PULSINCAP: A NEW APPROACH TO COLON SPECIFIC DRUG DELIVERY
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ABSTRACT
Oral administration of different dosage forms is the most common form of administration due to greater patient compliance and flexibility. Targeted drug delivery system is the system in which the dosage form is modified to deliver the drug at the target region or at the disease region. Targeted delivery to the colon is being explored not only for local colonic pathologies, but also for systemic delivery of drugs like proteins and peptides. There are several approaches use for targeted drug delivery for colon such as pH and time dependant, Microbial triggered, Pulsin cap and Port system. In which pulsing cap system the formulations develop in a capsule form. The plug placed in the capsule controls the release of drug. These kinds of formulations are used for the treatment of disorders of the large intestine (colon), such as Colon cancer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) i.e. ulcerative colitis and Crohn’s disease. This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina, hypertension and arthritis. This targeting of drug to the disease site lowers the requirement of higher doses of drug and thus reducing the dosage frequency and cost of the drugs, which ultimately leads to patients compliance.

KEYWORDS: Pulsincap technology, Circadian rhythms, Colon specific pulsatile drug delivery system.

INTRODUCTION
Oral route is the most preferred route for drug administration, especially for chronic therapies where repeated administration is required, till to date. In addition, greater convenience, less pain, higher compliance, reduced risk of cross infection and needle stick injuries are the added advantages for oral delivery when compared to other routes of administration. Hence, oral drug delivery systems continue to dominate more than fifty percent market share of the drug delivery. Despite these advantages, the oral route is not amenable to the administration of drug for lower gastro intestinal (GI) diseases due to their release at upper GI tract, which leads to their limited availability at the lower GI tract (1).
Colon targeted drug delivery of drugs reduces the systemic side effects. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon (1).

**PULSATILE DRUG DELIVERY SYSTEM** (2)

Pulsatile drug delivery system are important as they deliver a drug at time and site specific manner resulting in improved therapeutic efficacy as well as compliance. Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired.

**Time Controlled Pulsatile Release**

- **Single Unit System** (3)

  These are subdivided as capsule-based system, osmotic system, delivery system with soluble or erodible membranes, and delivery system with repturable coating.

**Capsule-based system**

Capsule based system consists of pulsincap system, which consists of an insoluble capsule body and swellable and degradable plugs made of approved substances such as hydrophilic polymers or lipids. The lag time is controlled by plug, which pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. Pulsincap®. A swellable hydrogel plug seals the drug contents in to capsule body. When this capsule body came in to contact with dissolution medium, the hydrogel plug swells, and after the lag time the plug pushed itself outside the capsule and rapidly released the drug. Various types of material used for formulation of swellable plug which include hydroxyl propyl methyl cellulose, poly vinyl acetate and poly ethylene oxide. The length of plug decides lag time. Plug material is generally made up of HPMC, polyvinyl alcohol, glyceryl mono oleate, pectin, polymethacrylates.

**Osmotic system**

Osmotic system consists of capsule coated with the semipermeable membrane. Inside the capsule there is an insoluble plug consisting of osmotically active agent and the drug formulation. Another system is also based on expendable orifice that contain capsular system in which liquid drug is absorbed on highly porous particles. Drug releases through orifice of a semi permeable capsule supported by an expend osmotic layer after the barrier layer is dissolved.
The Port® System (Port Systems, LLC) consists of a gelatine capsule coated with a semi permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation when in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness.

OSMOTIC SYSTEM

Delivery system with soluble or erodible membranes

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat. e.g.chronotropic system which consists of a drug containing core layered with HPMC optionally coated with an outer enteric coating. The lag time prior to drug release is controlled by the thickness and the viscosity grade of HPMC layer. Solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like Polyoxy ethylene sorbitan mono oleate. When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat.
RATIONAL FOR THE DEVELOPMENT OF ORAL COLON TARGETED DRUG DELIVERY (4):

1. Treatment of local pathologies.
2. Chronotherapy (asthma, hypertension, cardiac.
3. Arrhythmias, arthritis or inflammation.
4. Greater responsiveness to the absorption enhancers.
5. Less enzymatic activity.
7. Oral delivery of vaccines as it is rich in lymphoid tissue.

