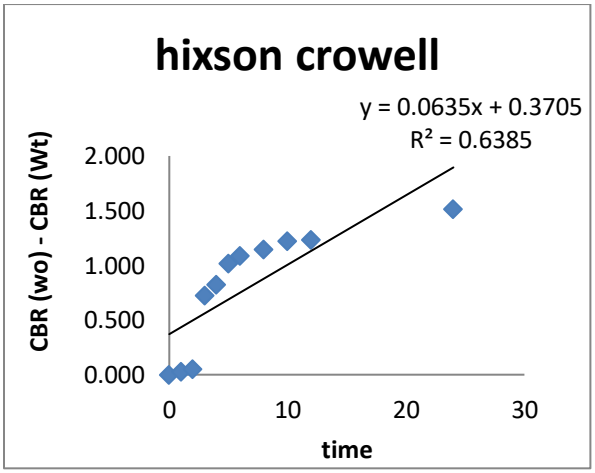
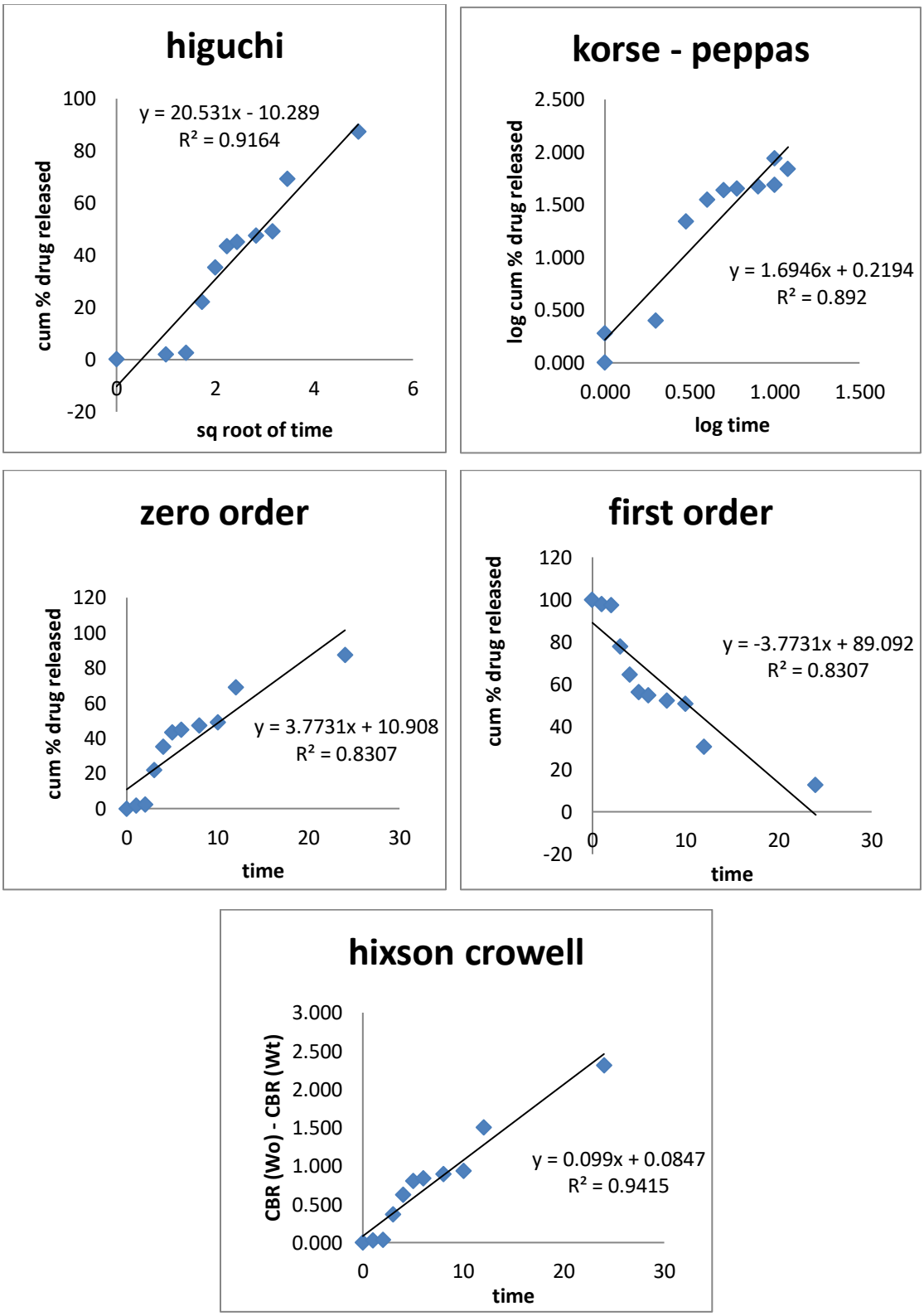


