

Development and Evaluation of Multiparticulate Colon Targeted Drug Delivery System by Combine Approach of pH and Bacteria.

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Abstract: Crohn's disease is the inflammatory bowel disease which can occur in any part of the GI tract but inflammation is mainly localized in the more distal regions of the small intestine i.e. the terminal ileum. Budesonide is synthetic, nonhalogenated glucocorticoid having higher intrinsic potency than cortisol and prednisolone. The similarity in pH between the small intestine and the colon makes pH dependent systems less reliable. For time-dependent formulations, the location of initial drug release predominantly depends on the transit time of the system in the GI tract. Despite the relative consistency of transit times in small intestine the retention times in the stomach are highly variable. That will result in a spread of initial release sites in the distal GI tract from time-dependent systems. Due to the intersubject variation in GI transit times, time-dependent systems are not ideal to deliver drugs to the colon. Major disadvantage of microbial approach is that the variability of drug release due to variation in microbial flora counts. Therefore it is planned to develop a system which will release the drug in colon based upon combined approach of pH and bacteria.

Key-words: Colonic drug delivery, Budesonide, pH and Microbial approach, Polymer, In vivo study.

Introduction

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome but also for the potential holds for the systemic delivery of proteins and therapeutic peptides [1-2]. The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters of the small intestine [3]. Due to the distal location of the colon in the GI tract, a colon specific drug delivery system should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. Such a system can be formulated utilizing some specific conditions existing in the colon in comparison to other parts of the GI

tract. Another challenge in developing therapeutically effective products for the treatment of colonic pathologies is the impact of disease on the delivery system [4]. For example, the luminal pH of the distal intestine in patients with inflammatory bowel disease (IBD) can be lower than that seen in healthy volunteers up to 5.3 [5, 6, 9, 15]. Various systems have been developed for colon-specific drug delivery. These include covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, time dependent release systems, and enzymatically controlled delivery systems [7]. A large number of anaerobic and aerobic bacteria are present throughout the entire length of human GI tract. Over 400 species of bacteria are found in the colon, which are predominantly anaerobic such as Bacteroids, Bifidobacterium, Eubacterium and

Clostridium and a small number of fungi. The bacteria within the colon are predominantly anaerobic and there is a low reducing environment (low reducing potential) [8]. Alteration in composition of the GIT flora occurs under certain diseased states, e.g. in acute diarrhoea, the resistant flora may be eclipsed by pathogen, anatomic physiologic derangement of GIT may lead to bacterial overgrowths which in turn may causes variation in microflora e.g. influence of the inflammatory bowel disease (IBD) on the intestinal microflora [9]. The pH dependent systems prepared with enteric polymers have found practical application in the development of commercial products for the treatment of ulcerative colitis with 5-aminosalicylic acid [10]. However, for such formulations, the large inter individual variability of intestinal pH values poses difficulties in achieving truly colon targeted delivery [11]. Also, in contrast to what was believed in the past, it is now known that the pH of the proximal and transverse colon is more acidic than that in the small intestine, especially in inflammatory bowel disease (IBD) [12]. Thus, the pH-based colon-specific formulations, which are designed to release drug at a higher pH, fail to release drug completely upon encountering the more acidic colonic pH. However, the inherent limitation of the time approach is the marked inter- and intra-individual variability in gastric emptying, small-intestinal and colonic transit time [13, 14]. This results in a spread of initial release sites in the gastrointestinal tract (GIT) from time-dependent systems [15].

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. 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 increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying [16]. Multiparticulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, microparticles and nanoparticles. The use of multiparticulate drug delivery systems in preference to single unit dosage forms for colon targeting purposes dates back to 1985 when Hardy and co-workers [17] showed that multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time. 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 intra subject variability. Moreover, multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption [18-19]. Therefore the objective of the present study was to develop colon targeted multiparticulate system which will be of combined approach of pH and enzyme controlled (bacterial dependant) by overcoming the demerits of both approaches such as intersubject variability in pH in disease condition as well as variation in microflora in IBD condition in individuals and to release the drug at desired site.

