



“FORMULATION AND EVALUATION OF COLON TARGETED PELLETS OF BUMADIZONE CALCIUM”

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ABSTRACT

Aim: The aim of this study was to Formulation and Evaluation of colon targeted pellets of Bumadizone Calcium

Objective: Bumadizone Calcium is an acetic acid derivative, having irritation in stomach. Bumadizone Calcium has short half-life (4hrs) and undergoes first pass metabolism. It is pH-dependent. This research work was carried out to improve the bioavailability, patient compliance on oral colon targeted drug delivery. Bumadizone Calcium sustained release enteric coated pellets were prepared, which minimize the release of drug in stomach for treatment of IBD formulated by Extrusion Spheronization process.

Experimental work done: Enteric coated pellets prepared by Extrusion Spheronization technique. Eudragit S100, HPMC, PVP K30, and Ethyl Cellulose were used as rate controlling polymers. In this study, a pH dependent colon targeted enteric coated pellets was established using 3² full factorial design by giving enteric coating with Eudragit S100. Different Concentration of Eudragit S100 as an enteric coating material (4%, 5%, & %6) and PVP K30 as a Binder (0.5%, 1% & 1.5%) are taken for the measurements of % Drug Release that are performed by using USP dissolution 1 (Basket type) at 50 rpm. The test is performed with gastric fluid (pH 1.2) at 37±0.5 for first 2 hours & then in phosphate buffer 6.8 for 4 hrs & finally in phosphate buffer pH 7.4 for 6 hrs. The prepared formulations were evaluated for drug-exipient compatibility study, flow property, drug content, and coating process efficiency.

Results and Discussion: Optimized batch shown that less than 0.50% of the drug released at the end of 2 hrs in pH 1.2, less than 20% of drug released after end of 4 hrs in pH 6.8 and more than 85% at the end of 12 hrs in pH 7.4.

Conclusion: Bumadizone Calcium Enteric Coated pellets can be successfully formulated by addition of PVP K-30 as a binder and Eudragit S100 as Coating polymer. It was also concluded that prepared formulation minimizes drug release in stomach and avoid side effect of the drug.

Keywords: Bumadizone calcium, Eudragit S100, Enteric coating, extrusion spheronization technique, 3² full factorial designs.

1. INTRODUCTION

1.1 Introduction of Disease

1.1.1 Inflammatory Bowel Disease

Crohn’s disease and ulcerative colitis are inflammatory bowel diseases that cause chronic inflammation and damage in the gastrointestinal (GI) tract (figure1) The GI tract is responsible for digestion of food, absorption of nutrients, and elimination of waste. Inflammation impairs the ability of affected GI organs to function properly, leading to symptoms such as persistent diarrhoea, abdominal pain, rectal bleeding, weight loss and fatigue. While ongoing inflammation in the GI tract occurs in both Crohn’s disease and ulcerative colitis, there are important differences between the two diseases. ^[1]

1.1.2 Irritable Bowel Syndrome

Irritable bowel syndrome is the condition that affects the function and behavior of the intestines. In this condition, the muscles lining the intestines intermittently contract and relax to move food along the

digestive tract. In IBS, this pattern resulting in uncomfortable symptoms. 40 million people around the world are affected by IBS. Patients with IBD can also have IBS. [1]

1.1.3 Crohn's Disease

Crohn's disease can affect any part of the GI tract from the mouth to the anus. It most commonly affects the end of the small intestine (the ileum) where it joins the beginning of the colon. Crohn's disease may appear in "patches," affecting some areas of the GI tract while leaving other sections completely untouched. In Crohn's disease, the inflammation may extend through the entire thickness of the bowel wall. [1]

1.1.4 Ulcerative Colitis

Ulcerative colitis is limited to the large intestine (colon) and the rectum. The inflammation occurs only in the innermost layer of the lining of the intestine. It usually begins in the rectum and lower colon, but may also spread continuously to involve the entire colon. [1]

1.1.5 Indeterminate Colitis

In some individuals, it is difficult to determine whether their IBD is Crohn's disease or ulcerative colitis. In these rare cases, people are given the diagnosis of indeterminate colitis (IC). [1]

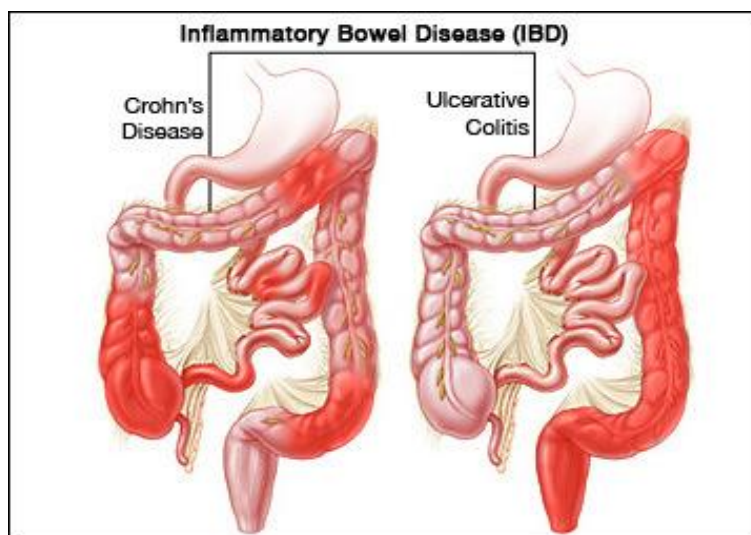


Figure 1: IBD

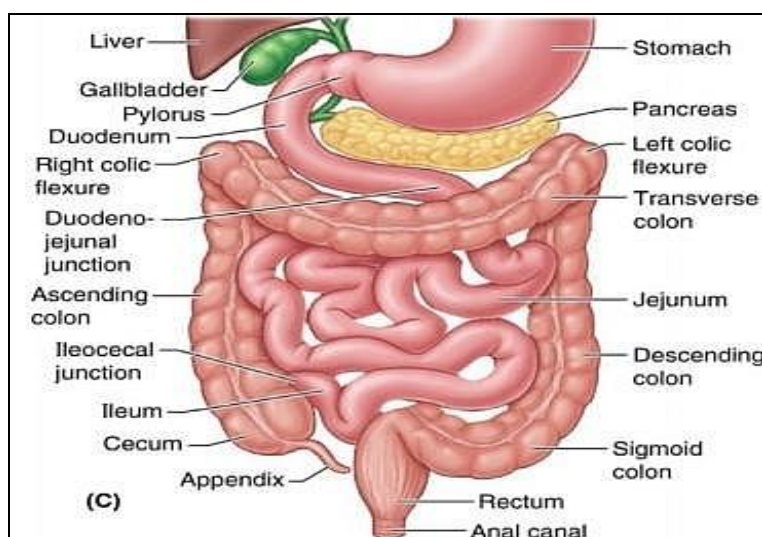


Figure 2: Gastrointestinal Tract

1.2 Introduction of Drug Delivery System

1.2.1 Anatomy of Colon:

The colon has four parts which have the same structure and functions:

i. The Ascending Colon: This part passes upwards from the caecum to the level of the liver where it curves acutely to the left at the *hepatic flexure* to become the transverse colon.

ii. The Transverse Colon: This part extends across the abdominal cavity in front of the duodenum and the stomach to the area of the spleen where it forms 'splenic flexure' and curves acutely downwards to become the descending colon.

iii. The Descending Colon: This part passes down the left side of the abdominal cavity then curves towards the midline. At the level of the iliac crest it is known as the sigmoid colon.

iv. The Sigmoid Colon: This part describes an S-shaped curve in the pelvic cavity that continues downwards to become the rectum.

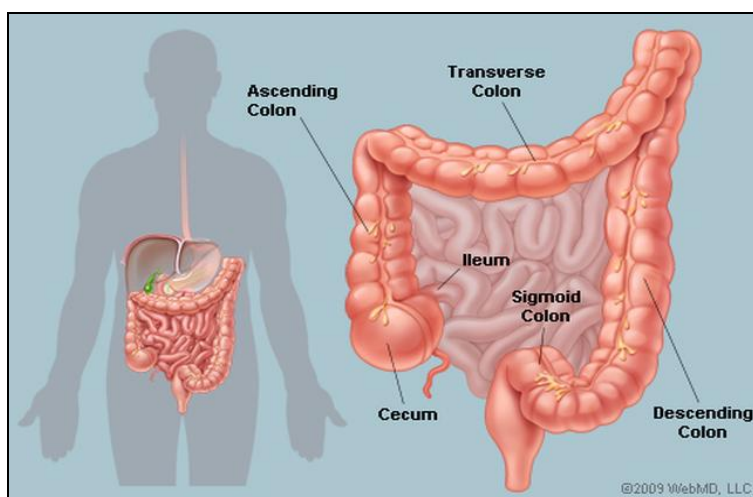


Figure 3: Anatomy of colon

Table 1.1 pH of digestive tract		
Stomach	Fasted state	1.5-2
	Fed state	2 - 6
Small intestine		6.6 - 7.5
Colon	Ascending	6.4
	Transverse	6.6
	Descending	7.0

Functions of colon: -

1. It creates appropriate condition used for the development of colonic microbes.
2. Expulsion of the inside of the colon.
3. The secretion K^+ and HCO_3^- .

Sr. no	Large Intestine	Length (cm)
1	Cecum	6-9
2	Ascending colon	20-25
3	Descending colon	10-15
4	Transverse colon	40-45
5	Sigmoid colon	35-40
6	Rectum	12
7	Anal canal	3

1.2.2 Colon targeted drug delivery system (CTDDS)^{[7][8][9][10]}

Colon targeted drug delivery system (CTDDS) maybe follow the concept of Sustained or controlled drug delivery system, for CTDDS oral route of administration has received most attention. This is because of the flexibility in dosage form designed for oral than parenteral route because,

- a) Patient acceptance for the oral administration of the drug is quite high.
- b) It is relatively safe route of drug administration compared with parenteral route and potential damage at site of administration is minimal.
- c) Most of the conventional drug delivery systems for treating the colonic disorder such as Inflammatory bowel diseases i.e. Ulcerative colitis, Cohn's diseases, Colon cancer and Amoebiasis are failing as drug do not reach the site of action in appropriate concentration. For effective and safe therapy of these colonic disorders, colon specific drug delivery is necessary. Today, colon specific drug delivery is challenging task to pharmaceutical technologists.
- d) Therapeutic advantages of targeting drug to the diseased organ include:
- e) The ability to cut down the conventional dose
- f) Reduced the incidence of adverse side effects
- g) Delivery of drug in its intact form as close as possible to the target sites.
- h) Colon specific drug delivery systems are also gaining importance for the delivery of protein and peptides due to several reasons as follow
- i) Rapid development of biotechnology and genetic engineering resulting into the availability of protein and peptide drugs at reasonable cost.
- j) Proteins and peptide drugs are destroyed and inactivated in acidic environment of the stomach or by pancreatic enzymes in small intestine.
- k) Parental route is expensive and inconvenient.
- l) Longer residence time, less peptidase activity and natural absorptive characteristics make the colon as promising site for the delivery of protein and peptide drug for systemic absorption.
- m) Less diversity and intensity of digestive enzymes.
- n) Comparative proteolytic activity of colon mucosa is much less than observed in the small intestine, i.e. CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to higher systemic bioavailability.

Dosage form	Transit time(h)		
	Stomach	Small intestine	total
Tablet	2.7±1.5	3.1±0.4	5.8
Pellets	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0
Solution	0.3±0.07	4.1±0.57	4.4

1.2.3 Advantages^{[12][13]}:

- Drugs are directly available at the target site.
- Comparatively lesser amount of required dose.
- Decreased side effects.
- Improved drug utilization

1.2.4 Advantages of CTDDS over Conventional Drug Delivery^[11]:

Chronic colitis, namely ulcerative colitis, and crohn's disease are currently treated with glucocorticoids, and other anti-inflammatory agents. Administration of glucocorticoids namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppressant, cushinoid symptoms, and bone resorption. Thus, selective delivery of drugs to the colon could not only lower the required dose but also reduce the systemic side effects caused by high doses.

1.2.5 Criteria for Selection of Drug for CDDS ^{[5][6]}:

CTDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhoea, and colon cancer are prominent for local colon delivery.

Drugs used for local effects in colon against GIT diseases

- Drugs poorly absorbed from upper GIT
- Drugs for colon cancer that degrade in stomach and small intestine
- Drugs that undergo extensive first pass metabolism
- Drugs poorly absorbed from upper GIT Drugs for targeting

1.2.6 Approaches for colon targeted drug delivery system

A. Covalent linkage of drug with carrier

Prodrug Approaches ^[14]: -

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site.

This approach involves covalent linkage between the drug and its carrier in such a manner that oral administration the moiety remains intact in the stomach and small intestine and after reached in the colon, enzymatic cleavage regenerates the drug.

When synthesizing prodrugs, the choice of carrier depends on the functional group available on the drug molecule for conjugation with the carrier e.g., the hydroxyl group present on the corticosteroids can enter into a glycosidic linkage with various sugars and the carboxyl group of biphenyl acetic acid forms an ester/amide conjugate with cyclodextrin.

Generally, a prodrug is successful as a colon drug carrier if it is hydrophilic and bulky to minimize absorption from the upper GIT, and if once in the colon, it is converted into a more lipophilic drug molecule, which is then available for absorption.

- Azo bond conjugate
- Glycoside conjugation
- Glucuronide conjugates
- Cyclodextrin conjugate
- Dextran conjugate
- Amino acid conjugation
- Polymeric prodrugs

B. Approaches to deliver intact molecule to colon

1) pH dependent approach ^[15]

This approach utilizes the existence of pH gradient in the GIT that increases progressively from the stomach (pH 1.5-3.5) and small intestine (5.5-6.8) to the colon (6.4-7.0).

By combining the knowledge of the polymers and their solubility at different pH environments, delivery systems can be designed to deliver drugs at the target site. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose.

i. Coating of the drug core with pH sensitive polymers.

Polymer	Threshold pH
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit® L-30D	5.6

Eudragit® FS 30D	6.8
Eudragit® L 100-55	5.5
Poly vinyl acetate phthalate	5.0
Hydroxypropyl methylcellulose phthalate	4.5-4.8
Hydroxypropyl methylcellulose phthalate 50	5.2
Hydroxypropyl methylcellulose phthalate 55	5.4
Cellulose acetate trimellate	4.8
Cellulose acetate phthalate	5.0

Drug	Trade name	Coating polymer/formulation
Budesonide	Entrocort®	Eudragit® L 100-55, ethyl cellulose
	Budenofalk®	Eudragit® S (dissolution pH 7)
	Targit®	Coated starch capsule
Mesalazine	Claversal®	Eudragit® L 100(dissolution pH 6)
	Asacolitin®	Eudragit® S (dissolution pH 7)
	Salofalk®	Eudragit® S (dissolution pH 6)
	Pentasa®	Ethyl cellulose coated pellets
	Mesazal®	Eudragit® L 100(dissolution pH 6)
	Calitofalk®	Eudragit® L 100(dissolution pH 6)
	Asacol®	Eudragit® S (dissolution pH 7)
Sulfasalazine	Azulfidine®	CAP (dissolution pH 6.2-6.5)
	ColoPleon®	Eudragit® L 100-55 (dissolution pH 5.5)

ii. Embedding in pH-sensitive matrices: -

The drug molecules are embedded in polymer matrix. Extrusion Spheronization technique can be used to prepare uniform-size sturdy pellets for colon targeted drug delivery when it is not possible to obtain mechanically strong granules by other methods. Excipients had a significant impact on the physical characteristics of the pellets. Eudragit S100 as a pH sensitive matrix base in the pellets increased the pellet size and influenced pellet roundness. Citric acid promoted the pelletization process resulting in a narrower area distribution. However, Eudragit S100 could not cause statistically significant delay in the drug release at lower pH.

Some market formulations

Asacol® Proctor & Gamble Pharmaceuticals, USA Delayed-release tablets containing mesalazine and coated with Eudragit® S-100 are marketed in a number of countries (Asacol). These tablets dissolve at pH 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon.

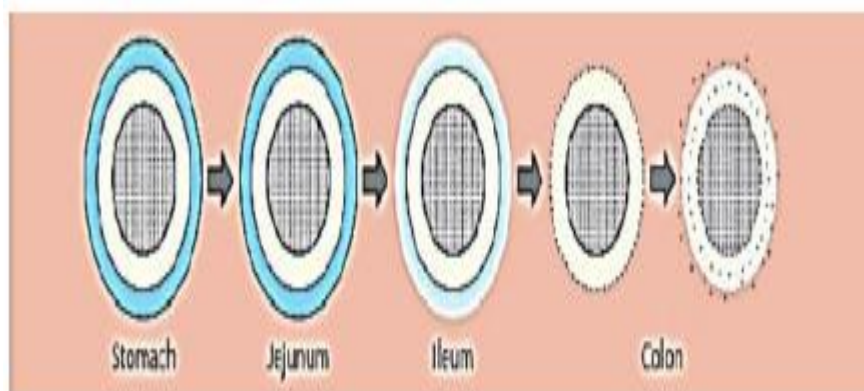


Figure 4: Drug release pattern of coated system at different pH

Conditions in GIT ^[17]

2) Time dependent delivery^{[18][19]}:-

It also known as pulsatile release or delayed release or sigmoidal release system. This approach is based on the principle of delaying the release of the drug until it enters into the colon.

Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug take place.

The lag time in this case is the time requires to transit from the mouth to colon.

A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered.

Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GI tract. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms.

Disadvantages of this system:

Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.

Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhoea and the ulcerative colitis. Therefore, time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. Time-dependent drug delivery includes:

- Pulsincap
- Time clock
- Time-Controlled- Explosion Drug-Delivery System (Pulsatile System Based on Rupturable Coating)
- Colon Targeted Delivery Capsule based on pH sensitivity and time-release principles
- Chronotropic® system
- PORT system

3) Microbially triggered drug delivery to colon^{[16][18]}

The microflora of colon is in the range of 10^{11} - 10^{12} CFU/mL, consisting mainly of anaerobic bacteria, e.g. Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc.

This vast microflora fulfils its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri- saccharides, polysaccharides etc.

For this fermentation, the microflora produces a vast number of enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase.

Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon- specific drug delivery seems to be a more site-specific approach as compared to other approaches.

These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon.

On reaching the colon, they undergo assimilation by micro-organism or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer.

CLASS	EXAMPLES
Disaccharides	Lactose, Maltose, Cyclodextrins, Lactulose, Raffinose, Stachyose
Polysaccharides	Alginates, Amylose, Cellulose, Chitosan, Starch, Chondroitin sulphate, pectin, xanthan gum, etc.

4) Bioadhesive systems^{[19][20]}

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time.

This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems.

Various polymers including polycarbophils, polyurethanes and polyethylene oxide-polypropylene oxide copolymers have been investigated as materials for bioadhesive systems.

Bioadhesion has been proposed as a means of improving the performance and extending the mean residence time of colonic drug delivery systems.

5) Pressure controlled system^{[25][26][27]}

The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents.

In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of faeces.

It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. Takaya et al. (1995) have developed pressure controlled colon delivery capsules prepared using an ethyl cellulose, which is insoluble in water.

In such systems drug release occurs following disintegration of a water insoluble polymer capsule as a result of pressure in the lumen of the colon.

The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. The preferred thickness of the capsule wall is about 35-60 μm ^[27]. The system also appeared to depend on capsule size and density.

In pressure-controlled ethyl cellulose single unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

6) Osmotic controlled drug delivery^{[28][29]}

The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule. Each push-pull unit is bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. In principle, semipermeable membrane is permeable to the inward entry of water and aqueous GI fluids and is impermeable to the outward exit of the drug. An orifice is drilled into the semipermeable membrane to the drug layer. The outside surface of the semipermeable membrane is then coated by eudragit® S100 to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at $\text{pH} \leq 7$. As a result, water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour post gastric delay to prevent drug delivery in the

small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hr. in the colon or can deliver drug over an interval as short as 4 hours.

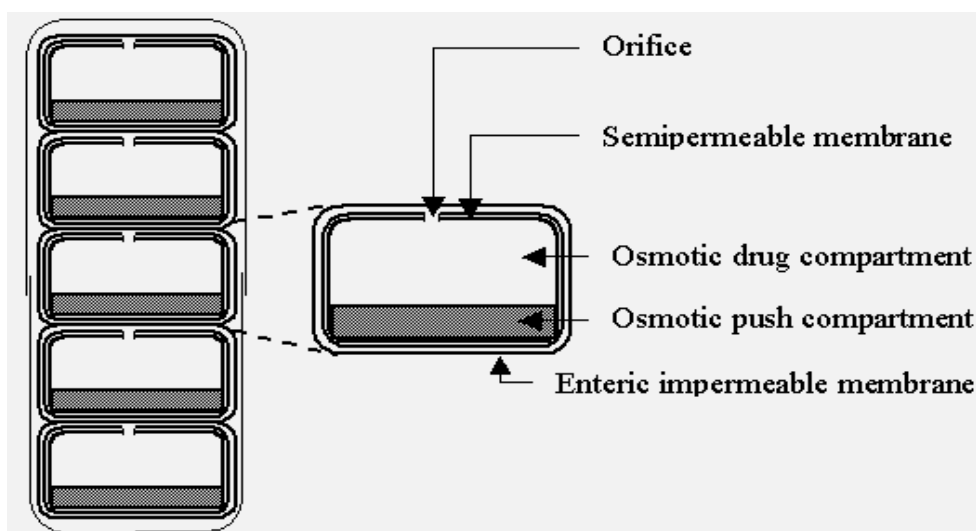


Figure 5: Cross section of the OROS-CT colon targeted drug delivery system.