Fig.31: Release Kinetics of Formulation12



Release Kinetics of Coated Tablets:

Table.37: Release Kinetics of F_{13}

F_{13}									
Time (Hr)	**cumulative % drug released**	**% drug remaining**	**Square root time**	**log Cumu % drug remaining**	**log time**	**log Cumu % drug released**	**% Drug released**	**Cube Root of % drug Remaining(Wt)**	**Wo-Wt**
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	0	100	1.000	2.000	0.000	0.000	0.00	4.642	0.000
2	0	100	1.414	2.000	0.301	0.000	0	4.642	0.000
3	0	100	1.732	2.000	0.477	0.000	0	4.642	0.000
4	0	100	2.000	2.000	0.602	0.000	0	4.642	0.000
5	3.78	96.22	2.236	1.983	0.699	0.577	3.78	4.582	0.060
6	7.76	92.24	2.449	1.965	0.778	0.890	3.98	4.518	0.124
8	25.83	74.17	2.828	1.870	0.903	1.412	18.07	4.202	0.440
10	45.96	54.04	3.162	1.733	1.000	1.662	20.13	3.781	0.861
12	66.51	33.49	3.464	1.525	1.079	1.823	20.55	3.223	1.419
24	99.34	0.66	4.899	-0.180	1.000	1.997	32.83	0.871	3.771

Table.38: Release Kinetics of F_{14}

F_{14}									
Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	0	100	1.000	2.000	0.000	0.000	0.00	4.642	0.000
2	0	100	1.414	2.000	0.301	0.000	0	4.642	0.000
3	0	100	1.732	2.000	0.477	0.000	0	4.642	0.000
4	0	100	2.000	2.000	0.602	0.000	0	4.642	0.000
5	0.36	99.64	2.236	1.998	0.699	-0.444	0.36	4.636	0.006
6	1.33	98.67	2.449	1.994	0.778	0.124	0.97	4.621	0.021
8	32.57	67.43	2.828	1.829	0.903	1.513	31.24	4.070	0.572
10	36.91	63.09	3.162	1.800	1.000	1.567	4.34	3.981	0.661
12	67.87	32.13	3.464	1.507	1.079	1.832	30.96	3.179	1.463
24	90.8	9.2	4.899	0.964	1.000	1.958	22.93	2.095	2.547

Table.39: Release Kinetics of F_{15}

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	0	100	1.000	2.000	0.000	0.000	0.00	4.642	0.000
2	0	100	1.414	2.000	0.301	0.000	0	4.642	0.000
3	0	100	1.732	2.000	0.477	0.000	0	4.642	0.000
4	0	100	2.000	2.000	0.602	0.000	0	4.642	0.000
5	18.43	81.57	2.236	1.912	0.699	1.266	18.43	4.337	0.305
6	24.47	75.53	2.449	1.878	0.778	1.389	6.04	4.227	0.415
8	32.59	67.41	2.828	1.829	0.903	1.513	8.12	4.070	0.572
10	42.58	57.42	3.162	1.759	1.000	1.629	9.99	3.858	0.784
12	72.72	27.28	3.464	1.436	1.079	1.862	30.14	3.010	1.632
24	92.42	7.58	4.899	0.880	1.000	1.966	19.7	1.964	2.678