Experimental

Materials:

Neutral pellets were obtained as a gift sample from Murlikrishnan Pharmaceuticals Pvt. Ltd. Pune, India. Budesonide was obtained as gift sample from Mepro Pharmaceuticals Pvt. Ltd. (unit II), Wadhawan, India, and Eudragit FS30D was obtained from the Degussa India Pvt. Ltd. Mumbai, as a gift sample. Guar gum (MW 220,000) was procured from Himedia Laboratories Limited, India. Other excipients used were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

Methodology:

Preparation of Eudragit FS 30 D Coated Budesonide pellets

Preparation of Coating Solution for Drug Loading:

Budesonide was incorporated on non-pareils seeds by spraying budesonide in a solution in dichloromethane containing polyvinyl pyrrolidone (PVP 30K) as a binder and talc as antisticking agent. The coating solution parameters are stated in Table 4. The stated amounts of budesonide and PVP 30 K (Table 1) were dissolved in methanol solution separately. After mixing each solution for 30 minutes, these two solutions were mixed together and methanol was added up to the 100 ml volume. The coating solution was sprayed over the non-pareils seed by using INSTA-COAT R & D Coater. During preliminary studies various combination of above mentioned composition were tried.

Preparation of aqueous Eudragit FS 30 D coating system [20]:

To prepare the Eudragit FS 30 D coating dispersion a 30 % (w/w) aqueous Eudragit FS 30 D dispersion was

used. Polystyrene 80 (Tween 80) as a wetting agent and glyceryl monostearate as a glident were added to water and the mixture was heated at 60⁰ C by stirring 10 min until a fine homogenous dispersion was obtained. After cooling, this dispersion to a room temperature it was gently added to Eudragit FS 30 D dispersion and mixed by magnetic stirrer. This coating dispersion was then passed through #100 sieve. For this coating dispersion no plasticizer was needed in the formulation since Eudragit FS 30D exhibits a minimum film-forming temperature of 14⁰ C and low glass temperature^[21]. Composition of coating solution is mentioned in Table 2.

Coating of Eudragit FS 30 D polymer coating solution to budesonide loaded pellets:

100 g of budesonide loaded pellets were coated with Eudragit FS 30 D polymer suspension by using the INSTA-COAT R & D coating machine. The various coating parameters controlled during coating process are given in Table 4. Samples of coated pellets were removed from apparatus at 10, 20, 30, 40% weight gain coating level. Based on the in-vitro drug dissolution study and desired lag time the final coating level was selected.

Evaluation of Eudragit FS 30 D Coated

Budesonide pellets

Drug content^[24]:

The budesonide content of the pellet formulations were evaluated over accurately weighed 100 mg pellets. After completely powdering pellets in mortar, the complete residue was transferred into a volumetric flask and added up to 100 ml with pH 7.4 phosphate buffer solution. This solution was kept in the orbital shaker for 24 hrs. The solution was filtered. The UV absorbance of the solution was measured at $\lambda=246$ nm by UV spectrophotometer.

Table 1: Composition for Solution Layering of Drug.

Sr. No.	Ingredient	Quantities
1	Budesonide	0.5 gm
2	PVP K30	3.5 gm
3	Talc	2 gm
4	Methanol	100 ml

Table 2: Formulation details of Eudragit FS30D aqueous coating Solution.

Sr. No.	Ingredients	Quantity
1	Eudragit FS 30D USP	63 %
2	Glyceryl Monostearate	0.93 %
3	Tween 80	1.17 %
4	Water	35 %

Physical Properties of pellets:

Angle of repose, bulk density, tapped density, hausner ratio and loss on drying were evaluated of all formulations in triplicate form.

In-vitro drug release study for Eudragit FS 30 D coated pellets:

The dissolution studies of budesonide loaded Eudragit FS30D coated pellets were carried out in a USP XXIII dissolution apparatus II (DA 6D Veego, TDT 08L Electrolab) at a rotation speed of 100 rpm in a 933.3 ml medium at 37⁰ C. The capsules (n=3) are transfer to dissolution medium and samples were taken at selected time intervals, filtered through Whatman filter paper no. 41 and analyzed by UV spectrophotometer (V-530 Jasco) at 247 nm for acidic medium and at 245 nm for phosphate buffer. The continuous dissolution method USP XXIII was used by simulating conditions of the GI tract. In this study pellets were filled in HPMC capsules and were added in 700 ml of 0.1 N HCl (pH 1.2) for 2 h. At the end of 2 h, 233.3 ml of tribasic sodium phosphate was added to all the dissolution vessels and the pH was adjusted to 6.5 (1h), 6.8 (2 h) and 7.2 (till end of test) by using 2 M NaOH or 2 M HCl.