NEED OF COLON TARGETED DRUG DELIVERY (4)

To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn’s Disease. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. A number of others serious diseases of the colon. e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

COLON TARGETED DISEASE AND DRUG (5)

<table>
<thead>
<tr>
<th>Target sites</th>
<th>Diseases</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical action</td>
<td>Inflammatory bowel diseases (Crohn’s disease, Ulcerative colitis)</td>
<td>Hydrocortisone, Prednisolone,</td>
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<tr>
<td></td>
<td>Irritable bowel Diseases</td>
<td>Sulfasalazine, Mesalazine,</td>
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<td></td>
<td>Amoebiasis</td>
<td>Mercaptopurine, Metronidazole,</td>
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<td></td>
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<td>Tinidazole, mebendazole.</td>
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<tr>
<td>Local action</td>
<td>Pancreatostomy, Chronic pancreatitis, Cystic fibrosis Colorectal cancer</td>
<td>Digestive enzymes</td>
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<tr>
<td></td>
<td></td>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>Systemic action</td>
<td>To prevent gastric irritation</td>
<td>NSAIDS</td>
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<tr>
<td></td>
<td>To prevent first pass metabolism of orally administered drugs</td>
<td>Steroids</td>
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<td></td>
<td>Oral delivery of Peptides</td>
<td>Insulin</td>
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<tr>
<td></td>
<td>Oral delivery of vaccines</td>
<td>Typhoid</td>
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</table>
APPROACHES FOR SITE SPECIFIC DRUG DELIVERY TO COLON (6):

Several approaches are used for site-specific drug delivery for colon specific drug delivery system which include the following,

- **Primary approaches for colon targeted drug delivery system:**
  - pH sensitive dependent delivery system.
  - Time controlled (delayed) release drug delivery system
  - Microbial triggered drug delivery
    - Prodrug approach
    - Polysaccharide based system

- **New approaches for colon targeted drug delivery**
  - Pressure controlled drug delivery system (PCDDS)
  - CODE (combination of pH dependent and microbial triggered CDDS)
  - Osmotic controlled colon drug delivery system:
    - Azo hydrogel

- **Pulsatile colon targeted drug delivery:**
  - Pulsincap system
  - Port system

- **Multiparticulate system based drug delivery**

**Primary approaches for colon targeted drug delivery system:**

- **PH- dependent delivery**

  In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve in the lower small intestine and the site-specificity of formulations can be poor. The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileocecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations.
## Time dependent delivery system

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 GIT. These systems are therefore particularly useful in therapy of diseases, which depend on circadian rhythms. Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay in delivery of the drug is time-based. In these systems, the site of drug release is decided by the transit time of a formulation in the GIT, which makes it challenging to develop a formulation in order to achieve a precise drug release in the colon. The formulations are designed such that the site of delivery is not affected by the individual differences in the gastric emptying time, pH of the stomach and small intestine or presence of anaerobic bacteria in the colon. An orally administered dosage form takes about 3 hrs to travel through the length of the small intestine to the beginning of the colon. Compared to gastric emptying rate, the small intestinal transit time is relatively consistent.

A system in the form of a tablet formulation, which could release the drug consistently in the colon via a time-dependent explosion mechanism. The formulation is comprised of three parts: (i) a central core containing the drug and swelling excipients (ii) an inner semi-permeable polymer membrane containing a plasticizer which allows water influx but prevents the outward diffusion of drug and (iii) an outer enteric-coating which dissolves at or above pH 5.5. The outer enteric coat keeps the tablet intact until it reaches the small intestine. Upon arrival in the small intestine, the enteric coat dissolves allowing for GI fluid to diffuse through the semi permeable membrane into the core. The core swells during the transit of the tablet through the small intestine. Finally, after a consistent period of 4-6 h transit in the small intestine, the swollen core burst the semi-permeable membrane releasing the drug in the colon.

## Microbially triggered system

The basic principle involved in this method is degradation of polymers coated on the drug delivery system by micro flora present in colon and thereby release of drug load in colonic region because the bio environment inside the human GIT is characterized by presence of complex micro flora, especially the colon is rich in microorganisms. In this method, drugs and/or dosage forms are coated with the biodegradable polymers i.e., the polymers degrade due to influence of colonic microorganisms. When the dosage form passes through the GIT, it remains intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating. This approach is different from...
probilotic approach because in probilotic approach, we are providing micro flora from external source which assist the interior flora.

**Prodrug Approach for Drug Delivery to Colon**⁸:

Pro drug 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 up on oral administration the moiety remains intact in the stomach and small intestine, and after reached in the colon, enzymatic cleavage regenerate the drug.