Fig.32: Release Kinetics of Coated Tablet F13

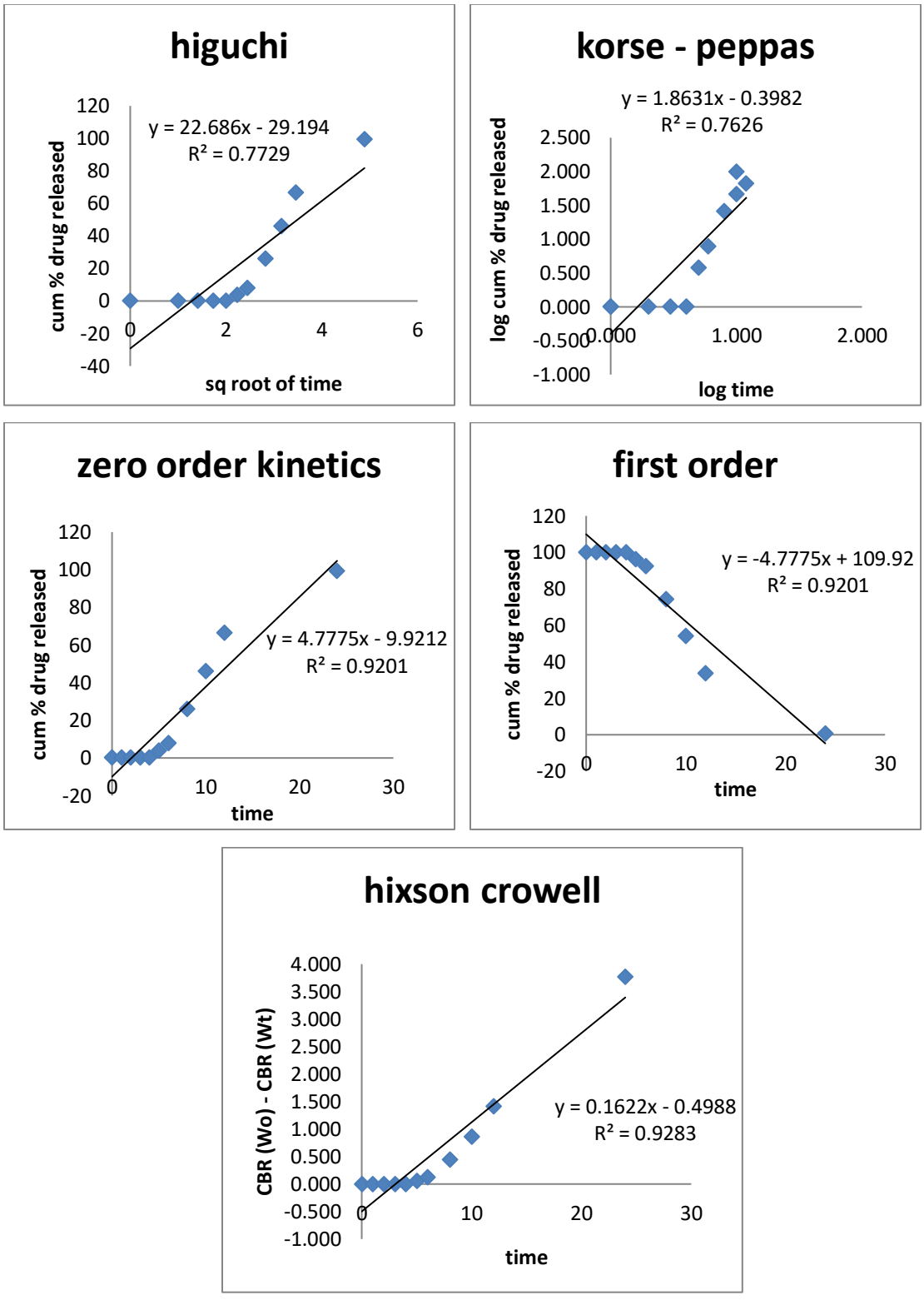