Preparation of Guar gum Coated Budesonide pellets

Budesonide loading to non pareils was performed as mentioned above in the preparation of Eudragit FS 30D coated budesonide pellets.

Preparation of Aqueous guar gum coating system^[22, 23, 24]:

To prepare the guar gum coating dispersion a guar gum (4% w/v) in ethanol/water or guar gum (1% w/v) in water/isopropanol (7/3) was used. Glyceryl monostearate and PEG400 were added to mixture as a glident. Mixture was stirred 10 min until a fine homogenous dispersion was obtained.

Coating of Guar Gum polymer coating solution to budesonide loaded pellets:

The non pareils for guar gum aqueous dispersion coating in 8-inch coating pan. The various coating parameters controlled during coating process are given in Table 4. Hundred gms of budesonide loaded pellets were coated with Eudragit FS30D polymer suspension by using the INSTA-COAT R & D coating machine. Samples of coated pellets were removed from apparatus at 40%, 45%, 50% weight gain coating level. Based on the in-vitro drug dissolution study and desired lag time the final coating level was selected.

Evaluation of Guar gum Coated Budesonide pellets

The guar gum coated budesonide pellets were evaluated for drug content, physical properties, scanning electron microscopic study, and in-vitro dissolution testing.

In-vitro drug release study for Guar Gum coated pellets:

The dissolution studies of budesonide loaded guar gum coated pellets were carried out in a USP XXIII dissolution apparatus II (DA 6D Veego, TDT 08L Electrolab) at a rotation speed of 100 rpm in a 933.3 ml medium at 37⁰ C. In order to simulate enzyme in GIT pepsin 0.32%w/v was added in the dissolution medium. The capsules (n=3) are transfer to dissolution medium and samples were taken at selected time intervals, filtered through Whatman filter paper no. 41

and analyzed by UV spectrophotometer (V-530 Jasco) at 247 nm for acidic medium and at 245 nm for phosphate buffer. The continuous dissolution method USP XXIII was used by simulating conditions of the GI tract. In this study capsules were added in 700 ml of 0.1 N HCl (pH 1.2) for 2 h. At the end of 2 h, 233.3 ml of tribasic sodium phosphate was added to all the dissolution vessels and the pH was adjusted to 6.5 (1h), 6.8 (2 h) and 7.2 (till end of test) by using 2 M NaOH or 2 M HCl. To evaluate enzyme-triggered drug release of guar gum-coated pellets, at the end of 3 hours pancreatin, a rich product of colonic microflora in a concentration of 1%w/w was added into pH 6.5 phosphate buffer to simulate the degradation of polysaccharide by microflora in the colon.

Preparation of Eudragit FS30D and Guar gum combination coated Budesonide pellets

Preparation of Eudragit FS30D and Guar Gum combined mixture:

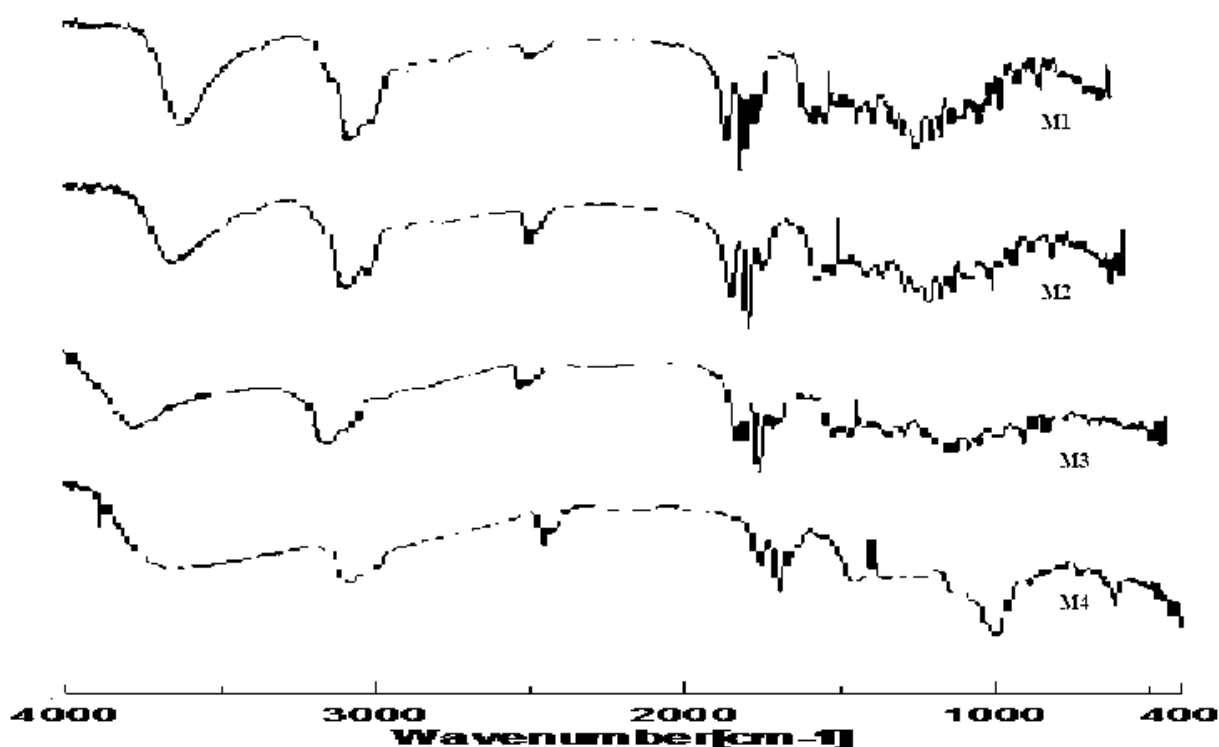
In order to achieve the objective of the present study to prepare the combined mixture of pH dependant and microbially degraded polymer is important. Various combination were tried for the preparation of the mixture(**Table3**).The Eudragit FS30D coating solution and Guar Gum coating solution were prepared as mentioned earlier and mixed in different proportions.