7) Multiparticulate systems^{[21] [22] [23] [24]}

Single unit colon targeted drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. Report suggests that drug carrier systems larger than 200 μm possess very low gastric transit time due to physiological condition of the bowel in colitis. For this reason and considering the selective uptake of micron or submicron particles by cancerous and inflamed cells/ tissues a multiparticulate approach is expected to have better pharmacological effect in the colon. Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like,

- Multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time and hence increased bioavailability.
- Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GI tract easily, leading to less inter and intrasubject variability.
- Moreover, multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption.
- Reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying.

Multiparticulate approaches tried for colonic delivery include formulations in the form of pellets, Granular matrix, Beads, Micro spheres, Nano particles.

1.2.7 ENTERIC COATING^[32]

• An enteric coating is a barrier applied to oral medication that controls the location in the digestive tract where it is absorbed. Enteric refers to the small intestine; therefore, enteric coating on the dosage form prevents the release of drug before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable to highly acidic pH of stomach, But breaks down rapidly at a less acidic (relatively more basic) pH.

1.2.8 Necessary Enteric coating-:

1. After Taking a Typical Supplement

- The tablet is swallowed and travels down the oesophagus to the stomach.
- In the stomach the tablet is churned and gyrated in highly acidic digestive Secretions with p H (1-4), for 45 minute to 2 hours.
- If there is anything left of tablet, it will be passed through the duodenum to the small intestine.



Figure 6: Highly acidic environment

2. Fate of Uncoated Tablets:

- Stomach acid breaks down tablets to prematurely release active ingredients (enzyme).
- The highly acidic environment of the stomach destroys the majority of the enzymes activities.
- If the tablet is of poor quality (contains Binder and fillers) the product may pass through both the stomach and intestine with no absorption.

1.2.9 Enteric coating is suitable for^[32]:

- Drugs that have irritant effect in stomach (like aspirin),
- Drugs which are unstable in acidic pH of stomach.
- Thus, enteric coating is aimed to prevent the formulations from gastric fluid in the stomach and
- Release the drug component in the intestinal region or once it has passed into the duodenum.
- Some of the most important reasons for the application of enteric coating to the dosage form are as follows:
 - To protect the acid-labile drugs from the acidic pH of gastric fluid. Example: enzymes and certain antibiotics.
 - To prevent gastric distress or nausea due to irritation caused by certain drugs. Example: Sodium salicylate.
 - To deliver drugs intended for the local action in intestines. Example: intestinal antiseptics could be delivered to their site of action in a concentrated form and bypass systemic absorption in the stomach.
 - To deliver drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
- To provide a delayed release component to repeat action tablets.

1.2.10 An ideal enteric coating material should possess the following properties^{[30] [31]}:

- Resistance to gastric fluids.
- Ready susceptibility to or permeability to intestinal fluids.
- Compatibility with most of the coating solution components and the drug substances.
- Stability alone and in the coating solutions i.e. the film should not change upon aging.
- Formation of a continuous film on the dosage form.
- Non-toxic and non-irritant.
- Low cost.
- Ease of application without specialized equipment.
- Ability to be readily printed or to allow film to be applied to debossed tablets.

1.2.11 Polymers used for enteric coating

Table 1.7: Different polymers used for enteric coating	
POLYMERS	DISSOLUTION pH
Shellac(esters of aleurtic acid)	7.0
Cellulose acetate phthalate(CAP)	6.2
Poly(methcrylic acid-co-methyl methacrylate)	5.5-7.0
Cellulose acetate trimellate(CAT)	5.0
Poly(vinyl acetate phthalate)(PVAP)	5.0
Hydroxypropyl methylcellulose phthalate(HPMCP)	4.5-5.5

1.2.12 PELLETIZATION ^[35]:

Preparation of pellets called palletization. Pellets can be defined as small, free flowing, spherical or semi-spherical solid, size rages from 0.5mm to 1.5mm, and intended usually for oral administration, manufactured by the agglomerated of fine powders or granules of bulk drugs and excipients using appropriate processing equipment. Pellets can be prepared by many methods, agitation, compaction, layering, globulation & other new techniques.

Significance

- Pellets ensure improved flow properties and flexibility in formulation and development and manufacturing
- Larger surface area of pellets enhances distribution.
- Improved appearance of the product.
- Various applications are possible in the pellet form. For e.g.: delayed release.
- Pellets are less susceptible to dose dumping.
- Pellets can reduce the variation in gastric emptying rate and transit time.
- Pellets can freely disperse in GIT and invariably maximize drug absorption and also reduce peak plasma fluctuation.

1.2.13 Pelletization techniques ^[36-39]:

1.2.13.1 Methods of Pelletization:

- Agitation/Balling Method
- Compaction Method
 1. Compression
 2. Extrusion/Spheronization
- Layering Method
 1. Powder layering
 2. Solution/Suspension layering
- Globulation Method
 1. Spray drying
 2. Spray congealing
- New techniques
 1. Cryopelletization
 2. Melt Spheronization

Agitation:

In agitation method, finely divided particles are converted to spherical pellets by continuous rolling or tumbling motion using a rotating drum, pan or disc. The liquid may be added prior to or during the agitation stage.

Compaction:

Particles and/or granules are forced together by mechanical force to generate pellets. Volume reduction is a common feature of this process.

i. Compression:

In this process mixtures of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size. During compression at high pressure, particles of a packed mass are forced against each other so that elastic and plastic deformation can take place and create strong inter-particle contact.

ii. Extrusion & Spheronization ^{[33, 34, 39, 40, 42].}

In extrusion & spheronization process, the powder is formed into a wet mass, which is forced through restricted extrusion area to form strands of extrudates that are broken into short lengths and rounded by placement on a rotating plate with in a cylinder. The resulting spherical granules or pellets are of uniform shape, size and density.



Figure 7: Extruder spheronizer

Table 1.8 Specifications of extruder spheronizer	
Working Capacity	100 grams / batch
Net Weight	NA
Gross weight	NA
Dimension	0.5,1.0,1.5 & 2.0mm of hole
Electrical Specifications	0.5 HP 230VAC/3/60

Layering:

i. Powder Layering ^{[41].}

Powder layering involves the deposition of successive layers of dry powder of drug and/or excipients on preformed nuclei or cores with the help of a binding liquid.

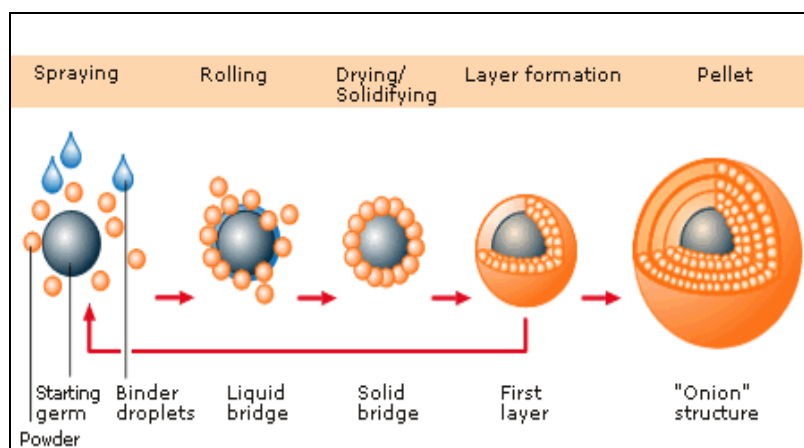


Figure 8: Powder layering

ii. Solution / Suspension Layering^[42]:

Solution and Suspension Layering involve the deposition of successive layers of solution and suspension. Respectively, on the starter seeds that are inert materials or crystals or granules. Principle of solution and suspension layering given below.

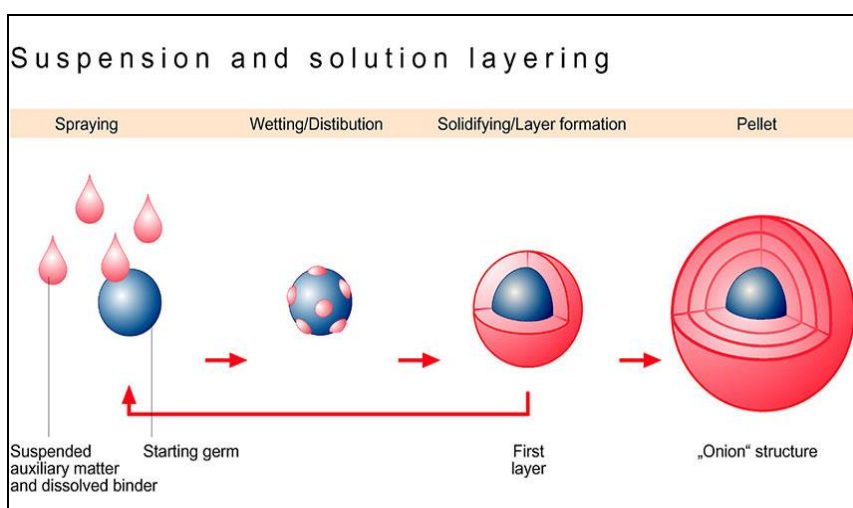


Figure 9: Solution layering

Globulation:

i. Spray drying^[43]:

In spray drying process, drug entities in solution or suspension form are sprayed, with or without excipients, into a hot-air stream to generate dry and highly spherical particles.

ii. Spray congealing^[43]:

In spray congealing process a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes, fatty acids etc. which further sprayed into an air chamber where the temperature going below the melting points of the formulation components, to provide, under appropriate processing conditions, spherical congealed pellets.

New Techniques:

1. Cryopelletization^[44]:

In cryopelletization technique, droplets of a liquid formulation are converted into solid spherical particles or pellets by employing liquid nitrogen as the fixing medium. Drug-loaded pellets are produced by allowing droplets of a solution or suspension to come in contact with liquid nitrogen at -1600°C.

2. Melt Spheronization^[44]:

In melt spheronization technique, drug substance and excipients are converted into a molten state or semi-molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets.

Equipments

The equipments used for the tablet/pellet coating are as per below.

I. Standard coating pan^[45]

- Also known as conventional pan system
- Circular metal pan which is mounted angularly on a stand
- 8-60 inches in diameter
- Rotated on its horizontal axis by a motor
- Heated air is directed into the pan & on to the tablet/pellets bed surface and is exhausted by means of ducts through the front of the pan Coating solution are applied to the tablets/pellets by layering and/or spraying the material on to the rotating bed.

Use of spraying systems-

- Produces faster and more even distribution of the solution and/or suspension.
- Reduces drying time between solution applications in sugar coating.

- Allows continuous application of the solution in film coating.
- In standard coating pan, the drying efficiency is improved by
 - Pellegrini pan
 - The immersion sword
 - Immersion tube systems

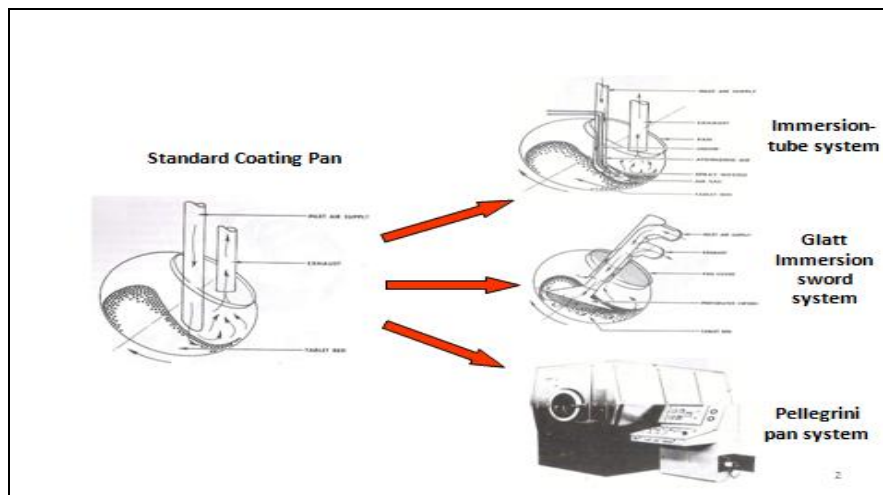


Figure 10: Standard Coating Pan

II. Perforated pan systems ^[46]

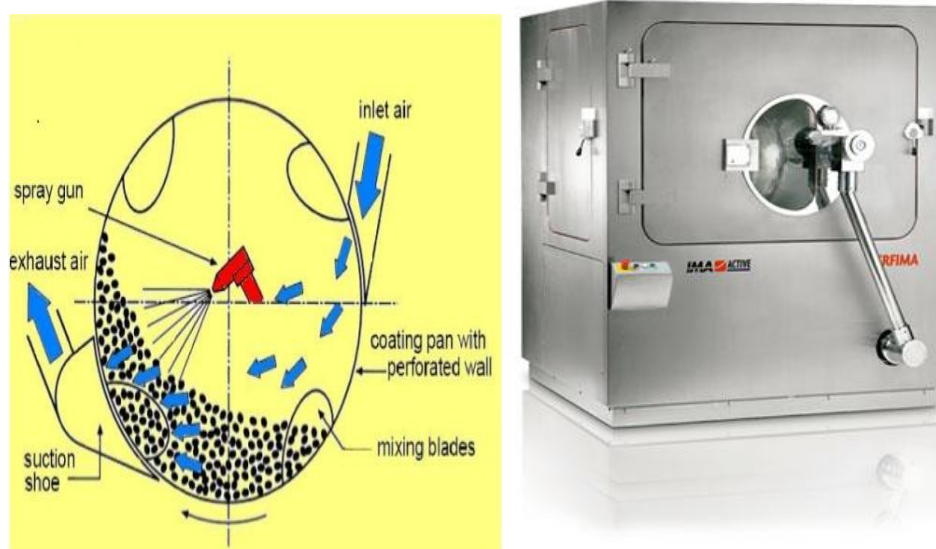


Figure 11: perforated coating pan

- Partially perforated or fully perforated drum.
- Rotates on horizontal axis in an enclosed housing.
- The coating solution is applied to the surface of the rotating bed of tablets through spraying nozzle, which is present inside the drum.
- Perforated pan coater providing efficient drying systems with high coating capacity.

Types of fluid bed technologies

→Top spray →Bottom spray →Tangential spray

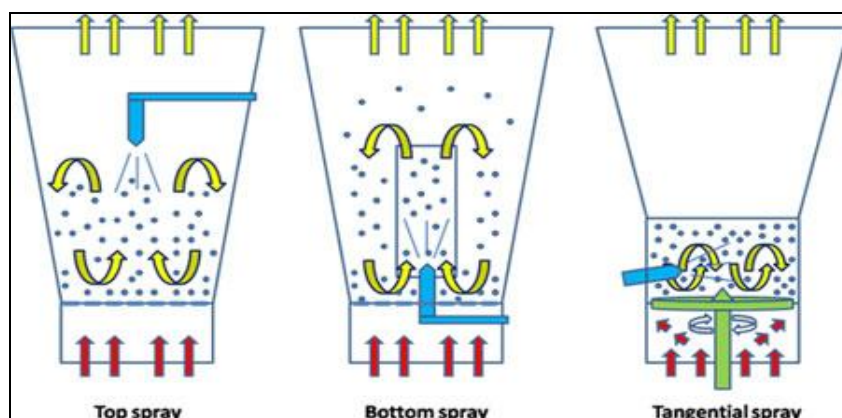


Figure 12: Types of fluid bed technologies

1.3 Introduction of Drug Profile

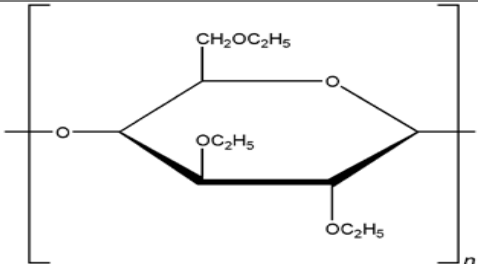
1.3.1 Bumadizone Calcium^[64]

Table 1.9 Bumadizone Calcium - Drug Profile	
Category	Non-Steroid anti-inflammatory drugs [NSAIDs]
Chemical Class	Acetic acid derivatives & related substance
Chemical Name	Bumadizon, Bumadizonum, Bumadizona
IUPAC Name	dicalcium;2-[anilino(phenyl)carbamoyl]hexanoate; hydrate
Indications	Acute & chronic inflammatory rheumatic diseases, open & closed injuries, other inflammatory condition.
Mechanism of Action	They act by blocking the synthesis of prostaglandins by inhibiting cyclooxygenase, which converts arachidonic acid to cyclic endoperoxides, precursor of prostaglandins. Inhibition of prostaglandin synthesis accounts for their analgesic, antipyretic, & platelet- inhibitory actions anti-inflammatory effects
State	Solid
Molecular formula	$C_{76}H_{86}Ca_2N_8O_{13}$
Structure	
CAS NUMBER	69365-73-7
Molecular weight	1399.723 g/mol
BCS Class	Class-2
Half life	4 hours
Bioavailability	More than 90% absorbed
Absorption	Blood
Excretion	Stool, Urine
Melting point	158 °c
Adverse effect	Carcinogenicity
Dose	50 mg to 300 mg, twice a day, once a day
Other dosage forms	Octomotol tablet
Stability and Storage Conditions	Oxidative degradation occurs in presence of direct sunlight or UV light at elevated temperature. It may be prevented by use of antioxidants. It should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat.

1.3.2 Excipients

1. Ethyl Cellulose^[46]

Table 1.10 Ethyl Cellulose

Non-Proprietary Names	BP, USP-NF: Ethyl cellulose, Ph.Eur: Ethyl cellulose.
Synonyms	Aquacoat ECD; Aqualon; ashacel; e462; ethocel; ethylcellulosum; surelease.
Chemical Name	Cellulose ethyl ether
Empirical Formula and molecular Weight	$C_{12}H_{23}O_6$ ($C_{12}H_{22}O_5$) _n $C_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights.
Functional Category	Coating agent; flavouring agent; tablet binder; tablet filler; viscosity increasing agent; thickening agent.
Structure	 <p>The diagram shows the repeating unit of ethyl cellulose. It consists of a six-membered pyranose ring with an oxygen atom at the top vertex. The ring is enclosed in large square brackets with a subscript 'n'. The left side of the ring is connected to another oxygen atom, and the right side is connected to another oxygen atom, both within the brackets. Three ethyl groups (-OC₂H₅) are attached to the ring: one at the C2 position (top-right), one at the C3 position (bottom), and one at the C6 position (bottom-left). A hydroxymethyl group (-CH₂OC₂H₅) is attached to the C4 position (top).</p>
Description	Tasteless, free-flowing, white to light tan-coloured powder.
Typical Properties	<p>Density(bulk): - 0.4g/cm³</p> <p>Moisture content: - absorbs very little water from humid air and that small amount evaporates readily.</p> <p>Solubility: practically insoluble in glycerine, propylene glycol, and water. Freely soluble in chloroform, methyl acetate, and tetrahydrofuran.</p>
Stability and Storage Conditions	Oxidative degradation occurs in presence of sunlight or UV light at elevated temperature. This is prevented by use of antioxidant. It should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat.

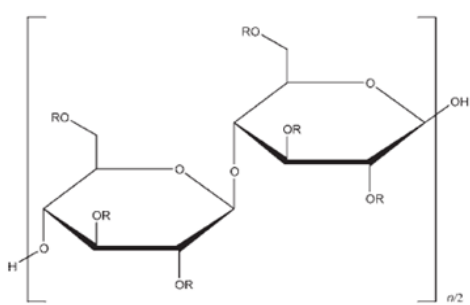
1.1 Applications in Pharmaceutical formulation or technology

Table 1.11 Applications of ethyl cellulose

Use	Concentration (%)
Microencapsulation	10.0-20.0
Sustain- Release Tablet Coating	3.0-20.0
Tablet Coating	1.0-3.0
Tablet Granulation	1.0-3.0

2. Hydroxy Propyl Methyl Cellulose ^[47]

Table 1.12 Hydroxy Propyl Methyl Cellulose

Non-Proprietary Names	BP, JP, PhEur, USP; Hypromellose,
Synonyms	Hypromellose, methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; metolose; MHPC; Hypromellosum; methocel.
Chemical Name	Cellulose hydroxy propyl methyl ether
Functional Category	Bioadhesive material; Coating agent; controlled-release agent; emulsion stabilizer; film-forming agent; foaming agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; viscosity increasing agent.
Structural Formula	 <p>The diagram illustrates the chemical structure of Hydroxy Propyl Methyl Cellulose (HPMC). It shows a repeating unit of a cellulose chain, represented by two pyranose rings connected by an oxygen atom. The left ring has a hydroxyl group (-OH) at the C2 position and a hydroxypropyl group (-CH₂CH₂CH₂OH) at the C6 position. The right ring has a methyl ether group (-OR) at the C2 position and a hydroxypropyl group (-CH₂CH₂CH₂OH) at the C6 position. The entire structure is enclosed in brackets with a subscript 'n/2'.</p>
Description	Odourless and tasteless, white or creamy-white fibrous or granular powder.
Typical Properties	<p>Moisture content: -It absorbs moisture from the atmosphere. The amount of water absorbed depends upon the initial moisture content, temperature and relative humidity of the surrounding air.</p> <p>Solubility: It is soluble in cold water. It is practically insoluble in hot water, chloroform, ethanol (95%), and ether.</p>
Stability and Storage Conditions	Solutions are stable at pH 3-11. It undergoes a reversible sol-gel transformation upon heating and cooling, respectively. Powder should be stored in a well-closed container and keep in a cool & dry place.