Fig.33: Release Kinetics of Coated Tablet F14

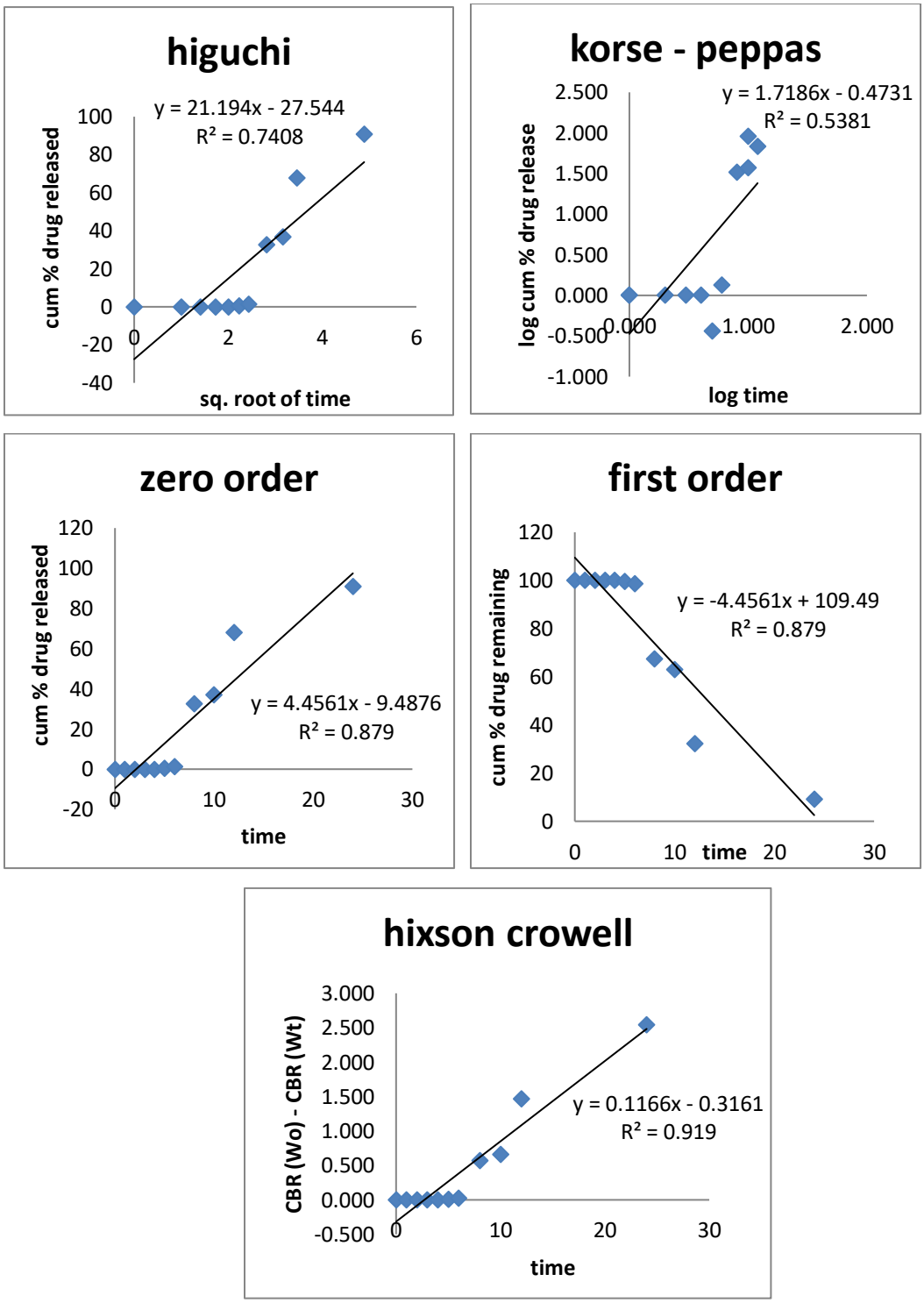
