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POLYSACCHARIDE AS A POTENTIAL CARRIER FOR MULTIUNIT COLON SPECIFIC DRUG DELIVERY SYSTEM

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ABSTRACT: In the present study maltose a polysaccharide was investigated as a promising carrier for colon specific drug delivery system. It was evaluated for pH change study, by using *in-vitro* and *In-Vivo* testing in Wistar rats. *In-Vitro* study shows that there is drop in the pH from 7.00 to 5.5 when incubated with ceacal content in the controlled condition. The *In-Vivo* experiment was carried out by administering maltose solution orally to the rats, which were sacrificed after six, seven and eight hours. Ceacal content was collected and pH was measured by using digital pH meter. The pH of ceacal content was not changed after oral administration of maltose which may be due to its absorption in upper G. I. Tract. To investigate maltose and ceacal content interaction and alteration of colon pH, the maltose spheres were prepared by extrusion and spheronization techniques and coated with different polymers to evade upper G. I. T. The developed coated maltose spheres were administered and evaluated for its pH change in same manner as discussed above. The pH of ceacal content dropped as sphere reaches and interacts with the colonic bacteria. Maltose was used to develop colon specific drug delivery system. The core minitab of Prednisolone was developed by using maltose as a polysaccharide and various excipients. The developed core minitabs were further coated with various polymers. The coating of all these polymers was optimized for specificity and feasibility of the system and evaluated. The result of this study reveals that maltose can act as a trigger for drug release in the colon by utilizing the action of colonic bacteria.

INTRODUCTION: Ulcerative colitis is an inflammatory disease of the large intestine, also called the colon. In ulcerative colitis, the inner lining or mucosa - of the intestine becomes inflamed (the lining of the intestinal wall reddens and swells) and develops ulcers (open, painful wound).

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Ulcerative colitis can occur in people of any age, but it usually starts between the ages of 15 and 35 and less frequently between 50 and 70 years of age.

It affects men and women equally and appears to run in families, with reports of up to 20 percent of people with ulcerative colitis having a family member or relative with ulcerative colitis or Crohn's disease. Prednisolone is a corticosteroid drug with predominant glucocorticoid and low mineralocorticoid activity, making it useful for the treatment of a wide range of inflammatory and auto-immune conditions such as Crohn's disease, ulcerative colitis, rheumatoid arthritis and pericarditis.

The necessity and virtues of colon specific drug delivery system have been well recognized and documented. In addition to providing more effective therapy of colon related diseases such as ulcerative colitis, colorectal cancer, irritable bowel syndrome and inflammatory bowel disease (IBD). Colon specific delivery has the potential to address important unmet therapeutic needs including oral delivery of macromolecular drugs. The colon is also viewed as the preferred absorption site for oral administration of protein and peptide drugs, because of the relatively low proteolytic enzyme activities in the colon.

Recently, much emphasis has been laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children.

Multiparticulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract.

If these subunits have diameters of less than 2mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability. Drug safety may also be increased by using multiparticulate dosage forms, particularly for modified release systems. For example, if the film coat of a single-unit (monolithic) enteric coated tablet is damaged, the complete dose will be released into the stomach where it may cause pain or ulceration or reduced efficacy, depending on the reason for choosing the protection of the enteric coating.

Equally, if there is damage to the film coating of a monolithic tablet with a sustained release formulation, this can lead to "dose dumping" and result in dramatic side effects.

By contrast, in multiparticulate formulation, the release characteristics are incorporated into every single subunit and any damage only affects the release behavior of the subunit involved, which represents a small part of the total dose, reducing the likelihood of safety problems [2, 3].

Masataka Katsuma *et al.,* investigated lactulose formulation for colon specific drug delivery system. In this study, they noticed that lactulose can act as a carrier to deliver the drug to the colon. The core formulation consists of lactulose and further coated with acid soluble polymer and then with an enteric coating polymer.

As the system reaches to the colon lactulose in core interact with microflora present in colon and releases acid. The microenvironment of acid created by lactulose is responsible for solubilization of acid soluble coat and thus drug releases in colon [4].

In present investigation polysaccharide (maltose) was investigated as a potential carrier for the development of more site specific colonic drug delivery system. In this regard, maltose was evaluated for pH change study by two methods using Wistar rats.

Firstly, maltose was incubated with isolated ceacal content of rat and pH at different time interval was measured. The pH change study was also performed by administering the maltose solution through oral route and ceacal content of rats were collected after six hours and pH was measured.

The study was again performed for maltose spheres coated with various polymers and administered to the rats and ceacal content at different interval were collected and pH was measured. The core minitabs were developed by using Prednisolone, maltose and various additives, the developed core minitabs were further evaluated for different physical parameters and dissolution studies.

The optimized core minitabs were coated with different polymers viz. Acid soluble polymer, Barrier layer coating and Enteric coating polymer. The coating layer of different polymers was optimized by performing dissolution studies.