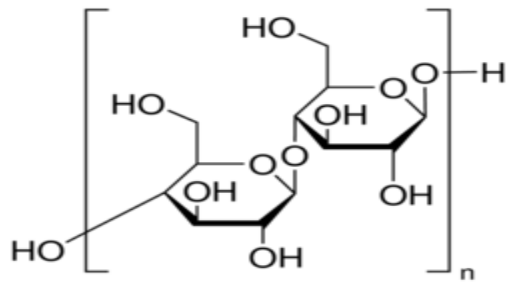
2.1 Application in pharmaceutical formulation and technology

Table 1.13 Applications of HPMC

Use	Concentration (%)
Suspending and/or thickening agent	0.25-5.0%
As a binder with either in wet or dry granulation processes	2-5%

3. Microcrystalline Cellulose ^[49]

Table 1.14 Microcrystalline Cellulose

Non-Proprietary Names	BP, JP, USP-NF: Microcrystalline cellulose Ph.Eur.: cellulose: microcrystalline
Synonyms	Avicel pH; Cellets; Celex; Cellulose Gel; Hellulosum Microcrystallinum; Celphere; Ceolus KG; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel.
Chemical Name	Cellulose
Empirical formula and molecular weight	$(C_6H_{10}O_5)_n = 36000$, where $n=220$.
Functional Category	Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.
Structure	 <p>The diagram illustrates the chemical structure of microcrystalline cellulose, showing a repeating unit of glucose rings linked by beta-1,4 glycosidic bonds. The structure is enclosed in large square brackets with a subscript 'n' at the bottom right, indicating a polymer chain. Each glucose ring is shown in its cyclic form with various hydroxyl groups attached to the carbons.</p>
Description	White, odourless, tasteless, crystalline powder. Available in different properties and applications.
Typical Properties	Moisture content: - less than 5% w/w. different grades may contain varying amount of water. It is hygroscopic. Solubility: slightly soluble in 5% w/v sodium hydroxide solution, Practically insoluble in water, dilute acids, and most organic solvents.
Stability and Storage Conditions	It is stable through hygroscopic material; the bulk material should be stored in a well-closed container in a cool, dry place.

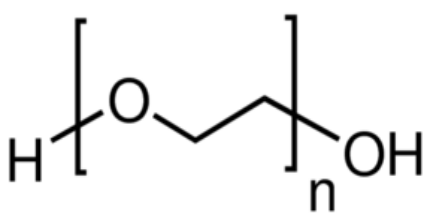
3.1 Application in pharmaceutical formulation or technology

Table 1.15 Applications of Microcrystalline Cellulose

Use	Concentration (%)
Adsorbent	20-90
Antiadherent	5-20
Capsule and tablet binder/diluents	20-90
Tablet disintegrant	5-15

4. Polyethylene Glycol 600^[49]

Table1.16 Polyethylene Glycol 600

Synonyms	Carbowx; carbowax sentry; lipoxol; lutrol E; macrogola; PEG; polyethelene glycol.
Chemical name and CAS registry number	a-hydro-o-hydroxypoly (oxy-1,2-ethanediyl) [25322-68-3]
Empirical formula and molecular weight	HOCH ₂ (CH ₂ OCH ₂) _m , Where m=average number of oxyethylene group.
Structure	
Description	Polyethylene glycol grades 200 to 600 are liquids. Grade 1000 and above are solids at ambient temperatures. Liquid grades (PEG 200 to 600) are clear, colorless or slightly yellow-coloured, and viscous liquids.
Functional category	Ointment base, plasticizer, solvent, suppository base, Lubricant in tablet and capsule formulation (1.0-5.0ml)
pH	3.0-7.0
Viscosity	15-20 mPa×s
Melting point	37-40°C
Solubility:	Soluble in acetone, alcohols, benzene, glycerine, and glycols.

5. PVP K30^[50]

Table 1.17 PVP K30

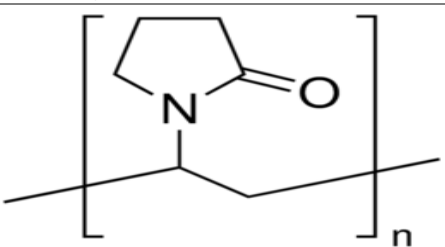
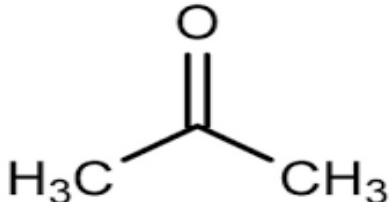
Synonyms	E1201, Kollidon, Plasdone, poly(1-(2-oxo-1-pyrrolidinyl)ethylene), Polyvidone, polyvinylpyrrolidone, PVP, 1-vinyl-2-pyrrolidone polymer.
Chemical name and CAS registry number	1-Ethenyl-2-pyrrolidinone homopolymer (9003-39-8)
Empirical formula and molecular weight	(C ₆ H ₉ NO) _n and 50000.
Structure	
Description	Fine, white to creamy-white coloured, odourless or almost odourless, hygroscopic powder.
Functional category	Used as a disintegrant, dissolution aid, suspending agent (up to 5%), tablet binder.
pH	3.0-7.0
Viscosity	5.5-8.5 mPa×s
Melting point	150°C
Solubility:	Freely Soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

Table 1.18 Property of PVP Grade

Molecular Weight	10 K	30 K	40 K	360 K
K value*:	12-18	27-33	28-32	90-103
Synonym:	PVP K 15	PVP K 30	PVP K 30	PVP K 90
Bulk Density (lb/cu ft.)	36	29	20	--

6. Acetone ^[51]

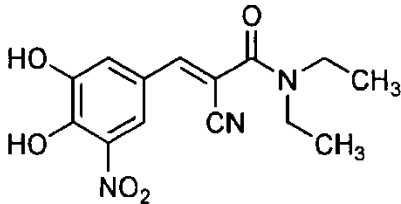
Table 1.19 Acetone

IUPAC Name	Propan-2-one
CAS No	67-64-1
Structure formula	CH ₃ -CO-CH ₃
Structure	
Water solubility	100% at 20°C
Colour	Colourless
Odour	Mildly pungent and aromatic
Solubility	Miscible in water, benzene, diethyl ether, methanol, chloroform, and ethanol.
Viscosity	0.295 mPa*s
Use	It is new in a variety of common medical and cosmetic application & is too scheduled as an element in food additives & food packaging. Dermatologists utilize acetone by alcohol used for acne treatments to peel dry skin. General agents used nowadays for chemical peels are salicylic acid, glycolic acid, Acetone or a combination of these agents is often used in this procedure.

7. Talc ^[52]

Table 1.20 Talc

Non-proprietary name	BP: Purified Talc, JP: Talc, Ph.Eur: Talc, USP: Talc
Synonyms	Altal; E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Imperial, Luzenac Pharma, magnesium hydrogen meta silicate. Magsil Osmanthus, Magsil Star, powdered talc, purified French chalk, Purtalc, soapstone, steatite, Superiore, Talcum.
Chemical name and CAS registry number	Talc [14807-96-6]
Empirical formula and molecular weight	It is a purified, hydrated, magnesium silicate. Approximating to the formula Mg ₆ (Si ₂ O ₅) ₄ (OH) ₄ . It may contain small, variable amounts of aluminium silicate and iron.

Structure	
Description	Talc is a very fine, white to greyish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness
Functional category	Anticaking agent; Glidant; tablet and capsule diluent; tablet and capsule lubricant
pH	7.0–10.0
Typical Properties	Density(bulk): - 0.4g/cm ³ Moisture content: - Talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%. Solubility: Practically insoluble in dilute acids and alkalis, organic solvents, and water.
Stability and storage conditions	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. Talc should be stored in a well-closed container in a cool, dry place.

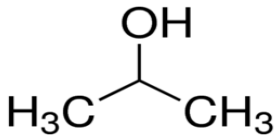
Applications in Pharmaceutical formulation or technology

Table 1.21 Applications of Talc

Use	Concentration (%)
Dusting powder	90.0-99.0
Glidant and tablet lubricant	1.0-10.0
Tablet and capsule diluent	5.0-30.0

8. Isopropyl alcohol^[53]

Table 1.22 Isopropyl alcohol

Non- proprietary name	BP: Isopropyl Alcohol, JP: Isopropanol, Ph.Eur: Isopropyl Alcohol, USP: Isopropyl Alcohol
Synonyms	Alcohol isopropylicus; dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; sec propyl alcohol; rubbing alcohol.
Chemical Name and CAS registry number	Propan-2-ol [67-63-0]
Empirical formula and molecular weight	C ₃ H ₈ O 60.1
Structure	
Description	Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.
Functional category	Disinfectant; solvent
Typical Properties	Boiling point: 82.4°C Melting point: -88.5°C

	Moisture content: 0.1–13%w/w for commercial grades (13%w/w corresponds to the water azeotrope). Solubility Miscible with benzene, chloroform, ethanol (95%), ether, glycerine, and water. It is soluble in acetone and insoluble in salt.
Stability and storage conditions	It should be stored in an airtight container in a cool and dry place.

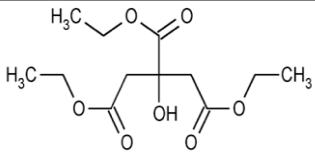
9. Titanium Dioxide ^[54]

Table 1.23 Titanium Dioxide

Non- proprietary name	BP: Titanium Dioxide, JP: Titanium Oxide, Ph.Eur: Titanium Dioxide, USP: Titanium Dioxide
Synonyms	Anatase titanium dioxide, brookite titanium dioxide, Color index number: 77891, E171, Hombitan FF-Pharma, Kemira AFDC, Kronos 1171, pigment white 6, Pretiox AV-01-FG, rutile titanium dioxide, Tioxide, TiPure, titanic anhydride, titaniidioxidum, Tronox.
Chemical name and CAS registry number	Dioxotitanium [13463-67-7]
Empirical formula and molecular weight	TiO ₂ and 79.88
Structure	$O = Ti = O$
Description	It is white, amorphous, odorless, and tasteless, nonhygroscopic powder. Although the average particle size of titanium dioxide powder is less than 1 mm, commercial titanium dioxide generally occurs as aggregated particles of approximately 100nm in diameter. Titanium dioxide may occur in several different crystalline forms: rutile; Anatase and brookite. Among of these, rutile and anatase are only forms of commercial importance. Rutile is the more thermodynamically stable crystalline form, but anatase is the form most commonly used in pharmaceutical applications.
Functional category	Coating agent; opacifier; pigment
Typical properties	Bulk Density: 0.4–0.62 g/cm ³ Melting point: -1855°C Moisture content: - 0.44% Solubility: Practically insoluble in dilute sulfuric acid, hydrochloric acid, nitric acid, organic solvents, and water. Soluble in hydrofluoric acid and hot concentrated sulfuric acid. Solubility depends on previous heat treatment; prolonged heating produces a less-soluble material.
Stability and storage conditions	Titanium dioxide is extremely stable at high temperatures. This is due to the strong bond between the tetravalent titanium ion and the bivalent oxygen ions. However, titanium dioxide can lose small, unweighable amounts of oxygen by interaction with radiant energy. This oxygen can easily recombine again as a part of a reversible Photochemical reaction, particularly if there is no Oxidisable material available. These small oxygen losses are important because they can cause significant changes in the optical and electrical properties of the pigment. Titanium dioxide should be stored in a well-closed container, protected from light, in a cool, dry place.

10. Triethyl Citrate^[55]

Table 1.24 Triethyl Citrate

Non-proprietary name	BP: Triethyl Citrate, Ph.Eur: Triethyl Citrate, USP-NF: Triethyl Citrate
Synonyms	Citric acid ethyl ester; Citroflex 2; Citrofol AI; E1505; ethyl citrate; Hydagen CAT; 1,2,3-propanetricarboxylic acid, 2-hydroxy-, triethyl ester (9CI); TEC; triethylscitras.
Chemical Name and CAS registry number	2-Hydroxy-1,2,3-propanetricarboxylic acid triethyl ester [77-93-0]
Empirical formula and molecular weight	C ₁₂ H ₂₀ O ₇ and 276.29
Structure	
Description	Triethyl citrate is a clear, viscous, odorless, and practically colorless, hygroscopic liquid.
Functional category	Plasticizer; solvent.
Typical Properties	Density(bulk): - 0.4–0.62 g/cm ³ Melting point: - 294°C Moisture content: - 0.44% Solubility: Soluble 1 part in 125 part of peanut oil, 1 part in 15 part of water. Miscible with ethanol (95%), acetone, and propan-2-ol.
Stability and storage conditions	It should be stored in cool & dry place in a closed container.

11. Eudragit S 100^[56]

Table 1.25 Eudragit S 100

Non-Proprietary Names	BP: Acidumm ethacrylicum et methyl is methacryl as polymer is atum 1:2, USPNF: Methacrylic acid copolymer
Synonyms	Polymericmethacrylates.
Chemical Name	Poly (methacrylate, methyl methacrylate) 1: 2 is known as Eudragit S-100.
CAS NO	25086-15-1

Functional category	Film forming agent, tablet binder, tablet diluent, enteric coating material.
Structure	$\left[\begin{array}{cccc} R^1 & R^3 & R^1 & R^3 \\ & & & \\ -C- & CH_2- & C- & CH_2- \\ & & & & & & \\ C=O & & C=O & & C=O & & C=O \\ & & & & & & \\ O & & O & & O & & O \\ & & & & & & \\ R^2 & & R^4 & & R^2 & & R^4 \end{array} \right]_n$
Empirical Formula and molecular Weight	<p>EUDRAGIT® S 100 are anionic copolymers based on methacrylic acid and methyl methacrylate.</p> <p>R1, R3 = CH3</p> <p>R2 = H</p> <p>R4 = CH3 125,000 g/mol.</p>
Description	Anionic, White free flowing powders.
Typical Properties	<p>Density(bulk): - 0.390 g/cm³</p> <p>Solubility: Eudragit S 100 is soluble in acetones, alcohols and 1N NaOH, also soluble in intestinal fluid from pH 7.</p>
Stability and Storage Conditions	<p>Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, but it does not affect the quality of the substance, This clump can readily be broken. Dry powder should be stored in a tightly closed container at less than 30°C. It will be stable for at least 3 years.</p>

2. LITERATURE REVIEW

2.1. Review of Literature on Drug & Excipients

- **Samia A. Nour et al., 2016**, studied formulation & evaluation of colon targeted chewable tablet of Bumadizone calcium using (PVP K 30), maize starch, mannitol and eudragit S-100, L-100 polymer to transport drug to colon for local treatment of ulcerative colitis. The result of two independent variables, Eudragit S100 & Eudragit L 100 and differ release was study at 12hrs. From in-vitro & in-vivo study formulation composed of (EU S100 1:3, 250 mg mannitol, 50mg maize starch and 20mg cinnamon powder) minimizes drug release in the upper gastrointestinal tract and at colon it gives highest release.
- **Maimana A. Magdy et al., 2013**, studied stability indicating spectrophotometric methods for determination of bumadizone in the presence of its alkaline degradation product The four methods were found to be specific for determination BUM in presence of different concentrations of DEG I and had successfully applied for the determination of BUM in Octomotol tablets.
- **Samia A. Nour et al., 2014**, studied Bumadizone calcium dihydrate microspheres were dense into tablet contain the (NSAIDS) non-steroidal anti-inflammatory. The effect of polymer Eudragit RS 100, ethyl cellulose, cellulose acetate butyrate. Candidate formula F15 (microspheres prepared using a ratio of 18:1 for BDZ:CAB and compressed into tablets using 50% pectin and 50% Avicel in the coat) was able to modulate drug release in colon by avoiding drug release in the gastric ambient, and reaching the colonic targeting where 99.7% release was achieved within 12 hrs.
- **Sateesh Kumar Vemula et al., 2015**, studied to formulate and study the pharmacokinetics of colon-specific pulsatile ketorolac tromethamine tablets using double-compression coating method In this, inner compression coat made of sodium starch glycolate as swelling layer and outer compression coat (release controlling layer) contains sodium alginate and Hydroxypropyl methylcellulose K 15M. From the in vitro drug release studies, F5 tablets sodium starch glycolate: **HPMC K15M** in ratio 1:1 showed $5.02 \pm 0.16\%$ drug release in 5 h and it was progressively expanded to $99.78 \pm 0.64\%$ in 24 h that demonstrate the colon-specific drug release.
- **Rohit Mehta et al., 2013**, studied to prepare matrix tablets of naproxen using a hydrophobic polymer, i.e., Eudragit RLPO, RSPO, and combination of both, by wet granulation method. The tablets were further coated with different concentrations of **Eudragit S-100**, a pH-sensitive polymer, by dip immerse method. In vitro drug release studies of tablets were carried out in different dissolution media, i.e., 0.1 N HCl (pH 1.2), phosphate buffers pH 6.8 and 7.4, with or without rat cecal content matrix tablet of naproxen was formulate with Eudragit S 100 like a pH sensitive polymer. The outcome demonstrate that the tablets coated with Eudragit S-100 show a sustain release of 94%.
- **Minjie Sun et al., 2014**, studied to develop colon adhesive pellets of 5-aminosalicylic acid (5-ASA) for the treatment of ulcerative colitis. The core of the pellet was formulated from bioadhesive agents, Carbomer 940 and Hydroxypropyl cellulose (HPC), by extrusion/Spheronization method and coated with Surelease1 as inner layer for waterproof and with Eudragit1 S100 as outer layer for pH control **Microcrystalline cellulose 101 (PH 301)** was found to be the best agent for pellet core. The ratio of CP940 to HPC should be kept as (1:1) to achieve high bioadhesion. When the amount of Surelease1 was from 16% to 20% and of Eudragit S100 was 28%, the dissolution profiles of coated pellets revealed no drug release in the artificial gastric fluid (pH 1.0) within 2 hrs and less than 10% was released in phosphate buffer (pH 6.0) within 2 hrs whereas complete dissolution was observed in colonic fluid of pH 7.4 for 20 hrs.
- **Zan Liu et al., 2016**, studied sticking of pellets caused by EudragitL30D-55 was observed during the release process, leading to change in drug release. Talcum powder (talc) was used in esomeprazole magnesium pellets to prevent sticking and modify release of pellets. Talc as antiadherent could successfully prevent the pellets from aggregating in vitro by the two methods tested: (i) physically mixed with resulted pellets and (ii) coating the resulted pellets. Besides, talc levels in sub coat had different influences on drug release from coated pellets in phosphate buffer solution (pH 6.8 and 6.0) and distilled water, attributing to the different release mechanisms of pellets in these three media. **Talc** could not only prevent the sticking during release process, but also affect the release of the EMZ from the enteric-coated pellets.

- **Pranjal Kumar S et al., 2012**, studied to develop colon targeted film coated tablets of ibuprofen using HPMC K4M, Eudragit L100 & **Ethyl cellulose** as carriers. The formulation of drug released 98.34%. & to provide targeting of ibuprofen for local action in the colon due its least release of the drug in the first 5 hr. The effect of film coated tablet system is a capable vehicle for prevent quick hydrolysis in gastric environment and recovering oral Bioavailability of ibuprofen for the treatment of disease of colon region.
- **Mihir K Raval, Riddhi V Ramani et al., 2013**, studied to develop intestinal-targeted pellets of Budesonide, a potent glucocorticoid, used for the treatment of ulcerative colitis and Crohn's disease by extrusion and Spheronization method. In this study, the pellets were coated by spray coating technique using Eudragit S100 as an enteric polymer. Optimization of binders like **PVP K30**, pectin, guar gum, sodium alginate, and xanthan gum in 2% w/v. On the basis of physical appearance roundness, smoothness, and strength of the pellets, PVP K30 was selected as a binder for further pellet preparation.
- **Cheng et al.25** developed Time- and pH-dependent colon-specific drug delivery systems (CDDS) for orally administered diclofenac sodium (DS) and 5-aminosalicylic acid (5-ASA). DS tablets and 5-ASA pellets were coated by Ethylcellulose (EC) and methacrylic acid copolymers (Eudragit® L100 and S100), respectively. Release profile of time-dependent DS coated tablets was not influenced by pH of the dissolution medium on the contrary release profile of pH dependent 5-ASA coated pellets was significantly governed by pH. It was concluded that, on using regular coating techniques also colon specific drug delivery can be obtained.