Table 3: Various ombinations of Eudragit FS30D and Guar gum polymer coating solution.

Sr. No.	Eudragit FS30D	GUAR gum	Resulting solution
1	0.5 %	1%	Semisolid mass formed.
2	1%	1%	Solution was stable for 24 hrs.
3	1%	0.5%	Semisolid mass was formed

Table 4: Coating parameters for Drug loading and Polymer coating to pellets.

Parameters	Drug Specification	Eudragit FS30D Specification	Guar gum Specification	Combination Specification
Batch size	50 gm	10 gm (~100 capsules)	10 gm (~100 capsules)	10 gm (~100 capsules)
Spray rate	0.5 ml/min	1.2 ml/min	1.2 ml/min	1.2 ml/min
Nozzle diameter	1mm	1 mm	1 mm	1 mm
Atomizing air pressure	2 – 3 lb/inch ²	1 bar	1 bar	1 bar
Air inlet temperature	55°C	30-35 ⁰ C	60-65 ⁰ C	30-35 ⁰ C
Pan speed	30 RPM	28 RPM	30 RPM	28 RPM
Coating efficiency	82 to 85 %	50-60%	50-60%	50-60%



- M1-Pure drug budesonide, M2- Drug + Eudragit FS 30D, M3-Drug + Guar gum, M4-Drug + Eudragit Fs30D+ Guar gum. (Final formulation)

Figure 1: FTIR results of drug and excipients study.

Coating of Eudragit FS30D and Guar Gum polymer mixture coating solution to budesonide loaded pellets:

The non pareils for guar gum aqueous dispersion coating in 8-inch coating pan. The various coating parameters controlled during coating process are given in Table 4. Hundred gms of budesonide loaded pellets were coated with mixture of polymer suspension by using the INSTA-COAT R & D coating machine. Samples of coated pellets were removed from apparatus at 40%, 45%, 50%weight gain coating level. Based on the in-vitro drug dissolution study and desired lag time the final coating level was selected.

Evaluation of Eudragit FS30D and Guar gum Combination coated Budesonide pellets

The Eudragit FS30D and Guar Gum combination coated budesonide pellets were evaluated for drug content, physical properties, scanning electron microscopic study, and in-vitro dissolution testing.