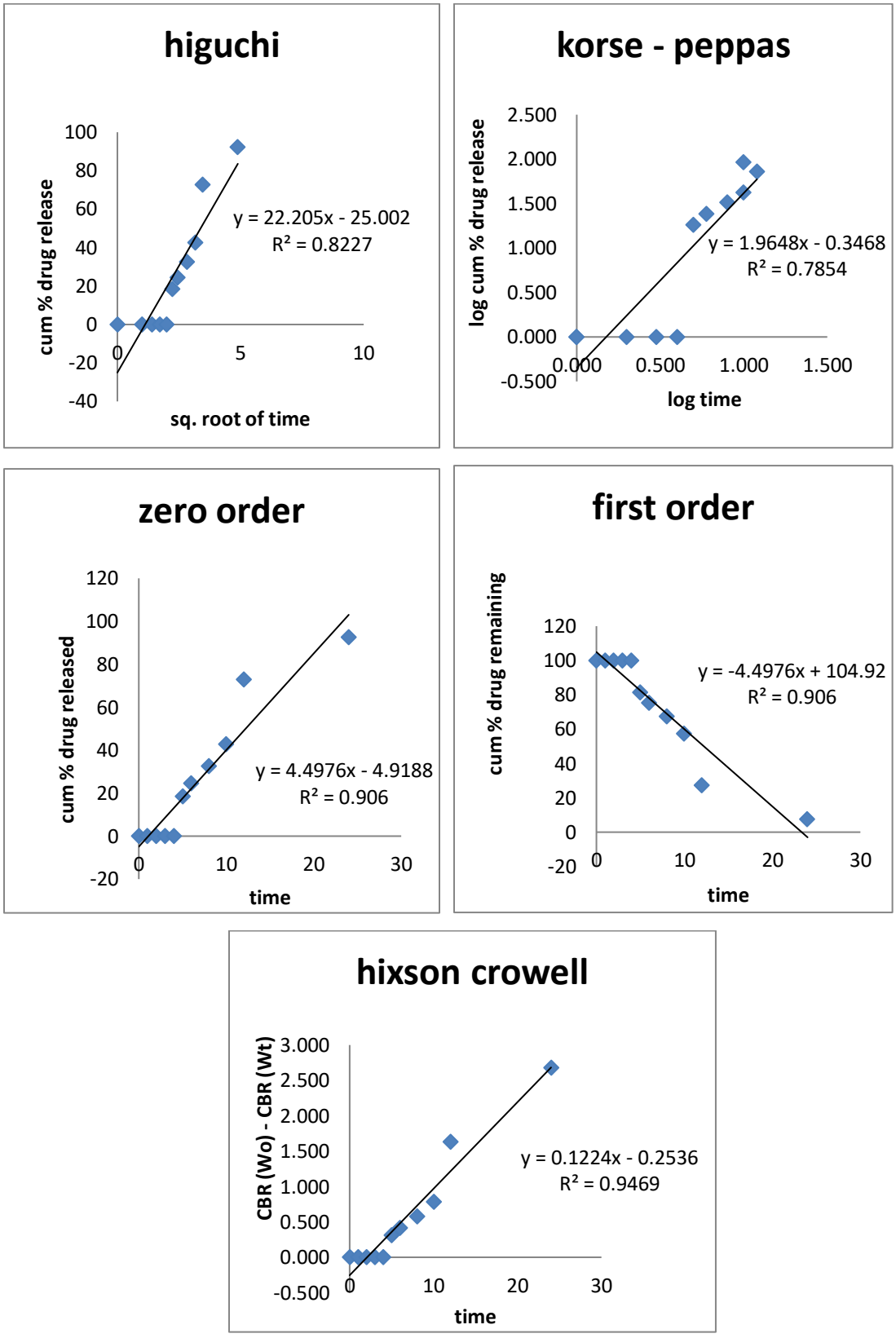
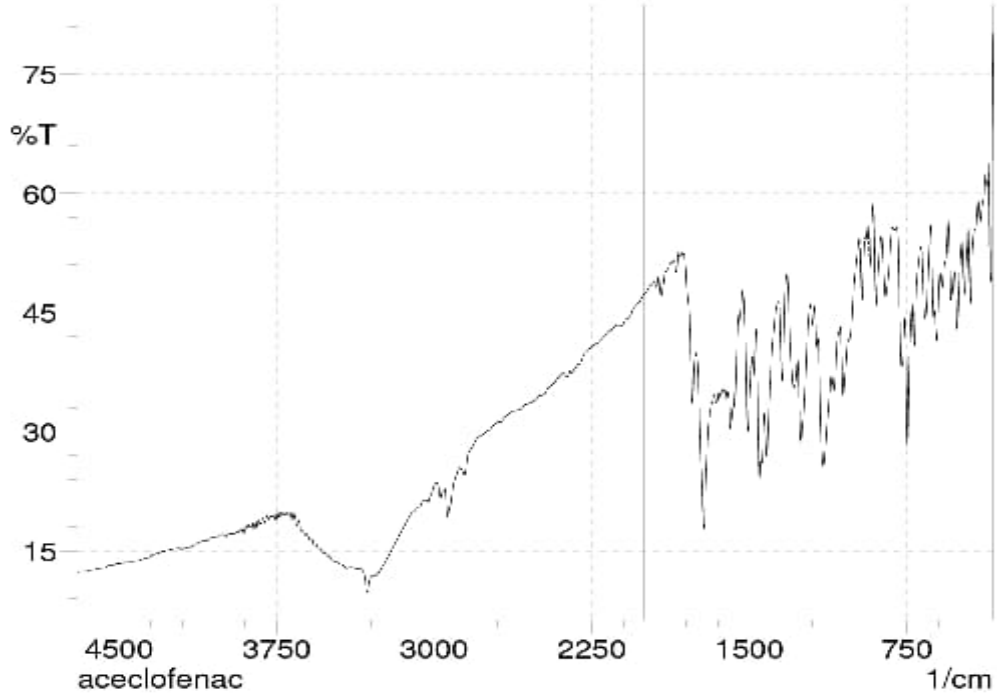