2.2 Review of Literature on Drug Delivery System

- **Uma Devi S, Suresh Set.al.,2010**, The aceclofenac using chitosan as a Microbially degradable polymeric transporter and to coat the optimized batches with a pH dependent polymeric coating solution containing **Eudragit L100 & S100**.The entire of aceclofenac released from the chitosan tablets at changed time interval was estimated by UV spectrophotometric method. The results of chitosan tablets are capable for colon targeting of match the Chrono biological symptom for effective treatment of rheumatoid arthritis.
- **Reza Mahjub et al., 2016**, Studied development of enteric coated pellets containing Lansoprazole by an extrusion/ Spheronization technique. Eight different formulations based on lactose and six different formulations based on mannitol, consisting of different portions of other excipients including sucrose, hydroxy propyl methyl cellulose, magnesium carbonate, and sodium lauryl sulfate have been prepared. Among different formulations, F14, which consists of mannitol, sucrose, HPMC, talc, magnesium carbonate, and lansoprazole, is considered to be the best formulation. Six other different formulations for the preparation of enteric coatings based on **Eudragit S100**, Eudragit L100, triethyl citrate, and talc were prepared and coating procedure on pellets (F14) was performed using coating pan.
- **D.I. Wilson et al., 2010** studied to develop an extrusion–spheronisation (E–S) route to manufacture pellets with a high loading (≥ 90 wt %) of 5-aminosalicylic acid (5-ASA).The influence of the API chemical and physical properties on the rheological behavior of MCC-based pastes undergoing extrusion was investigated. The performance as E–S aids of the standard **Avicel PH101** grade of MCC and of colloidal ones (i.e. Avicel RC591 and CL611), alongside high loadings of 5-ASA, was also evaluated. Multi particulate E–S formulation containing not less than 90 wt%5-ASA could be developed by combining an accordingly micronized API and colloidal MCC grade.
- **Simone Cristina Deo et al., 2011**, studied to develop and evaluate a multi particulate system consisting of pellets coated with polymer for pH-dependent release, derived from methacrylic acid and incorporated into the tablet dosage form of mesalazine as a model drug. The extrusion-spheronisation technique was used, resulting in smooth and spherical pellets with uniform size distribution, which were coated in fluidized bed using Opadry Enteric 94K28327 containing **Eudragit S100** as the agent regulating drug release. The dissolution profile of coated pellets showed good control of drug release from the polymer at the two levels of coating evaluated (8% and 10%), but only the 10% coated pellets were statistically similar to Asalit 400 mg.

- **M. S. Shetage et al., 2014**, studied Drug loaded pellets are coated with pH independent Eudragit RS100 and further coated with pH dependent Eudragit S100 in R and D pan coater. Here different concentration of Drug coating Eudragit RS100 and further coated with pH dependent Eudragit S100 in pan coater. The formulation was further characterized by in vitro dissolution study, drug release kinetics and Micromeritic properties. coating level of both the coats play a significant role in drug release property of which coating level of Eudragit RS 100 was more significant after the tablet reaches colon optimized batch having 20% w/w Eudragit RS 100 and 30% w/w with S100 as the drug release was below 20% in SIF so that it can be efficiently colon targeted, and the release is sustained up to 12 hrs which is desirable for twice daily dosing of metoprolol.
- **S. J. Kshirsagar et al., 2009**, studied to develop the polymer coated diclofenac tablet containing superdisintegrant for colonic drug delivery and compare the in vivo performance of two polymers for site specificity. Eudragit FS 3D and Eudragit S100 were used as pH sensitive polymers. Tablets were coated separately with Eudragit FS 30D and Eudragit S100 in various thicknesses and evaluated for in vitro drug release using changing pH method In vitro release studies reveals that Eudragit FS30D coated tablet with 10%w/w coating level start release of drug at pH 6.8 after suitable lag time in the same pH which corresponds to colonic arrival time, as compare to Eudragit S100 coated tablet which release only at higher pH, approximating the transverse colon.
- **Sanjay K. Jain et al., 2015** studied Eudragit S100 coated Citrus Pectin Nanoparticles (E-CPNs) were prepared for the colon targeting of 5-Fluorouracil (5-FU). Citrus pectin also acts as a ligand for galectin-3 receptors that are over expressed on colorectal cancer cells. In vitro drug release studies revealed selective drug release in the colonic region in the case of E-CPNs of more than 70% after 24 h. In vitro cytotoxicity assay (Sulphorhodamine B assay) was performed against HT-29 cancer cells and exhibited 1.5 fold greater cytotoxicity potential of nanoparticles compared to 5-FU solution. In vivo data clearly depicted that Eudragit S100 successfully guarded nanoparticles to reach the colonic region wherein nanoparticles were taken up and showed drug release for an extended period of time.
- **Minjie sun et al., 2014**, studied Preparation and evaluation of colon adhesive pellets of 5-aminosalicylic acid (5-ASA) for the treatment of ulcerative colitis. The core of the pellet was formulated from bioadhesive agents, Carbomer 940 and Hydroxypropyl cellulose (HPC), by Extrusion/Spheronization method and coated with Surelease as inner layer for waterproof and with Eudragit1 S100 as outer layer for pH control. **Microcrystalline cellulose 101(PH 301)** was found to be the best agent for pellet core. The ratio of CP940 to HPC should be kept as (1:1) to achieve high bioadhesion. When the amount of Surelease was from 16% to 20% and of Eudragit1 S100 was 28%, the dissolution profiles of coated pellets revealed no drug release in the artificial gastric fluid (pH 1.0) within 2 h and less than 10% was released in phosphate buffer (pH 6.0) within 2 h whereas complete dissolution was observed in colonic fluid of pH 7.4 for 20 hrs.
- **Raveendra M et al., 2012** studied to prepare floating microspheres of Timolol maleate using Eudragit S 100 and Eudragit L 100 as polymer. Timolol maleate is non-steroidal anti-inflammatory drug with short elimination half-life 1-3 hours. Floating microspheres of Timolol maleate were set by emulsion solvent diffusion method using Eudragit S 100 and Eudragit L 100 as polymer. Formulation EU2 prepared with Eudragit S 100 drug polymer ratio incorporation efficiency and percentage drug release 92.26 % for a period of 12 hrs.
- **Sharma Madhu et al., 2012**, studied the formulation of Mesalazine tablet with mixture of Eudragit S-100 and L-100 as enteric coating. The core tablets of Mesalazine were ready for using wet granulation containing a superdisintegrant. The plan of here study is to develop colonic drug delivery of Mesalazine for ulcerative colitis using HPMC K-4M & HPMC K-15M as a polymer. Results also establish that mixture of Eudragit S-100 and L-100 can be effectively used to coat tablets for colon targeted release of drug.
- **Vivek ranjansinhaet al., 2011**, studied to found the effectiveness of a mixed film composed of ethyl cellulose/Eudragit S100 for colonic delivery of 5-flourouracil (5-FU). Tablets cores containing 5-FU were prepared by direct compression method by coating at different levels with a non-aqueous solution containing ethyl cellulose/Eudragit S100. The release was establish to be higher in tablets containing Avicel as filler owing to its wicking action compare to that from lactose containing cores

- **Anuj Chawla et al., 2015**, studied the plan of the study was to get ready site specific drug delivery of naproxen sodium using sodium alginate and Eudragit S-100 as a mucoadhesive and pH-sensitive polymer, respectively. Core microspheres of alginate were prepared by a modified emulsification method followed by cross-linking with CaCl₂, which was further coated with the pH dependent polymer Eudragit S-100 to stop drug release in the upper gastrointestinal tract. Furthermore, drug liberates from Eudragit S-100 coated microspheres follow the Korsmeyer-Peppas equation, representing 2 years shelf life of the formulation.
- **Faizan Sayeed et al., 2014**, studied The polymers used to in the time dependent part of the release were HPMC and Ethyl cellulose with dissimilar ratios as the time with ethyl cellulose increases due to its insoluble nature and this is reduced by the soluble nature of HPMC which would give the coating layer some lipophilicity with which the release would be initiated for the drug release. The coating of these two polymers is done by dry coating method. The enteric coat over the time dependent polymer coat is to pass the dosage form from the stomach which gives a two hours lag time.
- **Akanksha Garud et al., 2013** studied to prepare, characterize and evaluate the colon-targeted microspheres of mesalamine for the treatment and management of ulcerative colitis (UC). Microspheres were prepared by the ionic-gelation emulsification method using tripolyphosphate (TPP) as cross linking agent. The microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach. The release profile of mesalamine from Eudragit-coated chitosan micro-spheres was found to be pH dependent.
- **Lorena Segale et al., 2016**, studied formulation and the coating compositions of biopolymeric pellets containing ranolazine were studied to improve their technological and biopharmaceutical properties. Eudragit L100 (EU L100) and Eudragit L30 D-55-coated alginate and alginate-hydroxypropylcellulose (HPC) pellets were prepared by ionotropic gelation using 3 concentrations of HPC (0.50%, 0.65%, and 1.00% wt/wt) and apply indifferent percentages (5%, 10%, 20%, and 30% wt/wt) of coating material. The pellets containing 0.65% of HPC and coated with 20% EU L100 represented the best formulation, able to limit the drug release in acidic environment and to control it at pH 6.8.
- **Dhiren Daslaniya et al., 2009**, studied Mesalamine pellets were prepared by Coating drug solution on sugar sphere followed by various functional coating. The influence of rate controlling membrane made up of Eudragit RSPO and Eudragit RLPO in combination with delay release polymer coating with Eudragit L100 in different proportions on drug release kinetics was studied. Optimized formulation containing 796% drug loading on sugar sphere followed by coated with Eudragit L100 (15%) and Eudragit RSPO & RLPO (10% in ratio of 7:3) were evaluated for In-vitro release profile. Prepared Pellets can be used in the treatment of the ulcerative colitis.

2.3 SUMMARY OF PSAR REPORT:-

Table 4.1 Summary of PSAR Report

Sr. No.	Patent number	Application	Title of Patent
1.	WO2008148798A2		Controlled release pharmaceutical compositions for prolonged effect
2.	WO2002076429A1		pH dependent sustained release, drug, delivery composition
3.	US5482718A		Colon-targeted delivery system
4.	US20070243253A1		Colonic drug delivery formulation
5.	US20100239667A1		Controlled release Pharmaceutical compositions for Prolonged effect

- Looking at above 05 patents, your Dissertation project is novel up to what extent?

Novelty grade: 50 to 90%

- **RATIONALE OF PATENT**

Above five patents describes formulation of pH dependent & controlled release drug for prolonged effect. It briefs pharmaceutical compositions of different dosage forms that facilitate colon target drug delivery of the drug. No any patented work done on colon targeted drug delivery of Bumadizone calcium pellets. Hence, the selected title is novel.

3. AIM, OBJECTIVE AND RATIONALE OF WORK

3.1. Aim of Work

- The Aim of present work is to Formulation and Evaluation of colon targeted enteric coated pellets of Bumadizone Calcium.
- Inflammatory Bowel Diseases primarily includes ulcerative colitis and Crohn's disease.
- Ulcerative colitis occurs when the lining of the large intestine (colon or bowel) and the rectum become inflamed.
- Crohn's most commonly affects the end of the small bowel (the ileum) and the beginning of the colon.
- One of the current treatments available for treating the IBD is with Cyclooxygenase (COX) inhibitor named Bumadizone Calcium. It has conventional formulations in form of conventional tablets, microsphere, Nanoparticles. Administration of drug used in treatment of ulcerative colitis is associate with a number of side effects decreased efficiency & drug dosing.

3.2 Objectives of Work

- To formulate colon targeted enteric coated pellets which will release the drug for sustained period of time.
- To study preformulation study of drug.
- To study the drug-exciipient compatibility
- To select excipients & coating material.
- To optimize the amount of coating material.
- To reduce release of drug in stomach
- To study the dissolution behaviour of drug and to evaluation of dosage form.

3.3 Rationale

3.3.1 Rationale for selection of sustained release dosage form: -

- Sustained release dosage forms maintain the plasma concentration of drug for longer period of time and avoid the fluctuations in plasma concentration, so that the dose related side effects can be avoided.
- Duration of action can be prolonged hence dosing frequency can be reduced.

3.3.2 Rationale for selection of COX Inhibitor for sustained release dosage form: -

- Sustained release dosage forms maintain the plasma concentration of Bumadizone Calcium for longer period of time and avoid the fluctuations in plasma concentration, so that the dose related side effects can be avoided e.g. ulcers erosions.
- We aimed to diminish the % of drug release before target area is to be less than 20% and to enhance the bumadizone release in the aimed area & total bumadizone release after 12 hrs. One of the most common side effects of NSAIDs is gastric discomfort and ulcers erosions.
- This is due to their ability to inhibit COX-I (Cyclooxygenase-1) enzyme leading to prostaglandin (PGs) deficiency. PGs have protective role in the stomach as they regulate bicarbonate and mucous production. So generally decreasing drug release before target area will lead to both decreasing side special effects of the drug and shifting drug release in the target area.

4. MATERIALS AND EQUIPMENTS

4.1 List of Materials, its category/use and their supplier

Table 4.1 List of Materials, its category/use and their suppliers		
Materials	Category/Use	Name of supplier.
Bumadizone calcium	Anti-inflammatory	Reine life Science, Ltd- Ankleshwar, India
MCC pH 101	Disintegrating Agent, Filler	Signet
Ethyl cellulose	Film Coating Agent	Molychem, Mumbai
PEG 600	Controlled release agent	Lobachemie Pvt. Ltd., Mumbai
Poly vinyl pyrrolidone 30 (PVP K30)	Binder	Sisco research lab. Pvt. Ltd., Mumbai
Hydroxy propyl methyl cellulose K-15	Polymer, Controlled release agent	Polycoat, Mumbai
Eudragit S 100	Enteric coating agent,	Evonik, Mumbai.
Titanium dioxide	Opacifying agent	Lobachemie Pvt. Ltd., Mumbai
Triethyl citrate	Stabilizer	Lobachemie Pvt. Ltd., Mumbai
Talc	Filler, Antiadherent	Molychem, Mumbai
Acetone	Organic solvent	Rankem, RFCL LTD., New Delhi
IPA	Organic solvent	Lobachemie Pvt. Ltd., Mumbai

4.2 List of Equipments used and their suppliers

Table 4.2 List of Equipments used and their suppliers	
Name of Equipment	Name of Company and Model
Digital pH Meter	Elico Li 612, Mumbai, India
Digital Weighing Balance	Sartorius, India
Dissolution Test Apparatus	Electrolab- Etd-1020, USP, Mumbai., India
DSC	Hitachi Hitech DC 7020
Electronic Balance	Shimadzu Aux220, India
Extruder Spheronizer	Caleva Multi Lab, Caleva Process solutions

Friability Test Apparatus	Electrolab- EF 2, USP, Mumbai, India
Hot Air Oven	Nova Instruments Pvt. Ltd, Ahmadabad, Gujarat, India
Precision Balance	Reputed Micro System, Ahmadabad, Gujarat, India
Pan Coater	Kalweka HD-410 AC
Tapped Density Apparatus	Electrolab- Tdt-060p, USP, Mumbai, India
UV-Visible Spectrophotometer	Shimadzu Analytical Pvt Ltd., Japan- UV 1800
FTIR	FTIR-8400s (Shimadzu, Kyoto, Japan)
Vernier Calliper	Model Ultratech
Stability Chamber	Thermolab India

4.3 Process Flow of Preparation

- **Extrusion Spheronization & Enteric Coating:-**

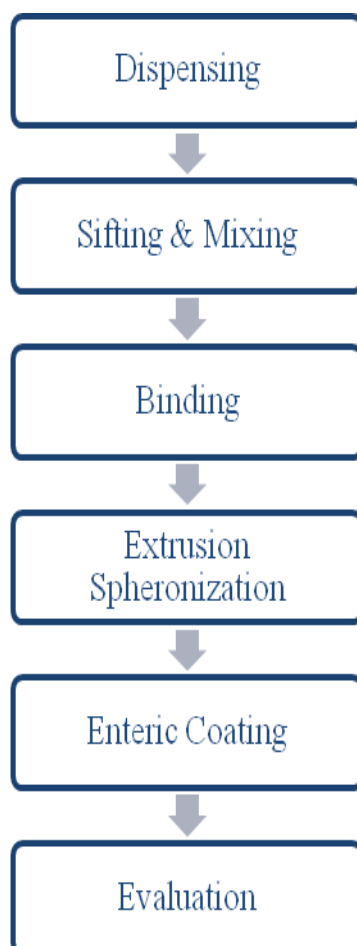


Figure 13 Process Flow of Preparation

5. METHODOLOGY

5.1. Preformulation studies

5.1.1. Analytical method for estimation of Bumadizone calcium

5.1.1.1 Preparation of 0.1N HCL

For preparation of 0.1 N HCL, take 8.5ml of conc. HCL and dilute with 1000ml of distilled water.

5.1.1.2 Preparation of phosphate buffer 6.8

Dissolve 0.19 g of potassium di hydrogen phosphate (KH_2PO_4), 2.89g of disodium hydrogen phosphate (Na_2HPO_4), and 8.0 g sodium chloride (NaCl) in sufficient quantity of water to produce 1000ml add phosphoric acid to adjust pH 6.8 (Pharmacopeia, 2010).

5.1.1.3 Preparation of phosphate buffer 7.4

Dissolve 2.38 g of disodium hydrogen orthophosphate, 0.19 g of orthophosphate and 8.0 g of chloride in sufficient water to produce 1000 ml and adjust the pH if necessary (Pharmacopeia, 2010).

5.1.1.4 Spectrum of Bumadizone calcium in for determination of λ_{max} by UV visible spectrophotometer.

A different concentration of Bumadizone calcium solution was prepared in pH 6.8, 7.4, 1.2 and methanol was scanned in UV range between 200 to 400nm wavelength (λ_{max}) for the analysis. (Narang and Sharma, 2011) Bumadizone calcium showed maximum absorbance at 237nm.

5.1.1.5 Standard Calibration Curve of Bumadizone in Methanol: -

Weigh accurate quantity of Bumadizone calcium (50mg) and transfer in 50ml of volumetric flask and volume was made up to 50ml with methanol. The stock solution obtained was 1000 $\mu\text{g}/\text{ml}$. Aliquots of 5 ml of stock solution was pipette out from 50 ml standard volumetric flask and final volume was adjusted up to 50 ml with methanol to give 100 $\mu\text{g}/\text{ml}$ solutions. Aliquots of 0.2, 0.4, 0.6, 0.8, 1.2, 1.4, 1.6, ml of stock solution were pipette out from diluted solution of volumetric flask and final volume was adjusted up to 10 ml with methanol to give concentration of 2,4,6,8,10,12,14, and 16 $\mu\text{g}/\text{ml}$. The absorbance was measured at 236nm in UV spectrophotometer against Blank methanol. (Kamble et al., 2014)

5.1.1.6 Standard Calibration Curve of Bumadizone in pH 1.2: -

Weigh accurate quantity of bumadizone calcium (50mg) and transfer in 50ml of volumetric flask and volume was made up to 50ml with pH 1.2 solutions. The stock solution obtained was 1000 $\mu\text{g}/\text{ml}$. Aliquots of 5 ml of stock solution was pipette out from 50 ml standard volumetric flask and final volume was adjusted up to 50 ml with pH 1.2 solutions to give 100 $\mu\text{g}/\text{ml}$ solutions. Aliquots of 1.2, 1.4, 1.6, 1.8, 2.0 ml of stock solution were pipette out from diluted solution of volumetric flask and final volume was adjusted up to 10 ml with pH 1.2 solution to give concentration of 10, 12,14,16,18 and 20 $\mu\text{g}/\text{ml}$. The absorbance was measured at 236nm in UV spectrophotometer against Blank pH 1.2 solutions. (Kamble et al., 2014)

5.1.1.7 Standard Calibration Curve of Bumadizone in pH 6.8: -

Weigh accurate quantity of bumadizone calcium (50mg) and transfer in 50ml of volumetric flask and volume was made up to 50ml with pH 6.8 buffer. The stock solution obtained was 1000 $\mu\text{g}/\text{ml}$. Aliquots of 5 ml of stock solution was pipette out from 50 ml standard volumetric flask and final volume was adjusted up to 50 ml with pH 6.8 buffer to give 100 $\mu\text{g}/\text{ml}$ solutions. Aliquots of 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0 ml of stock solution were pipette out from diluted solution of volumetric flask and final volume was adjusted up to 10 ml with pH 6.8 buffer to give concentration of 4, 6, 8, 10, 12, 14, 16, 18 and 20 $\mu\text{g}/\text{ml}$. The absorbance was measured at 236nm in UV spectrophotometer against Blank pH 6.8 buffer. (Kamble et al., 2014)

5.1.1.8 Standard Calibration Curve of Bumadizone in pH 7.4: -

Weigh accurate quantity of bumadizone calcium (50mg) and transfer in 50ml of volumetric flask and volume was made up to 50ml with pH 7.4 buffer. The stock solution obtained was 1000 $\mu\text{g}/\text{ml}$. Aliquots of 5 ml of stock solution was pipette out from 50 ml standard volumetric flask and final volume was adjusted up to 50 ml with pH 7.4 buffer to give 100 $\mu\text{g}/\text{ml}$ solutions. Aliquots of 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 ml of stock solution were pipette out from diluted solution of volumetric flask and final volume was adjusted up to 10 ml with pH 7.4 buffer to give concentration of 4, 6, 8, 10, 12,

14, 16 and 18 μ g/ml. The absorbance was measured at 236nm in UV spectrophotometer against Blank pH 7.4 buffer. (Kamble et al., 2014)

5.1.2 Identification of Drug:

Identification of drug was carried out by Melting point, Fourier transform infra-red absorption spectroscopy (FTIR) and Differential scanning calorimetry (DSC).