In-vitro drug release study for Eudragit FS30D and Guar Gum combination coated budesonide pellets:

The dissolution studies of budesonide loaded Eudragit FS30D and Guar Gum combination coated budesonide pellets were carried out in a USP XXIII dissolution apparatus II (DA 6D Veego, TDT 08L Electrolab) at a rotation speed of 100 rpm in a 933.3 ml medium at 37⁰ C. In order to simulate enzyme in GIT pepsin 0.32%w/v was added in the dissolution medium. The capsules (n=3) are transfer to dissolution medium and samples were taken at selected time intervals, filtered through Whatman filter paper no. 41 and analyzed by UV spectrophotometer (V-530 Jasco) at 247 nm for acidic medium and at 245 nm for phosphate buffer. The continuous dissolution method USP XXIII was used by simulating conditions of the GI tract. In this study capsules were added in 700 ml of 0.1 N HCl (pH 1.2) for 2 h. At the end of 2 h, 233.3 ml of tribasic sodium phosphate was added to all the dissolution vessels and the pH was adjusted to 6.5 (1h), 6.8 (2 h) and 7.2 (till end of test) by using 2 M NaOH or 2 M HCl. To evaluate enzyme-triggered drug release of

guar gum-coated pellets, at the end of 3 hours pancreatin, a rich product of colonic microflora in a concentration of 1%w/w was added into pH 6.5 phosphate buffer to simulate the degradation of polysaccharide by microflora in the colon.

Drug and Excipients compatibility studies:

The drug with excipients like Eudragit FS30D, guar gum (1:1 ratio) were subjected to storage at room temperature and elevated temperature of 40°C and 75% RH for one month. Sampling was done at a predetermined time intervals of 7, 14, 21 and 30 days. The mixtures of drug and excipients were then evaluated by % assay by using double beam UV spectrophotometer (Jasco V-550) and IR spectra by FTIR spectrometer (Jasco 460 plus). The FTIR results are shown in figure 1.

In Vivo X-Ray Studies of Eudragit FS30D and Guar gum mixture (1:1) coated pellets filled in HPMC Capsules of Budesonide Using Human Volunteers ^[25]:

The in-vivo X-ray imaging study is carried out to investigate the optimum formulation for the targeting the drug at the ileum. The Ethical Committee of the Medical Ethical Committee of Nagpur (Ref.no. 55721052009) in accordance with internationally accepted principles had approved the experimental protocol. X-ray imaging was used to monitor the pellets throughout the gastrointestinal system. Four healthy male volunteers, with a mean age of 25 years (range 22–40) and 50–80 kg body weight participated with in vivo studies. They were non-alcoholics, non-smokers and had not taken any drugs. The purpose of the study had been fully explained, and all volunteers gave their written consent. Each subject orally ingested barium sulphate containing pellets in HPMC capsules, pellets were coated with Eudragit FS30D and Guar gum(1:1) polymer; two volunteers received capsules with 40 w/w with 200 ml of water and the other two volunteers received 40% w/w coated tablets, after an overnight fast. Abdominal radiographs were taken at fixed time intervals, and the tablets were visualized using digital X-ray imaging to establish whether they had reached the large intestine or not over 6 h.

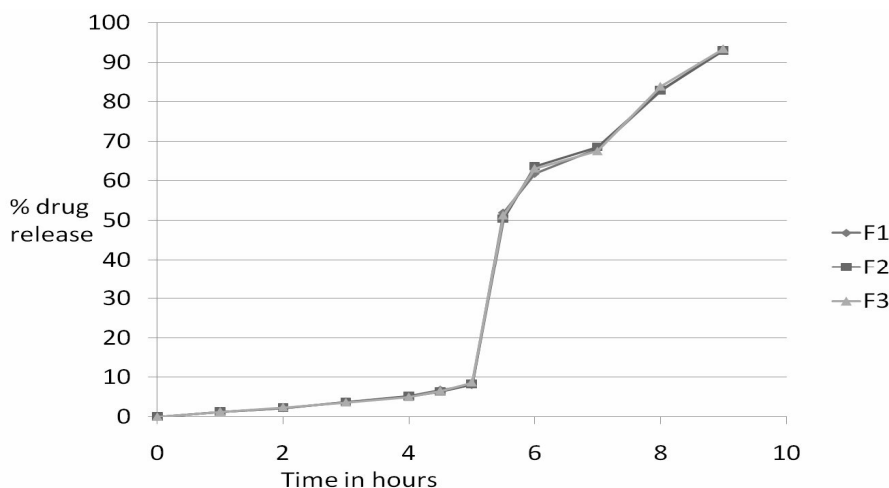


Figure 2: In-vitro drug release of Eudragit FS 30D coated budesonide pellets.