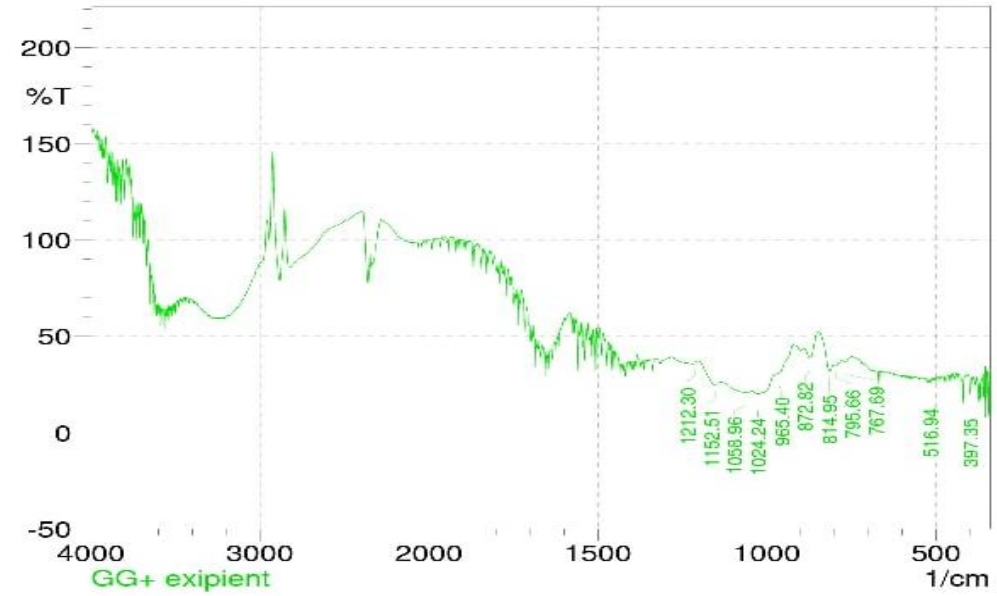
Fig.34: Release Kinetics of Coated Tablet F15