**Polysaccharide based system**⁶:

The polysaccharide which is polymer of monosaccharide retains their integrity, because they are resistant to digestive action of GI enzymes, matrices of polysaccharide are assessed to remain intact in physiological environment of stomach and small intestine, as they reach colon they are acted upon bacterial polysaccharides and results in degradation of the matrices. Family of natural polysaccharide has appeal to area of drug delivery as it comprised of polymer with large number of derivitizable groups, with wide range of molecular weight, varying chemical composition and forms most low toxicity and biodegradability, yet a high stability. Pectin is polysaccharides which contain α-1, 4 D – galactouronic acid and 1, 2 D-Rhamnose with D galactose & D-arabinose side chains. A novel colonic drug delivery is investigated. *In vitro* experiments demonstrated that high methoxy pectin, when applied as compression coat, proved capable of coat tablet during condition stimulating gastrointestinal environment and was susceptible to enzymatic attack.

**New approaches for colon targeted drug delivery system**⁶:

- **Pressure controlled drug delivery system (PCDDS):**

  Digestion mainly occurs due to the contractility of the stomach and peristaltic movement of the intestine. The contractility movement of stomach leads to the digestion or breakdown of larger particles to smaller ones which are then transferred to intestine. The peristaltic movement of intestine is responsible for the passage of bolus from one part of GIT to the next part. The peristaltic movement of ascending colon transfers the bolus to transverse colon called as mass peristalsis. These peristaltic movements occur in limited number i.e. three to four times a day. These peristaltic movements of intestine results in an increase in the luminal pressure. This increase in luminal pressure is the key

  Point in the development of pressure controlled drug delivery system. The pressure controlled drug delivery system 25 consists of a capsule in which the drug is present. These
gelatine capsules are coated with water insoluble polymer like ethyl cellulose on their inner side. The drug is introduced into the capsule along with suppository base. The thickness of ethyl cellulose coating determines the disintegration capacity of the capsule. After administration the suppository base dissolves at body temperature. The water from intestinal contents is absorbed resulting in increased viscosity which leads to an increase in the pressure in the capsule. The pressure in the capsule expels the drug into the colon. The intestinal pressure developed varies with the circadian rhythms, state of body, food administration, etc.

- **CODE (combination of pH dependent and microbial triggered CDDS)**
  
  This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine. This system consists of a core tablet coated with three layers of polymer coatings. The outer coating is composed of the polymer Eudragit L. This coating gets dissolved once the tablet passes through the pyloric and duodenum and exposes the next coating. The next coating is composed of Eudragit E.

- **Osmotic controlled colon drug delivery system:**
  
  This system consists of osmotic units. The osmotic units are used either singly or as many as 5-6 push pull lactulose present in the inner core. This released lactulose gets metabolized into short chain fatty acids that lower the surrounding pH where the Eudragit E layer dissolves. The dissolving of Eudragit E results in the exposure of the drug. The other polysaccharides that are used along with the drug in the core tablet are mannitol, maltose, etc. The bacteria present in the colon are responsible for the degradation of polysaccharides that are released from the core tablet. The degradation of polysaccharides results in organic acids formation that lowers the pH of the contents surrounding the tablet units that are encapsulated in a hard gelatine capsule.

  The push pull units are bilayered with outer enteric impermeable membrane and inner semi permeable membrane. The internal or central part of the push pull consists of the drug layer and push payer. The semi permeable membrane which is present next to the drug layer consists of an orifice through which the drug contents are expelled during the course of time. The capsule body enclosing the push pull units gets dissolved immediately after administration. During the passage of the push pull units through the GIT the enteric impermeable membrane prevents the water absorption into the unit. The coating gets dissolved once it reaches the small intestine due to higher pH (>7). Water enters the unit through the semi permeable membrane causing the push
layer to swell. The swelling of the push compartment forces the drug into the surrounding environment through the orifice. These osmotic controlled drug delivery systems deliver the drug at a constant rate for up to 24 hr.

**Azo hydrogel:**

The pH sensitive monomers and azo cross linking agents in the hydrogel produce the colon specificity. During their passage through the GIT these hydrogels swell as the pH increases. This swelling of hydrogels cleaves the cross links in the hydrogel network causing the release of drug entrapped in the hydrogel. These hydrogels are prepared by cross linking polymerization of N substituted (meth) acryl amides, N- tetra- butyl acryl amide and acrylic acid with 4, 4-di (methacryloylamino) azobenzene as cross linking agents. The hydrogels are also prepared by cross linking polymeric precursors, polymer-polymer reaction using same polymeric precursor with the corresponding copolymer containing side chains terminating in NH2 groups. The degradation rate of hydrogel is associated with the degree of swelling and inversely proportional to the cross linking density.