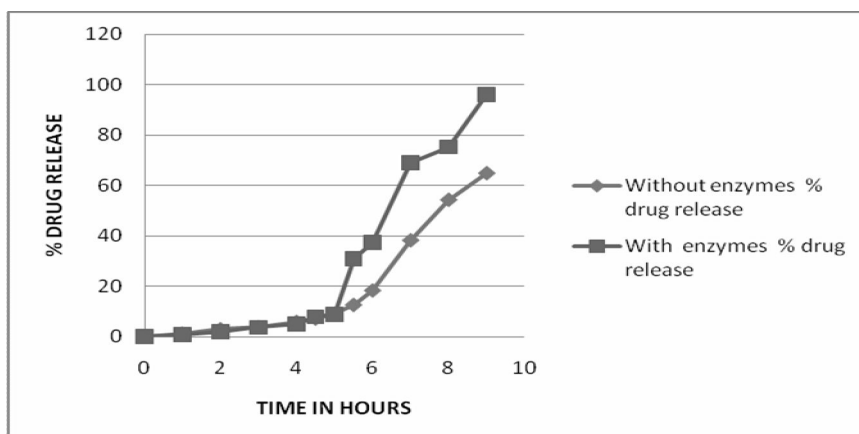


Figure 3: In-vitro drug release of Guar Gum coated budesonide pellets with and without enzyme.

Results and Discussion

Drug content:

Drug content of all formulations prepared was 96% to 98% and was found to be within limit.

Physical properties:

Various physical properties were evaluated such as bulk density, tapped density, angle of repose hausner ratio, loss on drying. Each formulation showed all physical properties within excellent flow properties limits.

In-vitro evaluation of Eudragit FS30D coated pellets:

Lag time (Tlag) is defined as the time elapsed between the administration of the system and the appearance of drug in dissolution medium. The transit time of the formulation through the small intestine is constant i.e. 3-4 h. So the average time required for any formulation to reach the ileo-cecal region is considered to be 4-5 h. As the transit time in the small intestine is relatively constant (approximately 3-5 h), simulation of small intestine was divided in three parts; proximal part of small intestine with pH 6.5 and residence time 1h, lower part of small intestine with pH 6.8 and residence time 2h and finally terminal ileum with pH 7.2 till end of test. Thus the continuous dissolution test was carried out for enteric coated budesonide capsules with pH 1.2, 6.5, 6.8 and 7.2 for 2, 1, 2 h and till end of study respectively. Drug release study was carried out in triplicate of all 3 formulations. When the coating level was above 30% the Eudragit FS30D coated pellets had sufficient acid resistant as evident from figure 2, drug release was below 10% for 40% weight gain up to colonic site due to poor solubility of Eudragit FS30D polymer and ability of good gastric

protection. Eudragit FS30D has a threshold dissolution pH value which is the key factor for the colon targeting. Hence when formulation reached to colonic site as pH increases up to 7.2 the solubility of polymer increases and polymer coat starts to dissolve at same pH with accelerated drug release. About 93% drug release with 4.5 hours lag time was observed at end of 9th hour of dissolution study. Figure 2 indicates the graph of % drug release vs. time in hours. The formulation was failed to showing the significant drug release below pH-7 which is an ideal IBD condition due to variation in pH at colonic site and could not be useful for IBD which is remarkable demerit of the pH dependant colon targeted drug delivery system.

In-vitro evaluation of Guar Gum coated pellets:

An outer guar gum coating can significantly slow down the release rate, which is negatively correlated to weight gain. Release profiles of the guar gum coated pellets are biphasic, typical of an initial constrained release and a later incremental release. It is highly hydrophilic in nature, film coating with guar gum seemed to be able to retard initial budesonide release significantly, even at a relatively small weight gain of 40%. In-vitro evaluation of guar gum coated budesonide pellets was carried out by changing pH dissolution method with enzyme and without enzyme at different pH conditions like pH 1.2, 6.5, 6.8 and 7.2 for 2, 1, 2 h and till end of study respectively. Study carried out without enzyme shows the drug release which is non uniform and in very low concentration. The retardation of drug release was due to absence of microbial flora and their degradation enzymatic products which are responsible for increase in redox potential to cause the degradation of biodegradable polymers. Drug release of 40% weight gain pellets was

found to be below 10% and gradually increased up to 64% in 9 h (Figure 3). In presence of enzyme pancreatin which was a rich product of enzymes in colon and the release rate was accelerated due to degradation of guar gum layer. Hence as soon as the addition of enzyme was done the drug release was markedly increased and finally about 96% drug release was observed at end of 9 hours which was indicative of obvious enzyme-triggering mechanisms (Figure3). The in-vitro evaluation clearly indicates that in absence of the enzyme drug release was retarded and in the presence of enzyme drug release was accelerated significantly. The variation in drug release pattern was due to the variation in microbial enzyme in dissolution medium which is the major disadvantage of the microbial controlled colonic delivery.