5.1.2.1. Determination of Melting Point of Bumadizone Calcium

The melting point of a solid is the temperature at which it changes state from solid to liquid. At the melting point, the solid and liquid phase exists in equilibrium. Melting point of drug was determined by capillary method using digital melting point apparatus (VEEGO VMP-DS). Fine powder of the drug was filled in glass capillary tube which was previously sealed at one end. This capillary tube was then inserted into the sample holder of the digital melting point apparatus and temperature at which the powder melted was recorded.

5.1.3. Drug-Excipients compatibility studies

It is the important prerequisite in development of any drug delivery system. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious and safe product. Drug-excipients compatibility study was carried out for Drug (Bumadizone calcium hemihydrate), Excipients (MCC, EC, HPMC, PVP K30, PEG 600, and Magnesium Oxide), Physical mixture (Drug and excipients) and Final formulation using FTIR and DSC analysis. (Akula et al., 2015)

5.1.3.1 Fourier transformed infra-red absorption spectroscopy (FT-IR)

Drug and excipients compatibilities were analyzed by IR spectral studies. IR spectra of drug, polymer, drug-polymer physical mixture and the formulation were obtained using FTIR spectrophotometer. Fourier-transformed infrared spectra were obtained on FTIR spectrophotometer (Thermo scientific) using the KBr disk method (2mg of sample in 200 mg of KBr). 1-2 mg of sample was gently triturated with KBr powder and compress into disc by applying pressure for 10 min in a hydraulic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1} . (Narang and Sharma, 2011)

5.1.3.2 Differential Scanning Calorimetry (DSC)

Drug and excipients compatibility studies of pure drug, excipients, physical mixture, and final formulation were analyzed by DSC. DSC analysis was carried out using aluminium sample pans in Differential Scanning Calorimetry (DSC-60, Shimadzu, Japan) at a heating rate 10 $^{\circ}\text{C}$ per minute in the range 30 to 300 $^{\circ}\text{C}$ using differential scanning calorimetry (DSC). (Kallakunta et al., 2012)

5.2 FORMULATION OF BUMADIZONE ENTERIC COATED PELLETS

5.2.1 PREPARATION OF PELLETS (Das b et al., 2012; Gowda D et al., 2012)

The pellets of bumadizone were prepared by using extruder and Spheronization. All The excipients and drug (bumadizone, HPMC, EC, and MCC) were passed through sieve no.40 prior to pelletization and mixed uniformly. Then PVP K30/xanthan gum/pectin (0.5, 1.0, 1.5%w/v) solution was added in sufficient quantity and mixed it. The obtained dough mass was extruded using a piston extruder (1.5mm orifice). The extrudates were immediately spheronized in 80mm diameter friction plate with groove space of 5mm for 15min at a rotation speed of various rpm. The pellets were dried over night at room temperature.

5.2.2 COATING OF THE PREPARED PELLETS

Eudragit S100 as a pH dependent polymer dispersed in the acetone and isopropyl alcohol (1:1) and made the (4, 5, 6%w/v) solution for the coating then added the triethyl citrate as a plasticizer. The details of the coating procedure are summarized in the table.

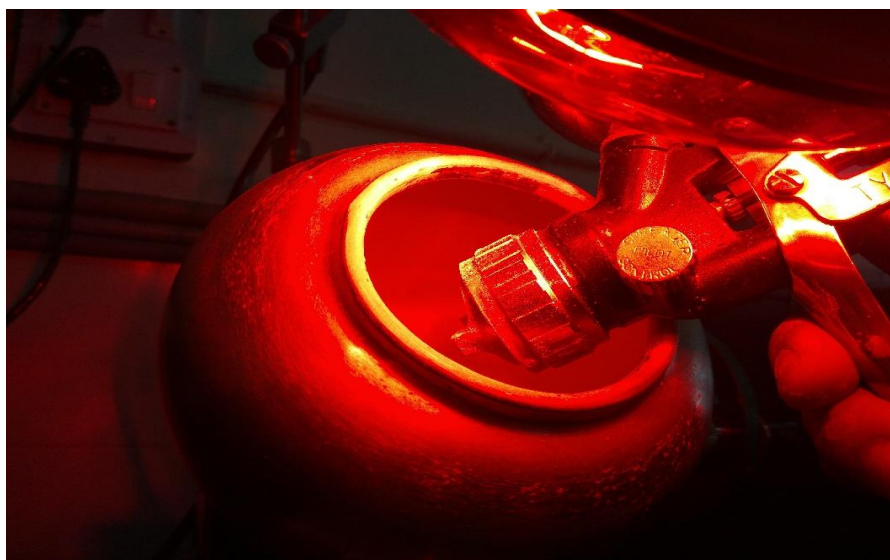


Figure 14: Coating of Pellets in pan coater

Table 5.1 Coating Process Parameters

Process parameter	Specific process condition
Inlet temperature (°c)	55
Product temperature (°c)	37-42
Exhaust temperature (°c)	35-40
Atomizing air pressure(bar)	1.0
Spray rate(mg/min)	8-12

5.3 Preliminary Trials

5.3.1 Screening of Diluent Concentration

MCC PH101 was used as a diluent for the preparation of pellets and different concentration of MCC were screening for the selection of suitable concentration.

Table 5.2 Screening of diluent

Name of Polymer	Quantity(gm)		
	F1	F2	F3
MCC pH 101	6	8	10
EC	1	1	1
HPMC	1	1	1
PVP K30 %(w/v)	1	1	1
PEG-600	1 ml	1 ml	1 ml

5.3.2 Screening of Binder Concentration

Preliminary work was carried out for screening of different binder and its concentration.

Table 5.3 Screening of Binder

Batch No.	F4	F5	F6	F7	F8	F9	F10	F11	F12
	Quantity (gm)								
MCC PH 101	8	8	8	8	8	8	8	8	8
EC	1	1	1	1	1	1	1	1	1
HPMC-k-15 M	1	1	1	1	1	1	1	1	1
Xanthan gum	0.5%	-	-	1%	-	-	1.5%	-	-
Pectin	-	0.5%	-	-	1%	-	-	1.5%	-
PVP K 30	-	-	0.5%	-	-	1%	-	-	1.5%
PEG 600	1 ml	1 ml	1 ml	1ml	1ml	1ml	1ml	1ml	1ml

5.3.3. Screening of Plasticizer Amount

PEG 600 was use as a plasticizer for the preparation of pellets and different amount of PEG 600 were screening for selection of suitable amount.

Table 5.4 Screening of plasticizer

Name of Polymer	Quantity (gm)		
	F13	F14	F15
MCC pH 101	8	8	8
EC	1	1	1
HPMC	1	1	1
PVP K30 %(w/v)	1	1	1
PEG-600	1 ml	2 ml	3 ml

5.3.4 Screening of Polymer

Preliminary study was carried out for screening of polymer (HPMC K4M, HPMC K15M and HPMC K100M)

Table 5.5 Screening of polymer

Batch No.	F16	F17	F18	F19	F20	F21	F22	F23	F24
	Quantity (gm)								
MCC	8	8	8	8	8	8	8	8	8
EC	1	1	1	1	1	1	1	1	1
HPMC K4M	0.5	-	-	1	-	-	1.5	-	-
HPMC K 15 M	-	0.5	-	-	1	-	-	1.5	-
HPMC K 100 M	-	-	0.5	-	-	1	-	-	1.5
PVPK 30%	1	1	1	1	1	1	1	1	1
PEG600	1 ml	1 ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml

5.3.5 Screening of Spheronization speed (rpm)

Preliminary work carried out for screening of Spheronization speed.

Table 5.6 Screening of Spheronization speed

Batch No.	Speed (rpm)	Name of Polymer				
		MCC	EC	HPMC K15M	PVP K30 %(w/v)	PEG 600(ml)
		(gm)				
F25	2000	8	1	1	1%	1
F26	2500	8	1	1	1%	1
F27	3000	8	1	1	1%	1

5.3.6 Effect of Polymer & Eudragit concentration on release profile

Preliminary work carried out for Effect of Ethyl Cellulose, drug to polymer ratio and Effect of concentration of Eudragit S100 on release profile.

Table 5.7 Formulation for study effect of Polymer & Eudragit concentration on release profile

Batch no.	F28	F29	F30	F31	F32	F33
Drug	1 gm	1gm	1gm	1gm	1gm	1gm
MCC 101	8	8	8	8	8	8
EC	0.5	0	0.5	0.5	0.5	0.5
HPMC K15M	1.5	1.5	1.5	0.5	1.5	1.5
PVPK 30(%)	0.5	0.5	0.5	0.5	0.5	0.5
PEG 600	1ml	1ml	1ml	1ml	1ml	1ml
COATING FORMULA						
Eudragit S100	4	4	4	4	5	6
Titanium dioxide	3.5	3.5	3.5	3.5	3.5	3.5
Triethyl citrate	1ml	1ml	1ml	1ml	1ml	1ml
Talc	4	4	4	4	4	4
Acetone	50ml	50ml	50ml	50ml	50ml	50ml
IPA	50ml	50ml	50ml	50ml	50ml	50ml

5.4 Optimization Enteric coated pellets by 32 Full Factorial Design

5.4.1 Experimental Design

5.4.2 Formulation optimization using 3² Full Factorial Design

A 32-randomized full factorial design will be used to quantify the significant independent variables revealed from preliminary studies. In this design 2 factors will be evaluated, each at 3 levels, and experimental trials will be performed at all 9 possible combinations generated by **Design Expert 10.0**. Two independent variables namely X1 (PVP K30), and X2 (% EUDRAGIT S100). (Patel et al., 2014)

On the bases of preliminary batches results, the low, medium and high values of independent variables will be selected and the batches from B1 to B9 will be formulated.

Table 5.8 Application of Full Factorial Design

Independent variable of the formulation			
Independent variables	Low (-1)	Medium (0)	High (+1)
PVP K30(X1)	0.5gm	1gm	1.5gm
Eudragit S100(X2)	4gm	5gm	6gm

The critical parameter of the Liquid-solid compact formation will be selected as responses. They will be as follows.

1. % CPR (12HRS)
2. % CPR after (2 HRS)
3. COATING PROCESS EFFICIENT (CPE)

5.4.2.1 Equation relating independent variables and responses

The equations relating independent variables and responses will be obtained by subjecting the results to statistical evaluation. Microsoft Excel version 2010 will be used to perform multiple linear regressions to determine the control factors that significantly affect the responses. The details of which is given below:

5.4.2.2 Independent Variables (Patel et al., 2014)

R-Value [concentration of binder (X1) and concentration of eudragit S100 (X2)].

5.4.2.3 Responses (Patel et al., 2014)

% CPR at 12hrs (Y1), CPR After 2hrs (Y2), coating process efficiency (Y3).

5.4.2.4 Polynomial equation for 32 full factorial design (Patel et al., 2014)

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_{12}X_1X_2 + \beta_{11}X_1^2 + \beta_{22}X_2^2 + E$$

Where, Y is the measured response,

β_0 is the constant,

β_1, β_2 are the coefficient for the factor X1, X2,

β_{12} , is the coefficient of interaction,

β_{11}, β_{22} , are the coefficients of the quadratic terms,

E is the error term

The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1 and X2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X11 and X22) are included to investigate nonlinearity. The significant factors in the equations will be selected using a stepwise forward and backward elimination for the calculation of regression analysis. The terms of full model having non-significant p value ($p > 0.05$) have negligible contribution in obtaining dependent variables and thus are neglected. A 32-factorial design will have been applied to optimize enteric coated Bumadizone calcium pellets formulation.

Table 5.9 Formulation batches as per 3² Factorial Design

Batch no.	Coded Value		Actual Value	
	x1	x2	X1(PVPK30)	X2(Eudragit S100)
F1	+1	+1	1.5	6
F2	-1	0	0.5	5
F3	0	0	1	5
F4	-1	+1	0.5	6
F5	0	-1	1	4
F6	0	+1	1	6
F7	-1	-1	0.5	4
F8	+1	-1	1.5	4
F9	+1	0	1.5	5

The positive sign of coefficient for factors that indicate synergistic effect on the response while negative sign of coefficient for factors that indicate antagonistic effect on response variable. The relationship between the dependent and independent variables will further elucidate using response surface plots. The equation enables the study of the effects of each factor and their interactions over the considered responses.

5.4.2.5 Formulation of 3² full factorial design batches

Table 5.10 Composition of 32 full factorial design batches

Batch no.	B1	B2	B3	B4	B5	B6	B7	B8	B9
Drug	1	1	1	1	1	1	1	1	1
MCC 101	8	8	8	8	8	8	8	8	8
EC	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K15M	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PVPK 30(%)	1.5	0.5	1	0.5	1	1	0.5	1.5	1.5
PEG 600	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
COATING FORMULA									
Eudragit S100	6	5	5	6	4	6	4	4	5
Titanium dioxide	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Triethyl citrate	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
Talc	4	4	4	4	4	4	4	4	4
Acetone	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml
IPA	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml

5.4.3 Counter Plots and Surface Response Plots

5.4.3.1 Counter plots (Patel et al., 2014)

Contour plots are diagrammatic representation of the values of the response. They are helpful in the explaining relationship between independent and dependent variables. The two-dimension contour plots will be prepared using statistic software. (Design Expert 10.0)

5.4.3.2 Surface response plots (Patel et al., 2014)

Response surface plots are more helpful in understanding both the main and the interaction effect of variables. The effect of different levels of independent variables on the response parameters can also be predicted from the respective response surface plots. For check point batch analysis Overlay plot will be prepared by using statistic software (Design Expert 10.0).

5.5 Evaluation Parameters

5.5.1 Drug Content Uniformity

Bumadizone content of the pellets were evaluated using accurately weighed 100mg pellets, after completely powdering pellets in a mortar. The completely powder was dissolve into methanol and made the volume up to 100 ml using phosphate buffer pH 7.4 and scanned between 200-400 nm using shimadzu 1800 U.V. spectrophotometer.

5.5.2 In-vitro Dissolution Study:

The release rate of bumadizone from pellets was determined using USP dissolution testing apparatus I (basket type). The test was performed using 900ml of simulated gastric fluid (pH 1.2) at $37\pm 0.5^{\circ}\text{C}$ and 50 rpm for first 2 hrs then dissolution medium replaced with 6.8 phosphate buffer for 2 hrs and finally it was 7.4 phosphate buffer for 8 hrs. (Dissolution study extended upto 8 hrs due to for colon target drug delivery).

5.5.3 Bulk Density (BD):

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/ml and is given by

Bulk Density = Weigh of powder/Bulk volume

5.5.4 Tapped Density (TD):

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/ml and is given by

Tap Density = Weigh of powder/Tap volume

5.5.5 Compressibility Index (CI):

The compressibility of the powder was determined by the Carr's compressibility index.

Compressibility Index (%) = $(\text{TD}-\text{BD})/\text{TD} \times 100$

5.5.6 Hausner's Ratio (HR):

The Hausner's ratio of the powder was determine by the following formula

Hausner's Ratio = TD/BD

5.5.7 Angle of Repose (θ):

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$\theta = \text{Tan}^{-1}(\text{height of pile}/\text{radius of pile})$

Table 5.11 Angle of repose data with type of flow

Angle of Repose (θ)	Flow of property
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very Poor
≥ 66	Extremely Poor

Table 5.12 Relationship between powder flow and Hausner's ratio

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
≥ 38	Extremely Poor	≥ 1.6

5.5.8 Friability:

Friability is interconnected to the capability of pellets to survive both shocks and abrasion lacking crumbling through manufacturing, packing, transportation & consumer handling. Friability can be calculated by means of friability test apparatus Roche friabilator. Compressed pellets that range are less than 0.5% to 1.0% in weight. **Method:** - Ten pellets were weighed (initial weight) and then transfer into Roche friabilator (Abrasion Drum). It was subjected to 100 revolutions in 4 min. The pellets were de-dusted and reweighed (final weight). These two weights were applied to following formula and friability was calculated.

$$\% \text{ Friability} = (\text{Initial weight} - \text{Final weight}) / (\text{Initial weight}) \times 100$$

5.6 Stability Study

The stability studies were carried out at $25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \pm 5\% \text{ RH}$, $30^{\circ}\text{C} \pm 2^{\circ}\text{C} / 65\% \pm 5\% \text{ RH}$ and $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{ RH}$ for selected formulations according to the ICH guideline. In the present work, only accelerated stability ($40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{ RH}$) study of one month was carried out for the optimized formulation.

In accelerated stability testing, the coated pellets to be stored under controlled conditions of $40^{\circ}\text{C} / 75\% \text{ RH}$ over a period of 1 month. The coated pellets were filled in capsules and packed in blister pack. Then kept in stability chamber at $40^{\circ}\text{C} / 75\% \text{ RH}$ over a period of 1 month. The pellets were evaluated for drug content, flow properties and other parameters at the end of 30 days.

6. RESULTS & DISCUSSION

6.1 Preformulation Study

6.1.1 Analytical Method for estimation of Bumadizone Calcium

6.1.1.1. Spectrum of Bumadizone calcium in for determination of λ_{max} by UV visible spectrophotometer.

A different concentration of Bumadizone calcium solution was prepared in pH 6.8, 7.4, 1.2 and methanol was scanned in UV range between 200 to 400nm wavelength (λ_{max}) for the analysis. (Narang and Sharma, 2011) Bumadizone calcium showed maximum absorbance at 236nm.

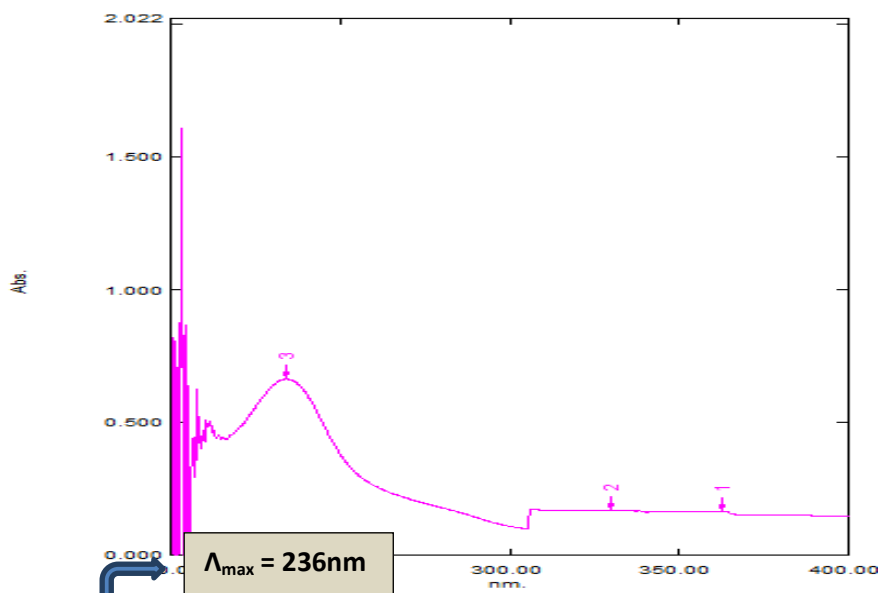


Figure 15 UV spectrum of Bumadizone calcium in Methanol

Table 6.1. Standard curve of Bumadizone Calcium in Methanol	
conc.($\mu\text{g/ml}$)	abs.(nm)
4	0.201 \pm 0.0026
6	0.284 \pm 0.0030
8	0.372 \pm 0.0011
10	0.454 \pm 0.0020
12	0.534 \pm 0.0005
14	0.619 \pm 0.0015
16	0.713 \pm 0.002

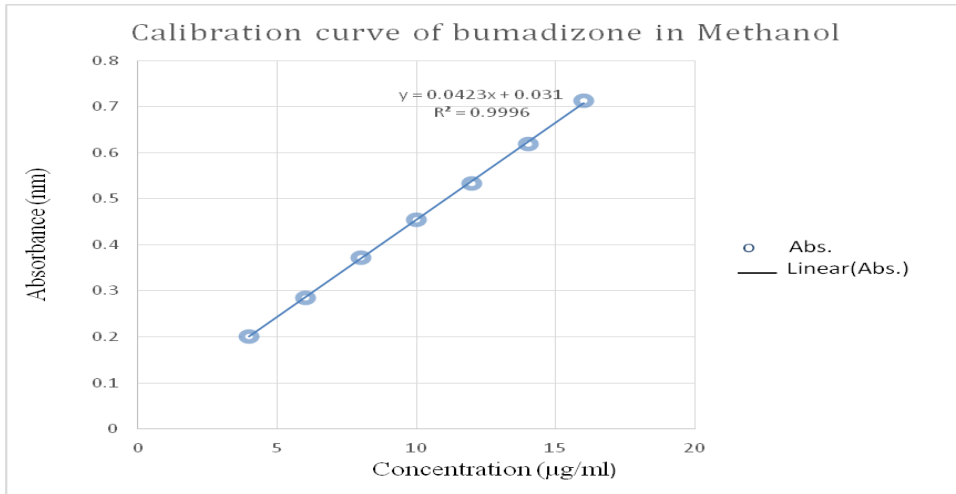


Figure 16 Standard calibration curve of Bumadizone Calcium in Methanol

6.1.1.2. Spectrophotometric scanning of Bumadizone Calcium in pH 1.2

Concentration of 10, 12, 14, 16, 18 and 20 µg/ml were prepared and scanned in UV spectrophotometer. Bumadizone showed maximum absorbance at 236 nm. Thus, 236nm was selected as λmax for Bumadizone Calcium.