- **Pulsatile colon targeted drug delivery:**

  **Pulsincap system:**

  In this system the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents. The capsule gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body.

  **Port system:**

  In this system the capsule body is enclosed in a semi permeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation. When the capsule comes in contact with the dissolution fluid the semi permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals.

- **Multiparticulate system based drug delivery:**

  The various advantages of multiparticulate systems are increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity. The various multiparticulate approaches
include pellets, micro particles, granules and nanoparticles. Multiparticulates systems are preferred over single unit dosage forms as the multiparticulate systems enable the drug to reach the colon quickly and retained in colon for long period of time. These systems pass through the GIT easily due to their smaller size. Multiparticulate systems are dispersed more uniformly in the GIT resulting in more uniform drug absorption. Nanoparticles, the preparation of nanoparticles is simple and these are capable of protecting the protein and peptide drugs from the chemical and enzymatic degradation in GIT resulting in an increase in their stability and absorption of through the intestinal epithelium. The polymeric nanoparticles are prepared by various techniques like polymerization, nanoprecipitation, inverse micro emulsion. The methods involve the use of organic solvents, heat and agitation. The drawback of these methods is that the heat, agitation is harmful to proteins and peptide drugs. Ionic gelation technique is the most widely used method for proteins and peptide drugs.

COLON SPECIFIC PULSATILE DRUG DELIVERY SYSTEM

The development of oral sustained and controlled release formulation offer benefits like controlled administration of therapeutic dose at the delivery rate, constant blood levels of the drug, reduction of side effects minimizations of dosing frequency and enhancement of patient compliance. Among modified-release oral dosage form increasing interest has currently turned to system designed to achieve time-specific (delayed, pulsatile) and site specific delivery of drug. The possibility of exploiting delayed release to perform chronotherapy is quite appealing for those diseases, the symptoms of which recur mainly at night time or in the early morning, such as bronchial asthma, angina pectoris and rheumatoid arthritis (9).

Dosage forms that deliver drugs into the colon rather than upper GIT offers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn’s disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Apart from retarding or targeting dosage forms, reliable colonic drug delivery could also be an important starting position for the colonic absorption of perorally applied, undigested, unchanged and fully active peptide drugs. The simplest method for targeting of drugs to the colon is to
obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coatings or extremely slow releasing matrices \(^{(10)}\).

- **KEY INGREDIENTS USED IN FORMULATION OF PULSIN CAP:**

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>EXAMPLES</th>
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</thead>
<tbody>
<tr>
<td>Solubility modifier in gelatine capsule</td>
<td>Formalin</td>
</tr>
<tr>
<td>Polymer</td>
<td>HPMC K(_4)M, Sodium alginate, Xanthan gum</td>
</tr>
<tr>
<td>Diluent</td>
<td>Lactose</td>
</tr>
<tr>
<td>Lubricant</td>
<td>Mg. stearate</td>
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<tr>
<td>Glidant</td>
<td>Talc</td>
</tr>
<tr>
<td>Sealing agent</td>
<td>Ethyl cellulose</td>
</tr>
<tr>
<td>Enteric coating agent</td>
<td>Cellulose acetate phthalate</td>
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</tbody>
</table>

**FORMULATION DEVELOPMENT \(^{(11)}\):**

**Preparation of Cross-Linked Gelatin Capsules**

Formalin treatment has been employed to modify the solubility of gelatin capsules. Exposure to formalin vapours results in an unpredictable decreases in solubility of gelatin owing to the cross-linkage of the amino group in the gelatin molecular chain aldehyde group of formaldehyde by Schiff’s base condensation.

- **Method**

  Hard gelatin capsule of size 0 was taken. Bodies were separated from cap, 25 ml of 15% (v/v) formaldehyde was taken into desiccators and a pinch of potassium permanganate was added to it, to generate formalin vapours. The wire mesh containing the empty bodies of capsule was then exposed to formaldehyde vapours. The caps were not exposed leaving them water-soluble. The desiccators were tightly closed. The reaction was carried out for 12 h after which the bodies were removed and dried at 50°C for 30 min to ensure completion of reaction between gelatin and formaldehyde vapours. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in a polythene bag.
Overview of capsule body in desiccators

Preparation of hydrogel plug

The formulation of pulsincap 90mg and 100mg hydrogel plug was prepared by compressing equal amount of different polymer and diluents as a lactose using 6 mm punches and dies on rotary tablet press keeping variation in thickness and hardness values of tablet plug.

Preparation of granules

Granules were prepared by wet granulation method using different concentration of polymers.