In-vitro evaluation of Eudragit FS30D and Guar Gum combination coated budesonide pellets:

Eudragit FS30D and guar gum (1:1) combination coated pellets under consecutive gradient pH conditions with and without enzymes. The amount of Budesonide released from Eudragit FS30D and Guar Gum combination coated budesonide pellets within the first 2 h was not more than 3% for both with and without enzyme. After changing the release medium to pH 6.8 phosphate buffer at 2 h, up to 8 % of budesonide was dissolved in the following 0.5 h. While in pH 7.4 phosphate buffer, upon dissolving of Eudragit FS30D film, approximately 52% of the drug was released within 30 min which indicated a pH controlled triggering was easily accomplished in the absence of enzymes. In presence of enzymes for Eudragit FS30D/guar gum combination (1:1) coated pellets, drug release was up to 5.21 % for the first 4 h in 0.1 mol/l HCl (pH 1.2) and phosphate buffer (pH

6.8). And the amount of drug release was only up to 6.60% after another 1 h. After changing the release medium to pH 6.5 phosphate buffer with pancreatin, budesonide kept releasing steadily even in the decrease in pH-occurs and amount of drug release was 51.28%. While no abrupt change in release profile was observed after addition of pancreatin enzyme which simulates the colonic enzymes and micro flora to medium under similar circumstance for only Eudragit FS30D coated pellets due to insolubility of Eudragit FS30D at pH<7. Figure 4 shows the percent budesonide released at 1, 3, 5, 5.5, 6.5 and 7.5 h in absence/presence of enzymes was 1.25/1.32%, 3.79/3.65%, 8.05/8.71%, 51.93/51.28% 68.23/67.55%, 97.86/97.94% respectively, which was indicative of obvious pH and enzyme-triggering mechanisms. The dramatic increase in release was indicative of the high sensitivity of coating of the combination of polymers to the pH as well as microbial enzyme. Hence the drug release was due to either of mechanism.

In-vitro dissolution testing at pH-5:

The effect of pH on drug release from combination coated formulations in different colonic pH mimicking patients with IBD (pH 5.0, acetate buffer) and healthy volunteers (pH 6.8, Tris-HCl buffer) is shown in Figure 5. The results suggested that pH has no effect on dissolution behaviour of the formulations; since Eudragit FS30D is pH dependent polymer hence does not show proper release but guar gum remain unaffected by pH, the formulation is able to release the drug specifically in colon irrespective of change in pH, this ability is very useful as the colon pH is found to be lowered in conditions such as IBD this might be due to guar gum coating.

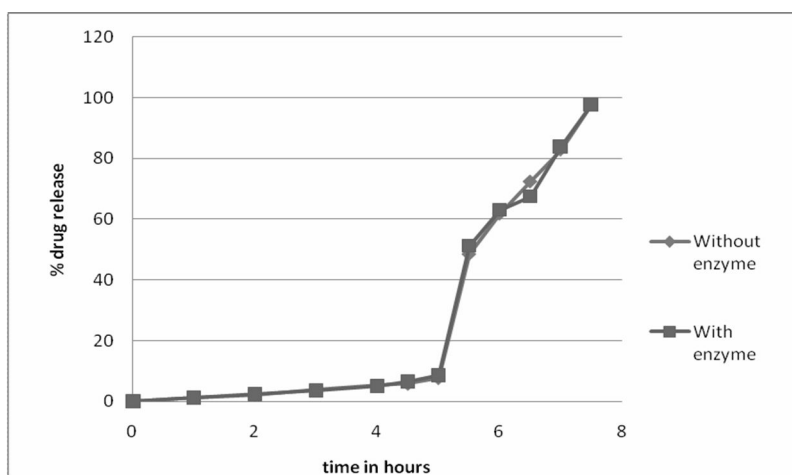


Figure 4: In-vitro drug release of Eudragit FS30D and Guar Gum combination coated budesonide pellets with and without enzyme.