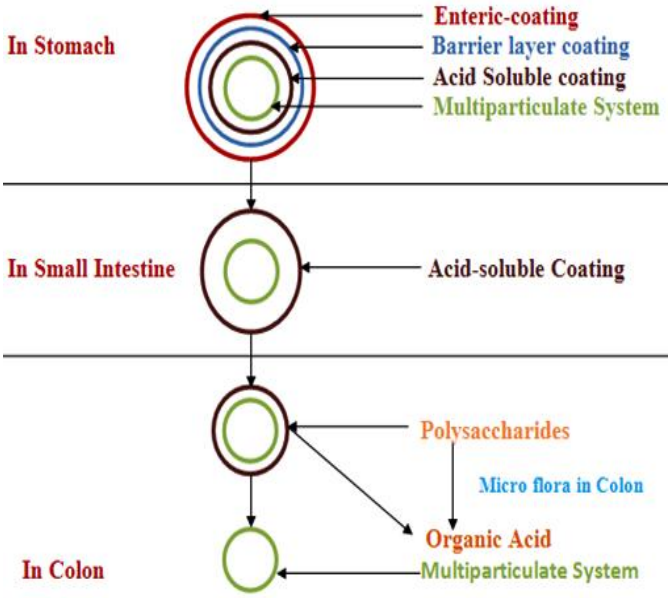

FIGURE 1: SCHEMATIC OF THE CONCEPTUAL DESIGN

MATERIAL AND METHOD:

Materials: Animals were obtained from serum institute, Pune (DYPIPSR/IAEC/10-11/P-29 and DYPIPSR/IAEC/10-11/P-18) Prednisolone was obtained as a gift sample from Naprod Life sciences Ltd., Mumbai, Eudragit E-100, and L-100 was obtained as a gift sample from Evonik Pharma, Mumbai, India and HPMC, was obtained as a gift sample from Colorcon Asia Pvt. Ltd, Goa. Maltose, Micro crystalline cellulose and Magnesium Stearate were purchased from Loba Chemical and S. D. fine, India.

Experimental / Methodology:

1. **pH change study of maltose after incubation with ceacal content (*In-vitro*) [4]:** The pH 7.0 phosphate buffer solution (PBS) was prepared according to Pharmacopoeial Method. The pH of the PBS was adjusted to pH 6.8 by bubbling CO_2 gas. Caecal contents were collected from male Wistar rats weighting 300-400 gm in order to prepare PBS supplemented with caecal contents (C-PBS). The caecal contents were dispersed in PBS and the concentration of the caecal contents were adjusted to 10%, 20% and 30% (w/v). Maltose 100 mg was added in to 10 ml of C-PBS and incubated at 37^0 C under anaerobic conditions. The pH of C-PBS was measured by using a pH meter. For the control experiment, C-PBS was incubated under the same condition.

2. **pH measurement of rat caecal contents after dosing with Maltose:** The male Wistar rats weighing 300-400 g were fasted for 12 hrs prior to and during experiments. Water was allowed *ad libitum*. An aqueous solution of maltose (100 mg/1 ml/rat) was administered orally using an oral feeding tube. Before and 5^{th}, 6^{th} and 7^{th} hour after administration of maltose, the rats were sacrificed. The caeca were isolated and their contents were dispersed in water. The pH was measured using digital pH meter.

3. **pH Change study of rat ceacal content after dosing with Maltose Spheres coated with various polymers:**

   a. **Preparation of maltose spheres:** Maltose spheres were developed by using extrusion and spheronization technology.

   b. **Coating of maltose Spheres:** Developed spheres were coated with different polymers viz. Acid soluble layer, Barrier layer and enteric coating layer.

   c. **pH measurement of rat caecal contents after dosing with Maltose Spheres coated with various polymers:** The male Wistar rats weighing 300-400 g were fasted for 12 hrs prior to and during experiments. Water was allowed *ad libitum*. An aqueous suspension of maltose spheres (100 mg/2 ml/rat) was administered orally using an oral feeding tube. Before and 6^{th}, 7^{th} and 8^{th} hour after administration of maltose, the rats were sacrificed. The caeca were isolated and their contents were dispersed in water and the pH was measured using a digital pH meter.

4. **Excipients compatibility study:** Prednisolone and the mixtures of drug and various excipients used in the preparation of colon specific formulations were characterized by FT-IR spectroscopy to know the compatibility.

5. **Preparation of blends and Core Minitab: Table 1** shows the composition of core Minitab. The excipients were mixed thoroughly and compressed by rotary compression machine (Minipress II, Karnavati, India) by using 4 mm standard concave round die punch set.