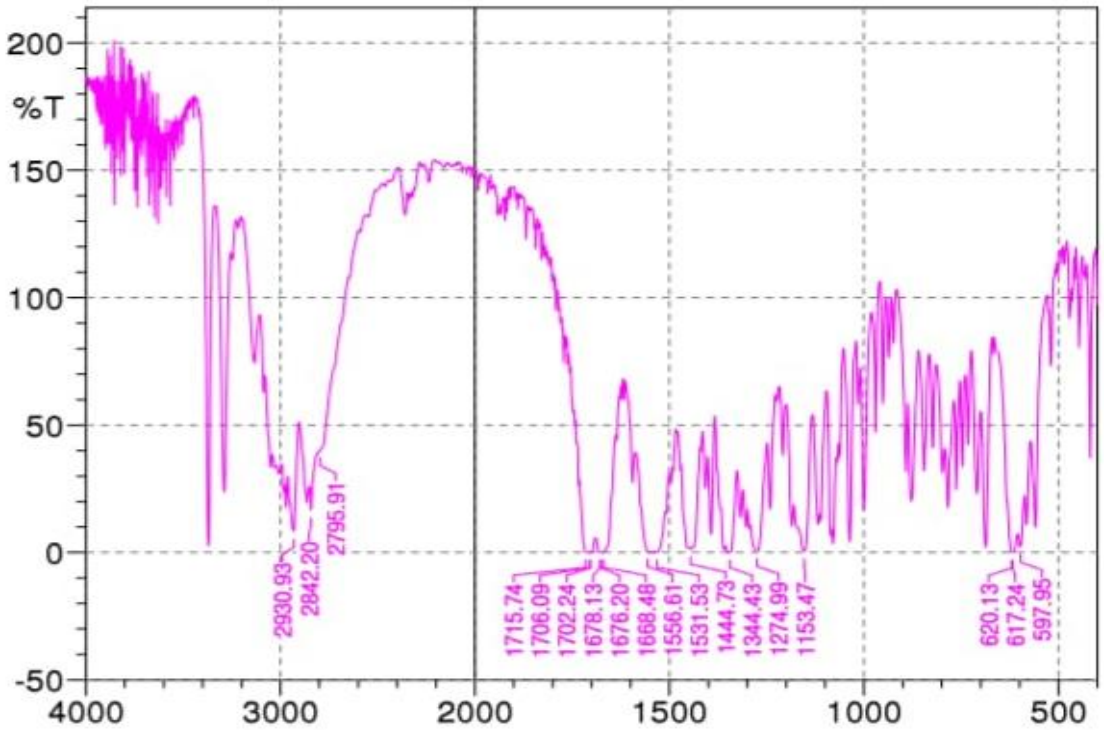
FTIR study of aceclofenac:



FTIR study of Guar Gum:



FTIR study of aceclofenac with Guar Gum:



***In-vitro* drug rease kinetics:**

The order and mechanism of drug release kinetics of candesartan cilexetil films was analysed by the *in-vitro* diffusion study data by plotting the following kinetics models, (zero order, first order, higuchi, Hixson, korsmeyer peppas by using equation.

Zero order kinetics:

Cumulative amount of drug released was plotted against time

$$C_0 = K_0 t$$

Where K_0t is the zero order rate constant expressed in units of concentration/time and t is the time in minutes. A graph of concentration Vs time would yield a straight line with a slope equal to k_0 and intercept the origin of the axis. This kinetics describes concentration independent drug release from the formulations.