Conc.(µg/ml)	Abs.(nm)
10	0.271 ± 0.0030
12	0.360 ± 0.0005
14	0.452 ± 0.0015
16	0.538 ± 0.002
18	0.626 ± 0.0015
20	0.721 ± 0.0005

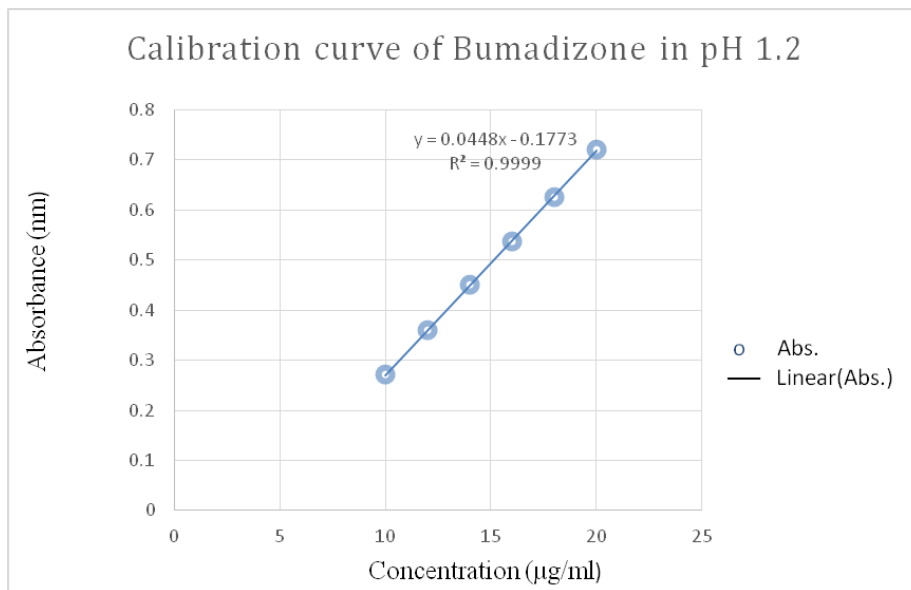


Figure 17 Standard calibration curve of Bumadizone Calcium in pH 1.2

6.1.1.3. Spectrophotometric scanning of Bumadizone Calcium in pH 6.8

Concentration of 4, 6, 8, 10, 12,14,16,18 and 20µg/ml were prepared and scanned in UV Spectrophotometer. Bumadizone showed maximum absorbance at 236nm. Thus, 236nm was selected as λmax for Bumadizone Calcium.

Table 6.3 Standard curve of Bumadizone Calcium in pH 6.8	
Conc.(µg/ml)	Abs.(nm)
2	0.097 ± 0.0011
4	0.205 ± 0.0025
6	0.313 ± 0.0032
8	0.426 ± 0.0005
10	0.530 ± 0.002
12	0.643 ± 0.0037
14	0.764 ± 0.0036
16	0.871 ± 0.0011

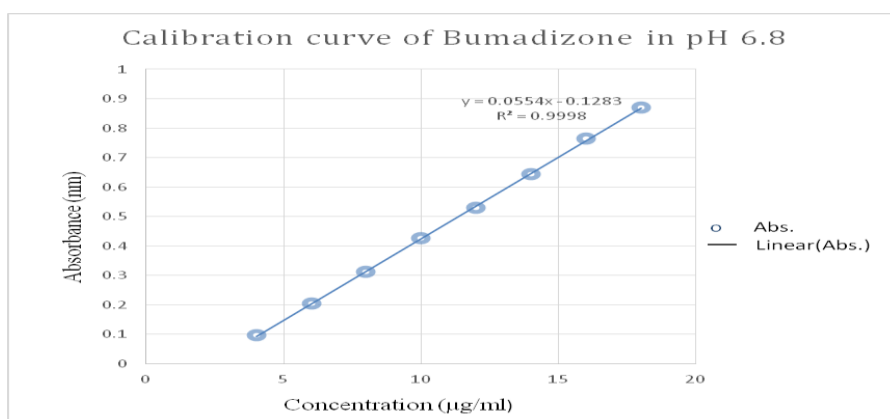


Figure 18 Standard calibration curve of Bumadizone Calcium in pH 6.8

6.1.1.4. Spectrophotometric scanning of Bumadizone Calcium in pH 7.4

Concentration of 4, 6, 8, 10, 12, 14, 16, and 18 µg/ml were prepared and scanned in UV spectrophotometer. Bumadizone showed maximum absorbance at 236 nm. Thus, 236 nm was selected as λmax for Bumadizone Calcium.

Table 6.4. Standard curve of Bumadizone Calcium in pH 7.4	
Conc.(µg/ml)	Abs.(nm)
4	0.281 ± 0.002
6	0.372 ± 0.0015
8	0.463 ± 0.0015
10	0.563 ± 0.002
12	0.653 ± 0.002
14	0.752 ± 0.001
16	0.821 ± 0.0015

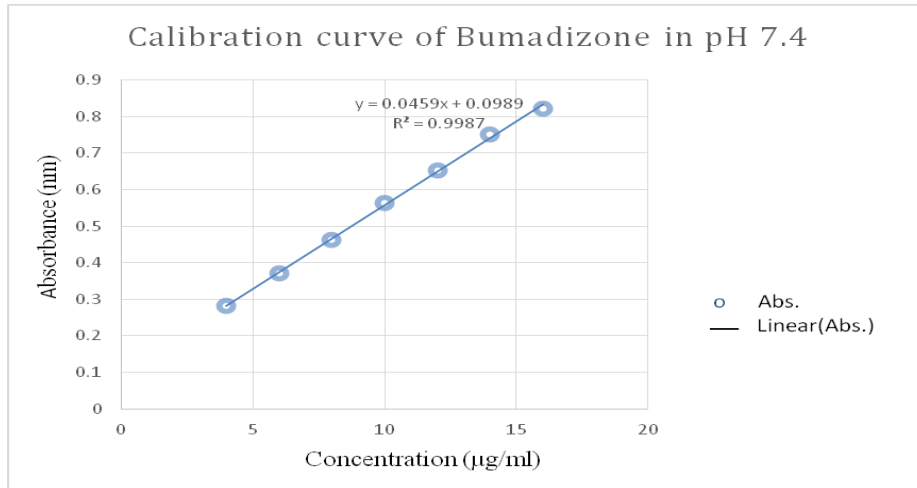


Figure 19 Standard calibration curve of Bumadizone Calcium in pH 7.4

6.1.2. Identification of drug

6.1.2.1. Melting point

The melting point observed (158 °C) was in accordance to the theoretical melting point (157-159°C).



Figure 20 Melting point Measurement Apparatus

6.1.2.2. Fourier Transform Infra-Red Spectroscopy (FT-IR)

The FT-IR spectrum of Bumadizone Calcium (Pure Drug) will be found in figure 20. The characteristic peaks of Bumadizone Calcium correspond to their functional groups are show in the table 6.5.

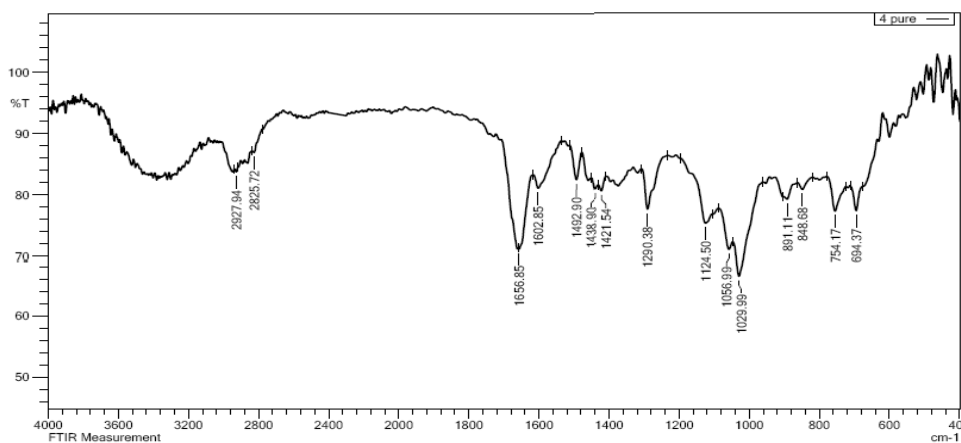


Figure 21 FTIR of pure Drug

SR NO.	WAVE NUMBER CM ⁻¹	DESCRIPTION
1	1602.85	C=O ring stretching
2	1438.90	C-C ring stretching
3	1665.85	N-N bond linkage
4	1290.38	C-N bond twisting
5	1124.50	N-H bond linkage

6.1.2.3. Differential Scanning Calorimeter (DSC)

DSC enables the Quantitative detection of all processes in which energy is required or produced (i.e., endothermic or exothermic phase transformation). The thermal behaviour of the prepared samples was studied by DSC at the rate of 10°C/min rise in temperature up to 350°C. The DSC thermograms of pure drug and physical mixture are shown in figure 21.

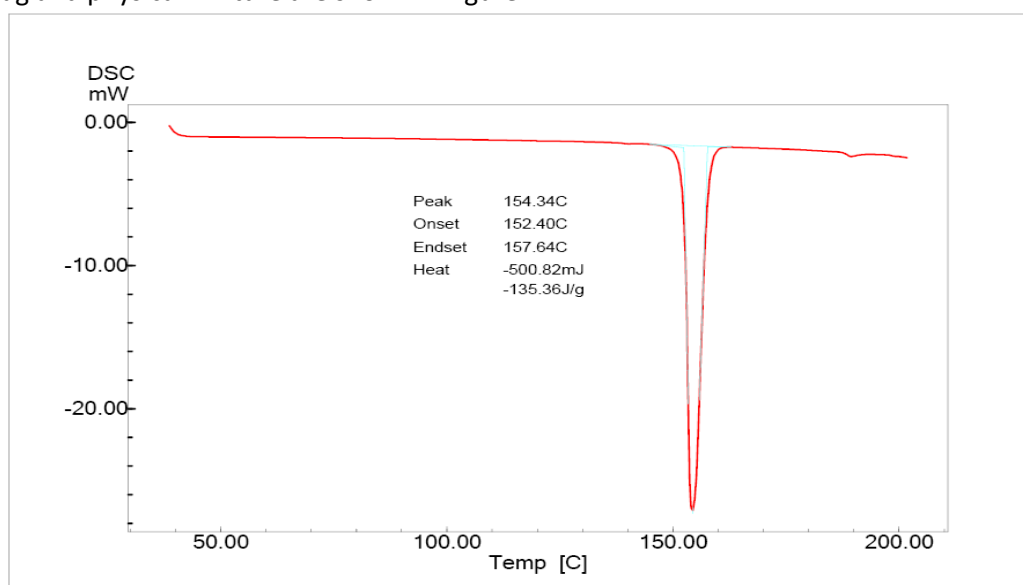


Figure 22 DSC of pure Drug

1.1.2.4 Micromeritic property of API

sample	Angle of Repose (°)	Bulk density(g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's Ratio
API	34	0.352	0.512	31.25	1.45

6.1.3 Drug-Excipient compatibility studies

6.1.3.1 Differential Scanning Calorimetry (DSC)

DSC enables the Quantitative detection of all processes in which energy is required or produced (i.e., endothermic or exothermic phase transformation). The thermal behavior of the prepared samples was studied by DSC at the rate of 10°C/min rise in temperature up to 350°C. The DSC thermograms of pure drug and physical mixture are shown in figure.

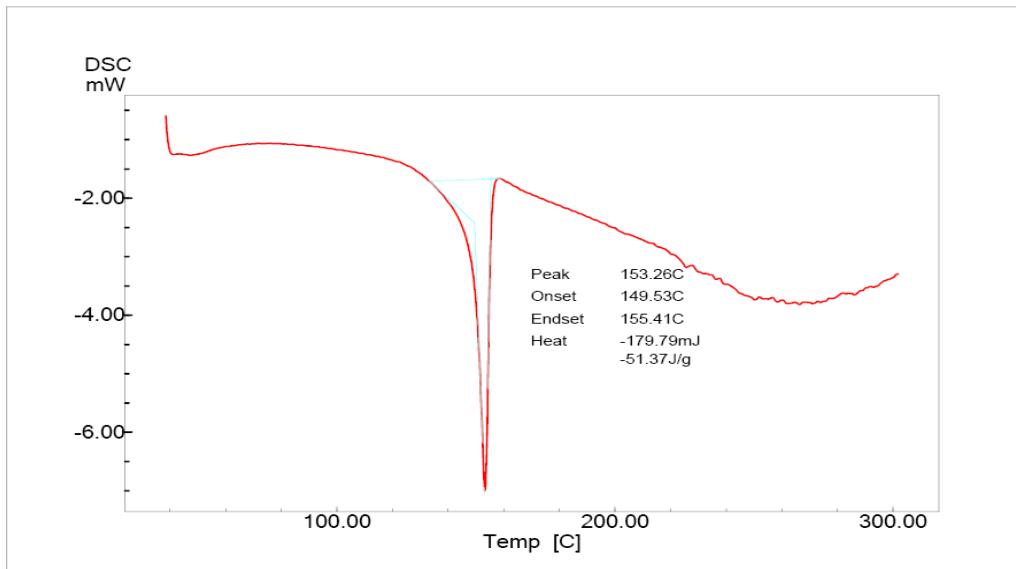


Figure 23: DSC of physical mixture

The DSC thermogram of Bumadizone and physical mixture shown in figure. DSC thermograph of Bumadizone Calcium exhibits endothermic peak at 154.34°C corresponding to its melting point. Mixture of excipients and Bumadizone Calcium shows endothermic peak at 153.26°C which indicates almost no interaction.

6.1.3.2 Fourier Transform Infra-Red Spectroscopy (FT-IR)

The FTIR spectrum of Physical mixture and Formulation (uncoated & coated pellets were shown in figure 23, 24 and 25 respectively. In the FT-IR spectrum of Physical mixture and Formulation characteristic peaks corresponding to their functional groups were identified, which were same in Bumadizone Calcium pure drug. Thus, there was no any interaction between drug and excipients.

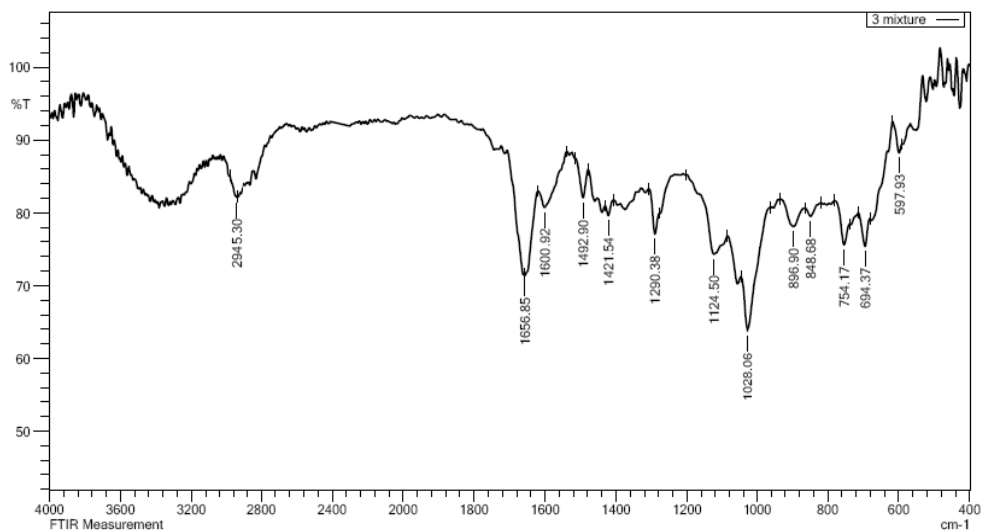


Figure 24 FTIR of physical mixture

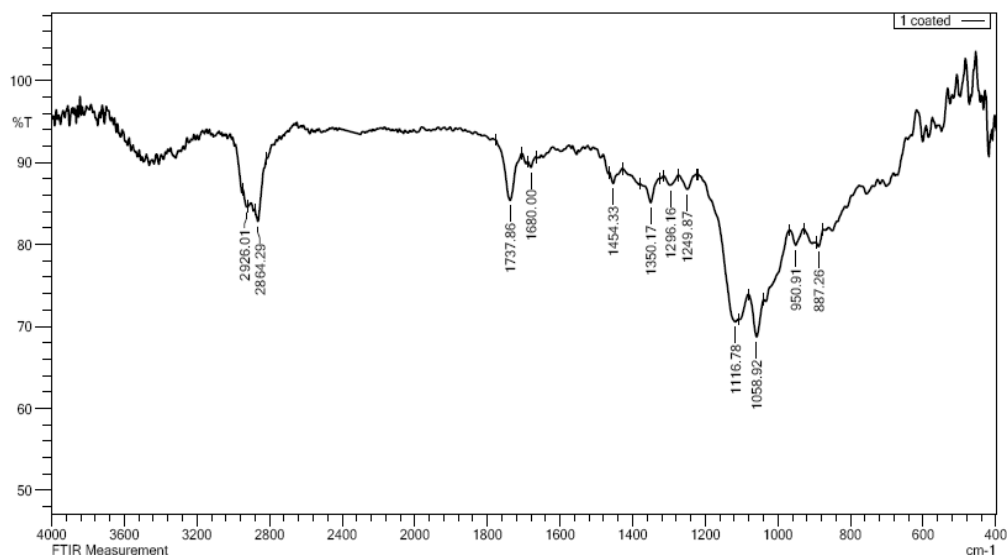


Figure 25 FTIR of coated pellets

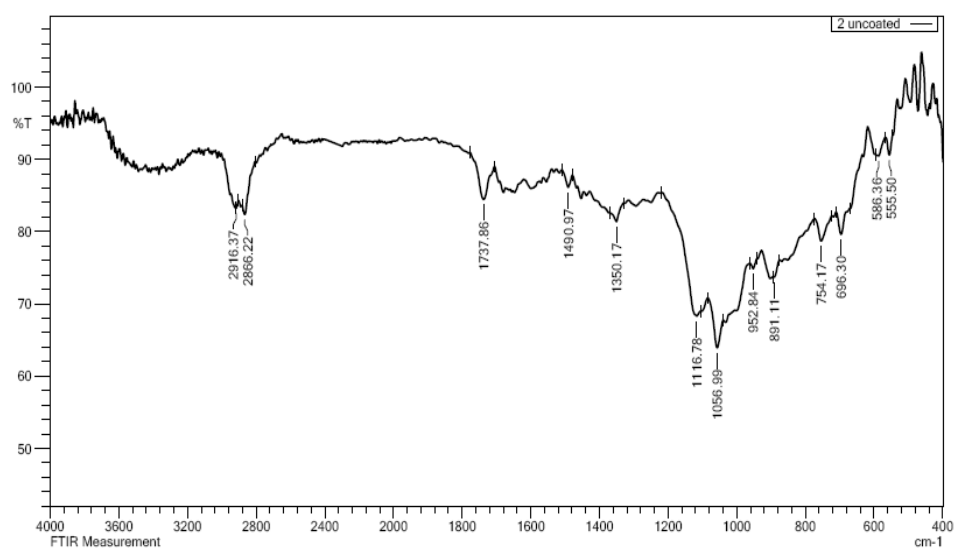


Figure 26 FTIR of uncoated pellets

Table 6.7 Characteristic peaks of Physical Mixture, Uncoated Pellets, and Coated Pellets.					
SR NO.	WAVE NUMBER CM ⁻¹ (Pure Drug)	WAVE NUMBER CM ⁻¹ (Physical Mixture)	WAVE NUMBER CM ⁻¹ (Uncoated Pellets)	WAVE NUMBER CM ⁻¹ (Coated Pellets)	DESCRIPTION
1	1602.85	1602.85	1600.92	1737.86	C=O ring stretching
2	1438.90	1421.54	1454.33	1490.97	C-C ring stretching
3	1665.85	1656.85	1737.86	1737.86	N-N bond linkage
4	1290.38	1290.38	1296.16	1350.17	C-N bond twisting
5	1124.50	1124.50	1116.78	1116.78	N-H bond linkage

6.2. Result of Preliminary Trials.

6.2.1 Result of preliminary trial for selection of diluent concentration

During screening of diluent concentration batches F1-F3 were prepared and they were evaluated with respect to size, shape, and strength.