Preparation of modified pulsincap

Equivalent to dose of mg in drug granules were filled in the capsule bodies and plugged with hydrogel plug. The treated body and the cap of the capsules were sealed with a small amount of 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated with enteric coating (5% CAP) to reduce variability in gastric emptying time, coating was repeated until an expected weight gain of 8-12% was obtained.
EVALUATION OF GRANULES

1. Precompression study.
   a) Angle of repose: The powder will allow to flow through the funnel fixed to a stand at definite height (h). The angle of repose will then calculate by measuring the height and radius of the heap of granules will be form.

\[ \tan \phi = \frac{h}{r} \]

\[ \phi = \tan^{-1} \left( \frac{h}{r} \right) \]

Where, \( \phi \) = angle of repose, \( h \) = height of the cone, \( r \) = radius of the cone

b) Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) will determine. A quantity of 10 g of powder from each formulation will introduce into a 10 ml measuring cylinder. Initial volume will observe, the cylinder will allow to tap. The tapping will continue until no further change in volume is noted. Bulk density is calculated by using formula:

Bulk density (\( \rho_b \)) = Bulk volume of the powder/Weight of the powder

Tapped density (\( \rho_t \)) = Tapped volume of the powder/Weight of the powder

c) Carr's index: The Carr’s index of the powder will determine by using formula:

Carr’s index (%) = \[ \left( \frac{TBD - LBD}{TBD} \right) \times 100 \]

Where, LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

d) Hausner’s ratio = \[ \frac{T}{d} \]

EVALUATION OF MODIFIED PULSINCAP

- Solubility study of treated capsules.
  The capsule bodies were exposed to 15% formaldehyde solution in varying time intervals. Then exposed capsule bodies were dried in hot air oven. The solubility of bodies was tested in 0.1N HCL. The time at which the capsule dissolves or forms a soft fluffy mass was noted.

- Qualitative test for free formaldehyde
  Standard used is formaldehyde solution and sample solution is formaldehyde treated bodies, cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 hrs with a magnetic stirrer, to solubilise the free formaldehyde. The solution was then filtered into a
50ml volumetric flask, washed with distilled water and volume was made up to 50ml with the washing.

**Method**

1ml of sample solution, 9ml of water was added. One millilitre of resulting solution was taken into a test tube and mixed with 4ml of water and 5ml of acetone reagent. The test tube was warmed in waterbath at 40°C and allowed to stand for 40 min. The solution was less intensely colored than a reference solution prepared at the same time and in the same manner using 1ml of standard solution in place of the sample solution.

- **Thickness of cellulose acetate phthalate coating.**
  The thickness of cellulose acetate phthalate coating was measured using screw gauge and expressed in mm.

- **Weight variation**
  10 capsules were selected randomly from each batch and weight individually for weight variation.

- **Drug content**

  Weigh accurately a quantity of the mixed contents of 5 capsules containing about dose of drug in mg, shake for 10 min with 150 ml of methanol or suitable media. Allow to stand, dilute 10ml of the supernant liquid to 100ml with methanol/suitable media and measure the absorbance of the resulting solution at the maximum at about λ max.

- **In-vitro release profile**

  Dissolution studies were carried out by using USP I dissolution test apparatus (Basket) method. Capsules were placed in a basket so that the capsule should be immersed completely in dissolution media but do not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs) then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hrs (average small intestinal transit time is 3 hrs) the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hrs. 900ml of the dissolution medium was used at each time. Rotation speed was 50 rpm and temperature was maintained at 37±0.5°C. Five milliliters of sample withdrawn at predetermined time intervals and replaced with fresh dissolution media. The withdrawn samples were analyzed at 260 nm by UV absorption spectroscopy.

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CONCLUSION

The pulsatile colonic drug delivery system shows better release of drug and also produced prolonged period of time for release. Pulsin cap system in drug release depends on the polymers used in the formulations. These include the topical treatment of colonic disorders, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) such as Crohn’s disease, Ulcerative colitis, Colon cancer, Diverticulosis, Diarrhea, Amebiasis etc. Many investigations have been carried out with the aim of discovering an ideal formulation for colon specific drug delivery and have a number of important implications in the field of pharmacotherapy. Formulations involving enteric polymers or pH dependent that react to changes in gastrointestinal pH have been extensively used recently. Enteric polymers have been shown to be safe and have been accepted for use in drug products. For in vitro evaluation of a colon specific drug delivery system, it seems that more than one testing method is necessary to characterize drug release and justify system design rationale.

REFERENCES:


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