First order kinetics:

First order kinetics as log cumulative percentage of drug remaining Vs time. This kinetics describes concentration dependent drug release from the formulations.

$$\textbf{Log C = Log } C_0\textbf{-kt/2.303}$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi's model:

Higuchi's model as cumulative percentage of drug released vs square root of time.

$$\textbf{Q = K}t_{1/2}$$

where k is the constant refelecting the design varables of the system and t is the time in minutes. This model describes the release of drug on the basis of Fickian diffusion as a square root of time dependent process from swellable matrix.

Korsmeyer-peppas equation:

The mechanism of drug release, the first were plotted in korsmeyer et.al' equation log cumulative percentage of drug released vs log time, and the exponent n ws calculated through the slope of the straight line,

$$\textbf{Mt /m}\infty \textbf{ = K}t^n$$

Where Mt /m∞ is the fractiona solute release, t is the release time K is kinetic constant. Charactersticks of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is fickian diffusion, and if 0.45 <n <0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of case-II transport or typical zero order release.

Hixson crowel:

Hixson crowel model as cube root of drug remaining vs time.

R^2 Values of Coated Formulations:

Table.40: R^2 Values of Coated Formulations (F_{13}-F_{15})

Formulations	Higuchi	korsemayer - peppas	zero order	First Order	Hixson Crowell
F13	0.7729	0.7626	0.9201	0.8591	0.9283
F14	0.7408	0.5381	0.879	0.917	0.919
F15	0.8227	0.906	0.9413	0.784	0.9469

From the above values of Table.40, it concluded that the compression coated tablets of formulations F_{13},F_{14},F_{15} follows a release kinetics of Hixson-Crowell Kinetics.

11. SUMMARY

The present study was carried out to develop colon-targeted delivery systems for Aceclofenac using guar gum, Eudragit L-100 and Eudragit S-100 as a carrier. These matrix tablets containing various proportions of guar gum, Eudragit L-100 and Eudragit S-100 were prepared and subjected to in vitro drug release studies. Aceclofenac matrix tablets containing 10% of polymers are not suitable for colon targeting as they disintegrated in the simulated physiological environment of stomach. Also, matrix tablets containing 40% of polymer are considered unsuitable for colon targeting as they released same percentage of which 10% polymer releases after 24 h of dissolution study. This is because the optimum ratio of polymer and Mcc used in a 20% and 30% formulation. But in place of 10% and 40% formulations the polymer and Mcc ratio deviated. Though matrix tablets containing 20% of guar gum completely degraded thereby releasing almost all Aceclofenac, matrix tablets containing 30% of guar gum also degraded partially in simulated colonic fluids. Thus, the matrix formulations containing either 20% or 30% guar gum are most likely to target Aceclofenac to colon with being released at lower or half the percentage of release in stomach and small intestine.

From the above data results, the formulation containing 10% of polymers are selected for the Compression Coating. The formulation F_{13} , F_{14} and F_{15} were Coating of formulation F_1,F_5 and F_9 .

The compression coated tablets pretend the release of aceclofenac on stomach and intestinal pH and the percentage release of drug at 24hrs was 99.34%, 90.8% and 92.42% for F_{13}, F_{14} and F_{15} (Table.36).

From the above values of Table.40, it concluded that the compression coated tablets of formulations F_{13},F_{14},F_{15} follows a release kinetics of Hixon-Crowell Kinetics.

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CME - "GERICON - 2018"

This is to certify that Mr. / ~~Ms~~. / ~~Dr~~. .....V. NAGASELVAN..... has participated as a ~~*Resource person*~~/~~*Chairperson*~~/*Delegate* in the CME on "GERIATRIC PHARMACOLOGY" on 24th September 2018 conducted by Institute of Pharmacology, Madurai Medical College, Madurai.

Accreditation

The Tamil Nadu Dr. M.G.R. Medical University has awarded **10** credit points under category II

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Innovations in Bioequivalence/ Bioavailability and Related Areas

CERTIFICATE OF PARTICIPATION

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