Table 6.8 Result of preliminary trial for screening of diluent concentration

Batch	Size	Shape	Strength
F1	Uneven Size	Rode Shape	Low
F2	Uniform Size	Spherical Shape	Good
F3	Improper Size	Various Shape	Less

From the result table, It was found that MCC PH101 (8gm) shows uniform size, spherical shape and good strength. Hence it was selected for further study.

6.2.2 Result of preliminary trial for selection of Binder

During screening of binder concentration batches F4-F12 were prepared and they were evaluated with respect to size, shape, and strength.

Table 6.9 Screening of Binder

Batch	Size	Shape	Strength
F4	Improper Size	Uneven	Low
F5	Size Reduce	Rode Shape	Less
F6	Uneven Size	Various Shape	Low
F7	Uneven Size	Rode Shape	Low
F8	Improper Size	Various Shape	Less
F9	Uniform Size	Spherical	Good
F10	Uneven Size	Various Shape	Low
F11	Size Reduce	Rode Shape	Less
F12	Improper Size	Uneven	Low

From the result table, It was found that PVP K30 (1%) shows uniform size, spherical shape and good strength. Hence it was selected for further study.

6.2.3 Result of preliminary trial for selection of plasticizer

During screening of plasticizer batches F13-F15 were prepared and they were evaluated with respect to size, shape, and strength.

Table 6.10 Screening of plasticizer

Batch	Size	Shape	Strength
F13	Uniform Size	Proper Round	Good
F14	Uniform Size	Big Rode Shape	Low
F15	Improper Size	Various Shape	Less

From the result table, It was found that PEG 600(1ml) shows uniform size, spherical shape and good strength. Hence it was selected for further study.

6.2.4 Result of preliminary trial for selection of polymer

During screening of polymer batches F16-F24 were prepared and they were evaluated with respect to size, shape, and strength.

Table 6.11 Result of preliminary trial for Selection of polymer

Batch	Size	Shape	Strength
F16	Improper Size	Uneven	Low
F17	Size Reduce	Rode Shape	Less
F18	Uneven Size	Various Shape	Low
F19	Uneven Size	Rode Shape	Low
F20	Uniform Size	Spherical Shape	Good
F21	Improper Size	Improper Size	Less
F22	Uneven Size	Various Shape	Low
F23	Size Reduce	Rode Shape	Less
F24	Improper Size	Uneven	Low

From the result table, it was found that HPMC K15M (1gm) shows uniform size, spherical shape and good strength. Hence it was selected for further study.

6.2.5 Result of preliminary trial for selection of Spheronization speed

During screening for selection of speed batches F25-F27 were prepared and they were evaluated with respect to size, shape, and strength.

Table 6.12 Screening of speed

Batch	Speed	Size	Shape	Strength
F25	2000	Uneven Size	Rode Shape	Low
F26	2500	Uniform Size	Spherical Shape	Good
F27	3000	Improper Size	Various Shape	Less

From the result table, it was found that Spheronization speed 2500rpm shows the pellets with uniform size, spherical shape and good strength. Hence it was selected for further study.

Figure 27: General Appearance of coated pellets



6.2.6 Effect of Ethyl Cellulose on release profile

Table 6.13 Effect of ethyl cellulose on release profile

Time (hr.)	% Release	
	With Ethyl Cellulose	Without Ethyl Cellulose
Batch No.	F28	F29
0	0.10	0.10
1	0.11	0.10
2	9.16	8.95
3	17.94	16.15
4	33.94	39.15
5	45.47	54.00
6	59.57	70.38
7	72.33	84.14
8	85.27	97.74
9	89.78	97.82
10	94.18	96.12
11	97.12	96.56
12	98.64	96.98

From the result table, it was found that Ethyl cellulose slows the release of drug.

6.2.7 Effect of drug to polymer ratio on release profile

Table 6.14 Effect of drug to polymer ratio on release profile

Time (hr.)	% Release	
	Drug: polymer(1:2)	Drug: polymer(1:1)
Batch No.	F30	F31
0	0.10	0.10
1	0.11	0.10
2	7.25	10.31
3	18.99	18.11
4	35.99	42.11
5	47.70	57.66
6	63.97	71.17
7	73.29	82.28
8	87.40	93.46
9	90.38	97.38
10	93.66	98.12
11	96.46	97.46
12	98.64	97.88

From the result table, it was found that drug to polymer ratio (1:2) slows the release rate so, it can be used for sustain release formulation.

6.2.8 Effect of concentration of Eudragit S100 on release profile

Table 6.15 Effect of concentration of Eudragit S100

Time (hr)	% Release (Eudragit S100)	
	F32	F33
Batch No.	5(%w/v)	6(%w/v)
0	0.00	0.00
1	0.101	0.099
2	0.106	0.102
3	8.59	9.98
4	19.13	18.9
5	46.19	37.96
6	58.63	49.61
7	66.12	56.93
8	73.30	64.63
9	78.15	71.60
10	82.74	77.64
11	88.90	81.18
12	93.96	85.89

From the result table, it was found that 5% Eudragit coating gives more than 90% release in 12 hours.

Table 6.16 Evaluation of pellets

Batch no.	Angle of repose	Carr's index	Hausner's ratio	% friability	Drug content
F28	26.21	8.72	1.093	0.30	96.38
F29	25.87	11.58	1.135	0.35	97.12
F30	26.58	8.53	1.004	0.28	96.18
F31	27.78	7.35	1.006	0.26	97.35
F32	26.12	10.42	1.117	0.29	96.52
F33	25.12	4.19	1.109	0.22	98.22

Different flow parameters of prepared pellets suggested that all the pellets showed excellent flow property range show it indicated that prepared pellets have excellent flow property. The friability of the pellets was found to be in the range 0.22-0.35%, which indicated good mechanical strength of pellets. Percentages of drug content in prepared enteric coated pellets were found to be in the range of 96.18 to 98.22 which is within the acceptable limit.

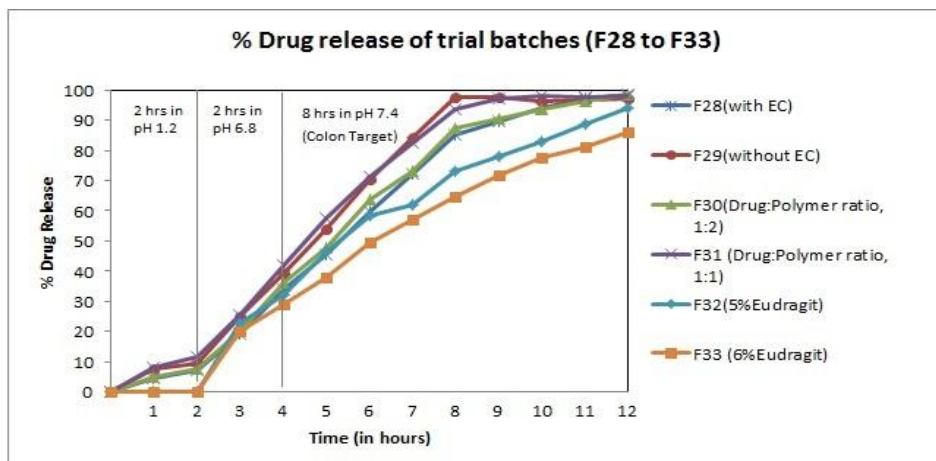


Figure 28 % Drug release of trial batches (F28 to F33)

6.3 Statistical analysis and optimization of experimental design batches

Table 6.17 3² full factorial design with it responses

Independent variables				Dependent variables		
Coded value		Decoded value				
X1	X2	X1 (% PVP K30)	X2 (% Eudragit S100)	Y1 (%CPR 2HRS)	Y2 (% CPR 12 HRS)	Y3 (%COATING PROCESS EFFICIENCY)
+1	+1	1.5	6	0.4	84.1	86.69
-1	0	0.5	5	0.48	97.36	95.66
0	0	1	5	0.45	95.17	94.25
-1	+1	0.5	6	0.43	91.86	91.78
0	-1	1	4	0.47	96.14	96.55
0	+1	1	6	0.45	93.91	92.4
-1	-1	0.5	4	0.42	89.05	89.84
+1	-1	1.5	4	0.51	99.4	96.25
+1	0	1.5	5	0.41	88.29	87.22

The 3²-full factorial design was used to optimize the amount of binder and coating material in formulation of Enteric coated pellets. The amount of binder and coating material is selected on the basis of in-vitro dissolution study.

3² full factorial design was used and prepared total 9 batches (F1 to F9). In those two independent factors % of Binder (X₁), and Concentration of Eudragit S100(X₂) were used and two factors had three levels low, medium, and high (-1, 0 and +1) which are given in table 5.16. The dependent factors were selected like % CPR at 12 hrs (% Cumulative drug release), CPR at 2hrs, and CPE (coating process efficiency) based on the selected dependent variable for optimization of formulation.

Table 6.18 Application of 3² full factorial design

Independent variable of the formulation			
Independent variables	Low (-1)	Medium (0)	High (+1)
PVP K30(X ₁)	0.5	1	1.5
Eudragit S100(X ₂)	4%	5%	6%

All possible 9 runs of formulation having a different coded value for optimization of Enteric coated pellets for maximum % drug release at maximum time and minimum release in stomach.

6.3.1 Formulation of 3² full factorial design batches

Table 6.19 Composition of 3² full factorial design batches

Batch no.	B1	B2	B3	B4	B5	B6	B7	B8	B9
Drug	1	1	1	1	1	1	1	1	1
MCC 101	8	8	8	8	8	8	8	8	8
EC	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K15M	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PVPK 30(%)	1.5	0.5	1	0.5	1	1	0.5	1.5	1.5
PEG 600	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
COATING FORMULA									
Eudragit S100	6	5	5	6	4	6	4	4	5
Titanium dioxide	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Triethyl citrate	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
Talc	4	4	4	4	4	4	4	4	4
Acetone	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml
IPA	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml

6.3.2 Comparison of % drug Release of 3² full factorial design

Table 6.20 In-vitro dissolution profile of B1 to B9 batches (3²full factorial design)

TIME (HR)	B1	B2	B3	B4	B5	B6	B7	B8	B9
	% Drug release								
0	0	0	0	0	0	0	0	0	0
1	0.37	0.417	0.399	0.395	0.415	0.378	0.426	0.395	0.394
2	0.4	0.473	0.45	0.431	0.488	0.417	0.518	0.456	0.427
3	6.54	8.46	8.18	7.14	8.12	8.14	7.98	8.12	8.06
4	18.86	19.03	19.76	18.19	18.66	19.27	18.96	17.35	16.75
5	31.7	40.01	38.34	34.27	45.57	32.96	47.52	43.28	36.69
6	43.82	54.92	51.61	47.31	58.88	45.5	60.86	56.02	49.89
7	54.98	65.81	62.57	59.24	68.25	56.27	71.83	64.9	60.72
8	61.1	72.76	68.09	64.2	73.95	62.67	79.18	70.09	65.56
9	66.67	78.43	74.27	71.64	80.12	69.06	86.57	76.8	71.33
10	71.01	85.22	80.91	77.1	85.16	73.15	91.83	83.17	77.16
11	78.12	91.71	88.27	84.42	92.19	81	95.16	88.82	84.21
12	85.1	96.14	93.91	91.86	97.36	88.29	99.4	95.17	89.05

*SD of 3 determinate

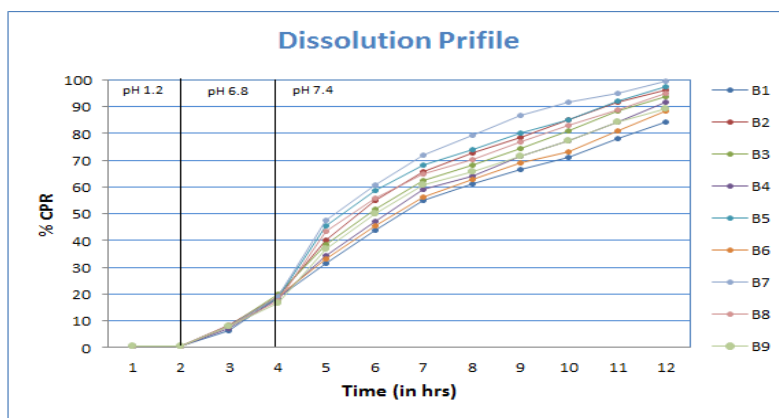


Figure 29 Dissolution profile for B1 to B9 batches

6.3.3 Statistical analysis of design batch

6.3.3.1. Regression analysis

Regression coefficient and p-value of full model was calculated for % CPR at 2hrs, % CPR at 12 hrs and Coating process Efficiency (CPE). P-value less than 0.05 indicate significance of factor. Coefficient value obtained from the regression analysis is shown in below table with their p-value.

Table 6.21 Regression coefficient and their p- value

Response	β_0	β_1	β_2	β_{12}	R^2
Y1 (% CPR 2hr)	+0.73500	-0.12167	-0.048333	+0.015000	0.985
p- value	< 0.0001	< 0.0001	< 0.0001	0.0035	
Y2 (% CPR 12hr)	+113.41056	+2.46500	-2.84833	-1.76500	0.973
P value	< 0.0001	< 0.0001	< 0.0001	0.0336	
Y3 (% CPE)	+106.22667	+3.12500	-1.86667	-1.54500	0.766
p-value	< 0.0001	0.0074	0.0013	0.2868	

From the regression analysis as shown in table, R values for % CPR at 2hrs, % CPR at 12hrs and Coating process Efficiency (CPE) are respectively, so there is good correlation between independent variables and dependent variables for Y1.

6.3.3.2 Polynomial equations for observed response Model Equation

From the regression analysis full model equations were generated.

Full model equation,

$$Y1 = +0.73500 - 0.12167X1 - 0.048333X2 + 0.01500X12$$

$$Y2 = +113.41056 + 2.46500X1 - 2.84833X2 - 1.76500X12$$

$$Y3 = +106.22667 + 3.12500X1 - 1.86667X2 - 1.54500X12$$

6.3.4 ANOVA

Analysis of variance for 3² full factorial design variables was carried out. Result Obtained are shown in table 5.30.

Table 6.22 ANOVA table for analysis and optimization of 3² full factorial designs

Response	Sources of variation	dF	SS	MS	F Value	R ²
Y1 (% CPR 2hr)	Regression	3	0.010	3.386 E-003	406.33	0.985
	Residual	5	4.167 E-005	8.333 E-006	27.00	
	Total	8	0.010	12.193 E-0.009	433.33	
Y2 (% CPR 12hr)	Regression	3	191.49	63.83	172.79	0.990
	Residual	5	1.85	0.37	8.43	
	Total	8	193.33	64.2	181.22	
Y3 (% CPE)	Regression	3	103.96	34.65	20.62	0.925
	Residual	5	8.40	1.68	1.42	
	Total	8	112.37	36.33	22.04	

6.3.5 Counter plots and surface plots

Contour plots and Surface plots are the two dimensional (2D) and three dimensional (3D) representation between Dependent and Independent variables respectively.

The results obtained from experimental work were used to draw the contour plot and surface plot for each response variable such as % CPR at 2hrs (Y1), % CPR at 12hrs (Y2) and Coating Process Efficiency (CPE) (Y3) with the help of design expert 10.0 software.

6.3.5.1 Counter plot and surface plot of % CPR after 2hrs (Y1)

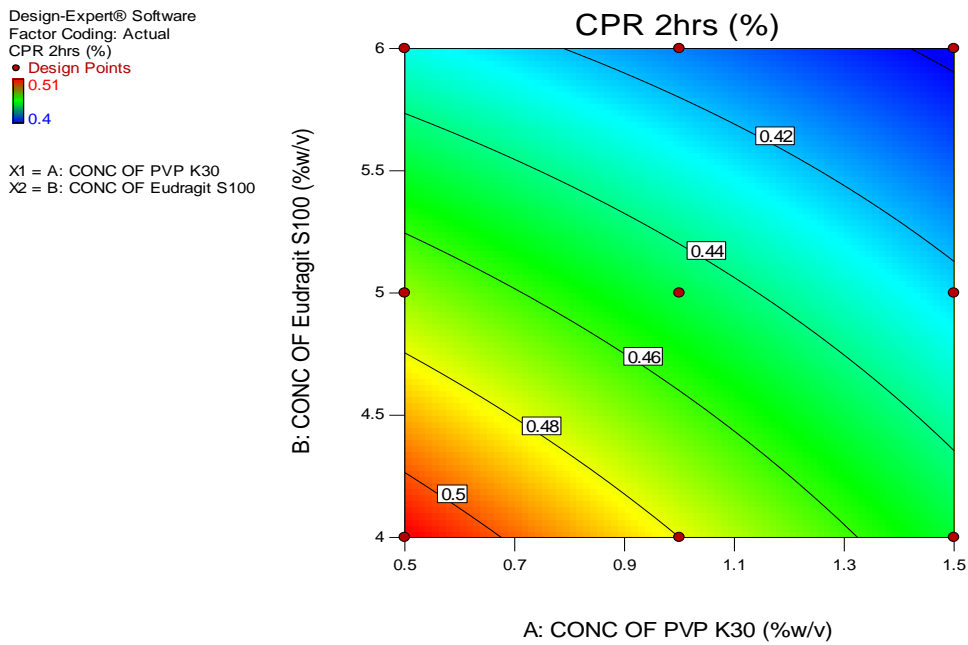


Figure 30 Counter plot of % CPR after 2hrs (Y1)

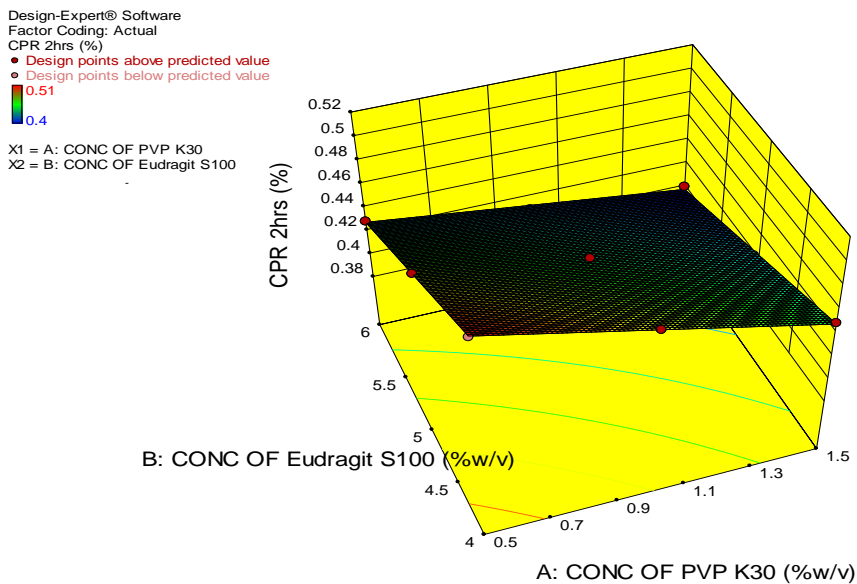


Figure 31 Surface plot of % CPR after 2hrs (Y1)

The analysis of contour plot and surface plot of % CPR (Y) against conc. of PVP K30 (%w/v) (X1), and conc. of Eudragit S100 (%w/v) (X2) were shown in figure 5.28, and 5.29. From the figure it could be concluded that % CPR after 2hrs was affected by selected Independent variables. Conc. of PVP K30 (%w/v) (X1) was increase then % CPR after (Y1) was decreased. Conc. of Eudragit S100 (%w/v) (X2) increased the % CPR after 2hr (Y1) also decreases.

From the figure (X1) and (X2) are significant for the % CPR after 2hrs (Y1).