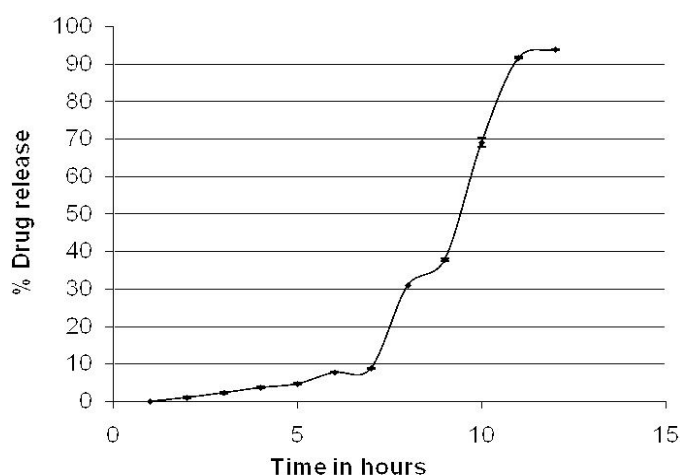


Figure 5: In-vitro drug release of Eudragit FS30D and Guar Gum combination coated budesonide pellets at pH- 5 (IBD conditions)

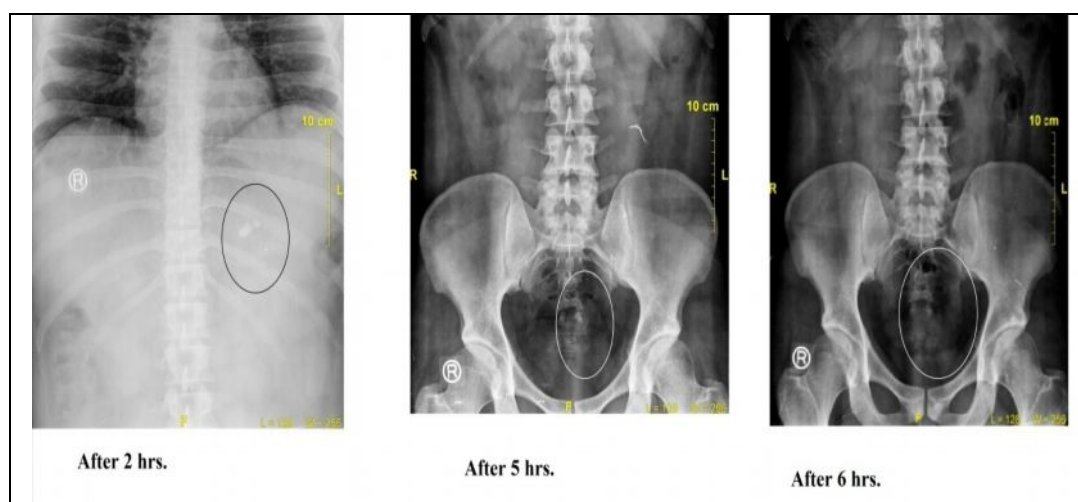


Figure 6: In-vivo study of combination of polymer coated pellets.

In-vivo X-ray results of Eudragit FS30D and Guar Gum combination coated budesonide pellets filled in HPMC capsules.

The X-ray image of Ileo-cecal region (Figure 6) of a subject after administration of barium sulphate suspension. For in-vivo study formulations coated with 40% w/w of Eudragit FS30D and Guar Gum combination (1:1) was used. From the abdominal radiographs, taken at different points of time, it was seen that after 2 h the pellets remained unchanged in the stomach in all subjects. The pellets reached the ileo-cecal region in 5 h in a subject. The pellet after 6 h in subjects was disappeared. This indicates the dissolution of pellets had occurred after reaching to the ileo-cecal region. These results show similarities with in vitro drug release study. Pellets with 40 w/w coating

level showed dissolution in the ileo-cecal region after a lag time of 4.45 to 5 h which correspond with the in vitro lag time of capsule. This is due to the sensitivity of polymer to higher alkaline pH 7.2 and resistant low pH condition. As Eudragit FS30D contains the carboxylic group which hydrolyzed at higher pH and causes breaking of polymer structure and dissolution of pellets to give the desired response.

Conclusion

The combination of polymer mixture coated with 40% weight gain formulation had shown the same drug release pattern in the presence and absence of enzyme and at pH 5 which is an ideal IBD condition with lag time observed of 5 hours. In-vivo study of combination of polymer mixture coated formulation also concluded

that formulation was found to be stable to acid environment of stomach and formulation was reached to ileo-cecal junction within 5th h and at 7th h of study the formulation was not observed anywhere in colon which was indicating the dissolution of polymer coat in colon to release the drug specifically in colon.

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