6.3.5.2 Counter Plot And Surface Plot of % CPR after 12hrs.

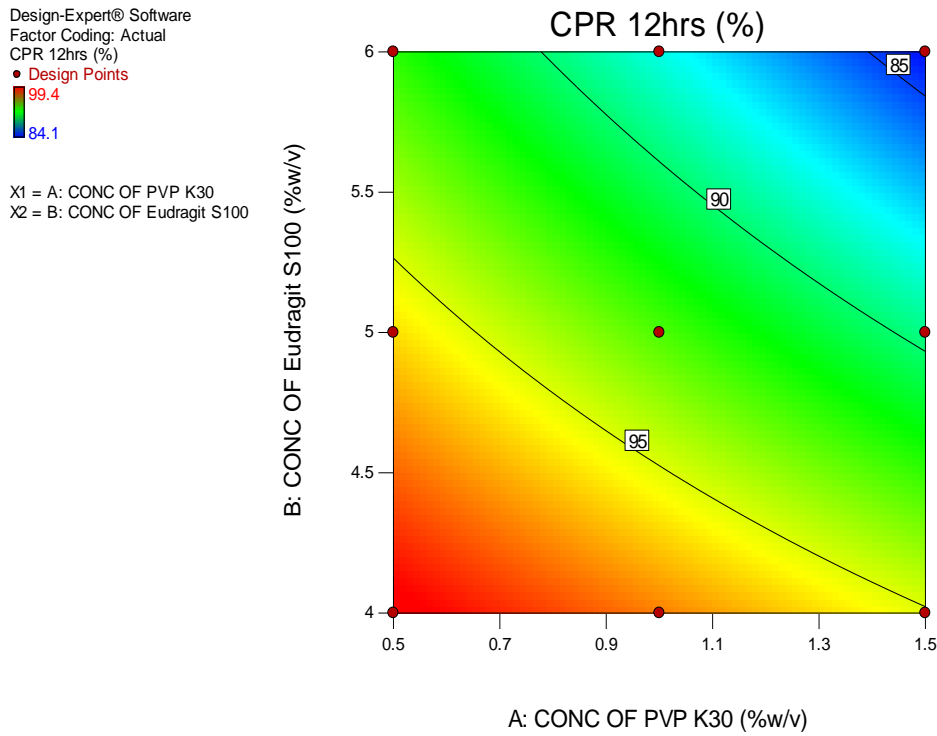


Figure 32 Counter plot of % CPR after 12hrs (Y2)

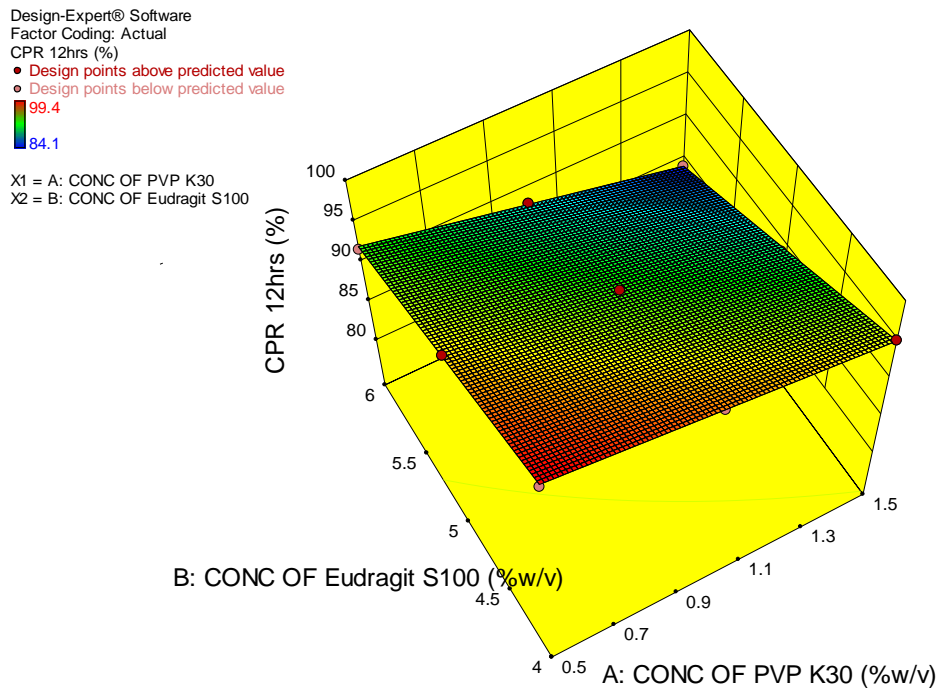


Figure 33 Surface plot of % CPR after 12hrs (Y2)

The analysis of contour plot and surface plot of % CPR after 12hrs (Y2) against conc. of PVP K30 (%w/v) (X1), and conc. of Eudragit S100 (%w/v) (X2) were shown in figure 5.30, and 5.31. From the figure it could be concluded that that % CPR after 12hrs was affected by selected Independent variables. Conc. of PVP K30 (%w/v) (X1) was increase then % CPR after 12hrs (Y2) was decreased. conc. of Eudragit

S100(%w/v) (X2) increased the % CPR after 12hr (Y2) also decreases. From the figure (X1) and (X2) are significant for the % CPR after 12hrs (Y2).

6.3.5.3 Counter Plot and Surface Plot of % CPE (coating process Efficiency)(Y3).

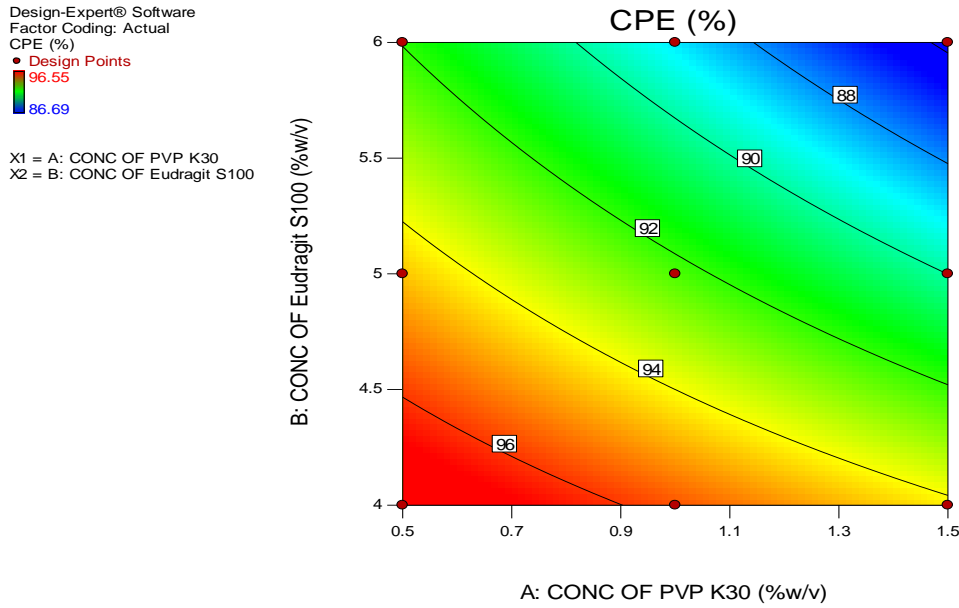


Figure 34 Counter plot of % CPE (Y3)

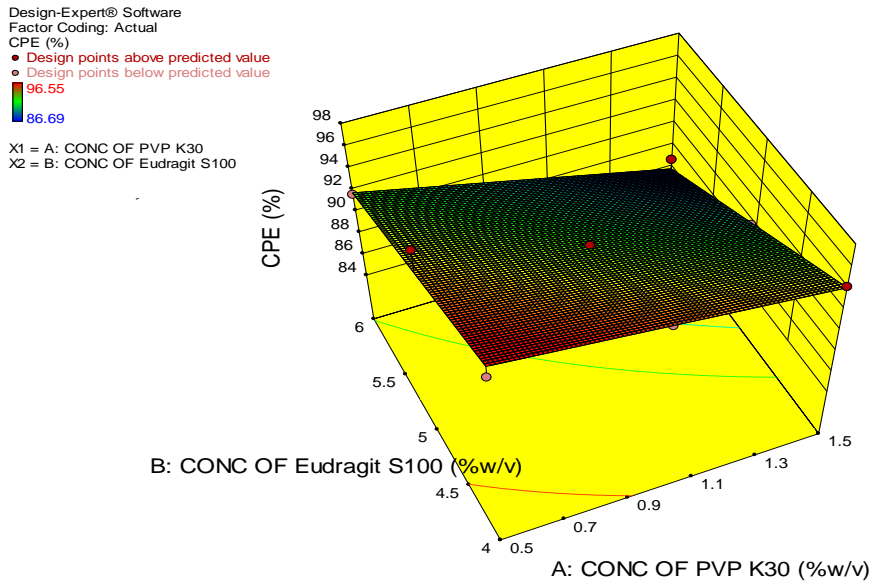


Figure 35 Surface plot of % CPE (Y3)

The analysis of contour plot and surface plot of % CPE (Y3) against conc. of PVP K30 (%w/v) (X1), and conc. of Eudragit S100 (%w/v) (X2) were shown in figure 5.30, and 5.31. From the figure it could be concluded that that % CPE was affected by selected Independent variables. Conc. of PVP K30 (%w/v) (X1) was increase then % CPE (Y3) was decreased. Conc. of Eudragit S100 (%w/v) (X2) increased the % CPE(Y3) also decreases.

From the figure (X1) and (X2) are significant for the % CPE (Y3).

6.3.6 Overlay plot

Effect of conc. of PVP K30 (%w/v) (X1) and conc. of Eudragit S100(%w/v) (X2) on % CPR after 2hrs(Y1), then % CPR after 12hrs(Y2), then % CPE(Y3) of bumadizone calcium pellets.

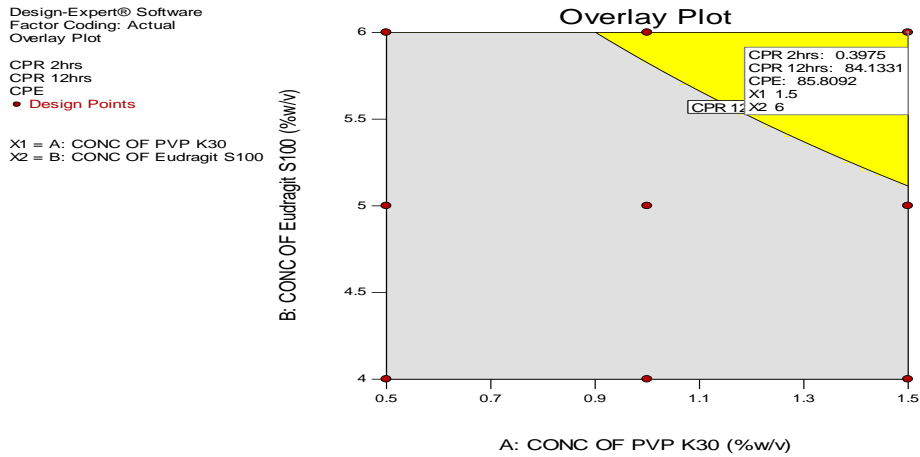


Figure 36 Overlay plot showing combined effect of factors X_1 and X_2 on Y_1 , Y_2 and Y_3 .

Overlay plots of three responses could be used to determine desired concentration of PVP K30 and Eudragit S100. In above figure, yellow region of overlay plot showed desired range of responses. By choosing any concentration of PVP K30 and Eudragit S100 in this region, desired responses could be achieved.

6.3.7 Check point batch analysis

From the overlay plot, check point was selected in order to obtain desired value of factors. On the basis of desired criteria of drug release % after 2hrs, % drug release after 12hrs and coating process efficiency, following batch was formulated to assess the reliability of the evolved equations. The experimental values and predicted values of each response are shown in table.

The percentage relative error of each response was calculated using the following equation:

$$\% \text{ relative error} = \frac{[(\text{predicted value} - \text{Experimental value})]}{\text{predicted value}} \times 100$$

Table 6.23 Formula for check point batch

Ingredients	Level	Quantity(gm)
PVP K30	1	1.5
Eudragit S100	1	6

Table 6.24 Cumulative percentage drug release of check point batch & optimized batch

Time (in hrs)	% Cumulative Release of check point batch	% Cumulative Release of optimized batch
0	0.00	0.00
1	0.370942±0.0011	0.400246±0.0008
2	0.389031±0.001	0.450789±0.0010
3	12.61613±0.0011	8.181257±0.0012
4	23.37668±0.0005	19.763289±0.0008
5	31.86506±0.001	38.342498±0.001
6	44.83561±0.001	51.612697±0.0018
7	53.98346±0.0011	62.573894±0.0008
8	61.31165±0.0015	68.090497±0.001
9	66.59735±0.0005	74.276942±0.0014
10	70.11289±0.0011	80.918452±0.0005
11	77.35443±0.0011	88.273976±0.001
12	83.91513±0.001	93.911289±0.0015

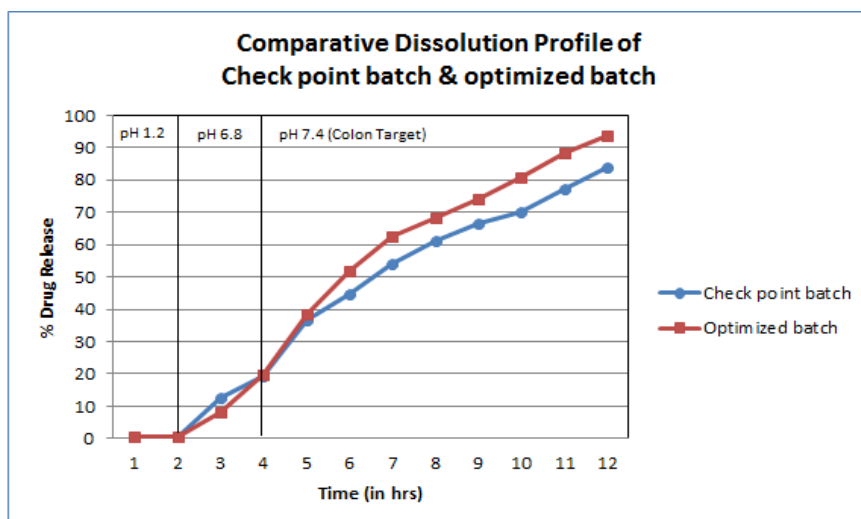


Figure 37 Comparative Dissolution Profile of Check point batch & optimized batch

Table 6.25 Responses of check point batch

Formulation	Parameter	Predicted value	Experimental Value	% relative Error
Check point batch	CPR at 2hrs	0.3975	0.3890	2.13
	CPR at 12hrs	84.13	83.91	0.26
	CPE	85.80	84.69	1.29

The % relative error for the checkpoint batch was in the range of 0.26-2.13. This is less than 8%, so statistically acceptable. It was concluded that the experimental values and predicted values showed good agreement between each other.

6.4 Evaluation Parameters

6.4.1 Evaluation of pellets by size, shape & strength

All Pellets are uniform size, spherical shape and with good strength. Core (uncoated) pellets are 1.4 to 1.6 mm of diameter range. Coated Pellets are ranged from 1.8 to 2.2mm of diameter range.

6.4.2. Evaluation of pellets by its flow property & drug content

Enteric Coated pellets blend was characterized for micrometrics properties like, Angle of repose, Bulk density, Tapped density, Carr's index and hausner's ratio.

Table 6.26 Evaluation of pellets by related flow property

Batch no.	Angle of repose	Carr's index	Hausner's ratio	% friability	Drug content
B1	25.41±0.21	8.72±0.055	1.095±0.013	0.34±0.03	98.14±0.13
B2	24.32±0.1	11.56±0.08	1.130±0.005	0.31±0.05	97.52±0.22
B3	26.18±0.28	8.57±0.053	1.093±0.04	0.28±0.08	96.43±0.18
B4	27.64±0.11	7.38±0.035	1.079±0.006	0.27±0.06	97.45±0.35
B5	25.53±0.06	10.58±0.042	1.118±0.17	0.24±0.09	96.59±0.52
B6	25.38±0.12	4.093±0.19	1.042±0.109	0.25±0.02	98.32±0.22
B7	26.12±0.11	9.71±0.17	1.107±0.049	0.22±0.04	97.61±0.35
B8	27.18±0.05	11.04±0.13	1.124±0.007	0.20±0.07	95.85±0.80
B9	26.35±0.14	11.79±0.11	1.133±0.005	0.22±0.09	98.64±0.37

± SD of 3 determinate

Different flow parameters of prepared pellets suggested that all the pellets showed excellent flow property range show it indicated that prepared pellets have excellent flow property. The friability of the pellets was found to be in the range 0.20-0.35%, which indicated good mechanical strength of pellets (Gowda D et al., 2012). Percentage of drug content in prepared enteric coated pellets were found to be in the range of 95.85 ± 0.80 to 98.64 ± 0.37 , which is within the acceptable limit.

6.5 Stability Study

The samples of optimized batch (B3) were kept in accelerated condition ($40^{\circ} \pm 2^{\circ}C/75\% \pm 5\% RH$) for one month. Then samples were analyzed for physical evaluation, assay and dissolution. The results are given in Table.

Sr. No.	Evaluation parameters	Initial	1 month
1	Size, Shape & Strength of pellets	Uniform size, Spherical shape and good strength	Uniform size, Spherical shape and good strength
2	Angle of repose	26.18 (Excellent flow)	26.88 (Excellent flow)
3	Carr's index	8.57 (Excellent flow)	8.78 (Excellent flow)
4	Hausner's ratio	1.093 (Excellent flow)	1.088 (Excellent flow)
5	% friability	0.28	0.27
6	Drug content	96.43	96.12
7	% Drug Release	Time (In hrs)	
		0	0
		1	0.40
		2	0.45
		3	8.18
		4	19.76
		5	38.34
		6	51.61
		7	62.57
		8	68.09
		9	74.27
		10	80.91
		11	88.27
12	93.91		

After 1 month of accelerated stability, the pellets were uniform size, spherical shape and good strength. They also maintained excellent flow property. The drug content of optimized batch before and after accelerated stability study had no major change. The comparative release profile of optimized batch before and after stability study results no significant change in release pattern.

7. CONCLUSION

The objective of the study was to prepare and evaluate bumadizone calcium colon targeted pellets by extrusion and spherization followed by coating for sustained release. By using Eudragit S100 (pH resistant polymer), HPMC K15 M, Ethyl Cellulose and PVP K30, it can successfully to obtain desired drug release and gastric retention. 3^2 full factorial designs applied and got desirable optimized batch which show the sustained release of the drug up to longer duration of time. The method applied was simple, rapid and economical and did not imply the use of toxic solvents. Based on result, 5% coating level formulations are suitable for the successful delivery of the drug into the lower part of intestine and colon. By preparing sustained release pellets of Bumadizone calcium, bioavailability of Bumadizone calcium can be achieved. Summary of the above results were listed below.

The results of micromeritic properties of pellets show excellent flow property.

- From the FTIR and DSC studies, it was observed that there is no chemical interaction between drug and excipients used in the formulations.
- Drug loaded pellets exhibited spherical shape with uniform and smooth coating.
- The Drug content and Friability of pellets is uniform and found satisfactory.
- Optimized batch shown that less than 0.50% of the drug released at the end of 2hrs in pH 1.2, less than 20% of drug released after end of four hrs in pH 6.8 and more than 85% at the end of 12hrs in pH 7.4.
- Accelerated stability study data for 1 month was found satisfactory.

From the above results of the research work, we can conclude that colon targeted enteric coated pellets of bumadizone calcium has been successfully prepared and can be used for sustained delivery in the treatment of Inflammatory Bowel Disease.

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Appendix A List of Abbreviations

ABBREVIATION		FULL NAME
%	:	Percentage
°C	:	Degree centigrade
DDS	:	Drug Delivery System
nm	:	Nanometer
mg	:	milligram
ml	:	milliliter
GI	:	Gastro Intestinal
IBD	:	Inflammatory Bowel Disease
CDDS	:	Controlled Drug Delivery System
IC	:	Indeterminate Colitis
CD	:	Crohn's Disease
UC	:	Ulcerative Colitis
CTDDS	:	Colon Targeted Drug Delivery System
DP-I	:	Dissertation Phase - I
No.	:	Number
PSAR	:	Patent Search and Analysis Report
HPMC	:	Hydroxy Propyl Methyl Cellulose
PVP K 30	:	Polyvinyl Pyrrolidone K 30
API	:	Active Pharmaceutical Ingredient
OROS-CT	:	Colon Targeted Oral Osmotic System
FTIR	:	Fourier-transform infrared spectroscopy
DSC	:	Differential Scanning Calorimetry
5-ASA	:	5-Aminosalicylic Acid
6-MP	:	6-Mercaptopurine
TNF	:	Tumour Necrosis Factor
h or hrs	:	Hour
Min	:	Minute
S	:	Second
GIT	:	Gastro Intestinal Tract
USA	:	United States of America

CFU	:	Colony Forming Unit
µm	:	Micrometer
NA	:	Not Applicable
°C	:	Degree Celsius
NSAIDS	:	Non-Steroid anti-inflammatory drugs
g/cm ³	:	Gram per cubic centimeter
UV	:	Ultra Violet
°F	:	Degree Fahrenheit
BP	:	British Pharmacopeia
JP	:	Japanese Pharmacopoeia
Ph.Eur./Eur.Ph.	:	European Pharmacopoeia
USP	:	United States Pharmacopoeia
NF	:	National Formulary
mPA	:	Megha Pascal
BDZ	:	Bumadizone
COX	:	Cyclooxygenase
World J. Pharm	:	World Pharmaceutical Journal
DK	:	Denmark
®	:	Registered Trademark