TABLE 1: FORMULATION OF CORE MINITAB

Ingredients	M-1 Weight (mg/Minitab)
Prednisolone	01
Maltose	25
Microcrystalline Cellulose	13.125
Cross Carmellose Sodium	0.75
Magnesium Stearate	0.125
Total	**40**

6. **Coating of Core Minitabs:** Core minitabs were coated using pan coating technique with three successive layers. First layer next to the core was Eudragit E-100, the second layer was HPMC barrier and the outer layer was Eudragit L-100. (Composition of different coating solutions is given in **Table 2**). The process parameters for coating were optimized and coating of different layer was done. Process parameters used during coating are given in **Table 3**.

TABLE 2: COMPOSITION OF COATING SOLUTIONS

Sr. No.	Ingredients	Quantity
	1. Acid soluble coating:-	
1	Eudragit E-100	35 g
2	Methylene chloride	490 mL
3	Castor oil (plasticizer)	10 mL
	2. Barrier layer coating:-	
1	HPMC	10 g
2	Isopropyl alcohol	300 mL
3	Methylene chloride	200 mL
	3. Enteric coating:-	
1	Eudragit L-100	45 g
2	Methylene chloride	490 mL
3	Castor oil (plasticizer)	10 mL

TABLE 3: PROCESS PARAMETERS FOR THE COATING EXPERIMENTS

Sr. No.	Process Parameter	Parameter Used
1.	Coating nozzle diameter (mm)	1
2.	Spraying rate	4 ml/min
3.	Pan Speed (RPM)	15-20
4.	Inlet air temperature (°C)	60-70
5.	Baffles	04
6.	Air Pressure (Kg/cm^2)	2-2.5

Evaluation of minitabs [4, 6, 7]:

The Core minitabs and coated minitabs were evaluated for different parameters like weight variation, hardness, friability, drug content and in vitro dissolution study.

1. **Weight variation:** Twenty minitabs were selected randomly from the lot and weighted individually to check for weight variation and then the average weight was determined and compared with average weight the positive and negative deviation. The minitabs meets USP specifications if no more than 2 minitabs are outside the percentage limit and if no minitabs differs by more than 2 than the percentage limit.

2. **Hardness and friability:** The hardness of the prepared minitabs was determined using a digital hardness tester. Ten tablets were tested for hardness from each batch and the mean and SD was calculated. Pre-weighed 20 tablets were placed in a plastic chambered friabilator (Roche) attached to a motor revolving at a speed of 25 rpm for 4 min. The minitabs were then de-dusted, reweighed and percentage mass loss (friability) was calculated.

3. **Drug content:** Twenty minitabs were weighed and powdered. An amount of the powder equivalent to 50mg of Prednisolone was dissolved in 100 mL of pH 7.4 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 248nm using UV Visible spectrophotometer.

Optimization of coating layers of different polymers: Influence of Eudragit E layer (acid soluble coat) composition on drug (Prednisolone) release was evaluated in phosphate buffer (PBS) (pH 6.8) for four hours. Acid- resistance of Eudragit L100 coat was tested using 0.1N HCL pH 1.2 for 2 hrs.

***In-vitro* drug release studies [4, 8, 16]:** The dissolution study of the core minitabs formulation was conducted in a USP basket apparatus in pH 7.4 at 50 rpm at 37 ± 0.5 °C. Five minitabs equivalent to 5mg of Prednisolone were packed in capsules (size 00) and placed in basket in 900ml of dissolution medium pH 7.4 phosphate buffer solution. Sample were withdrawn and measured by using UV visible spectrophotometer the drug release from core minitabs were measured and noted. For the optimized formulation, measurement of Prednisolone release was carried out as a function of time at various pH, which were selected to simulate pH conditions at different locations of GIT. The dissolution of optimized formulation was carried out at pH 1.2 dissolution medium for 2 hours followed by pH 6.8 for 4 hrs and further studies simulating the drug release in colon were carried out in USP dissolution test apparatus I at 100 rpm and 37 °C with slight modification. A beaker of capacity 500 ml containing 200 ml of pH 6.8 phosphate buffer saline consisting 4% ceacal content as dissolution medium was kept in water bath of dissolution test apparatus. The experiment was carried out with the continuous CO2 supply into beakers.

The samples were withdrawn at various time intervals and replaced with an equivalent amount of fresh dissolution medium. Dissolution samples were filtered through a 0.45-mm filter and analyzed using a validated UV spectroscopy method. Absorbances of all samples were measured at 248 nm using UV visible spectrophotometer.

RESULTS: The polysaccharide (maltose) was evaluated for pH change study to act as a potential carrier to deliver drug to the colon.

Firstly maltose was evaluated for *in-vitro* pH change study by incubating 100mg of maltose with 10%, 20%, and 30% ceacal content in phosphate buffer solution pH 6.8. The 20% ceacal content with maltose shows drop off the pH from 6.8 to pH 5.5 (**Fig. 2**).

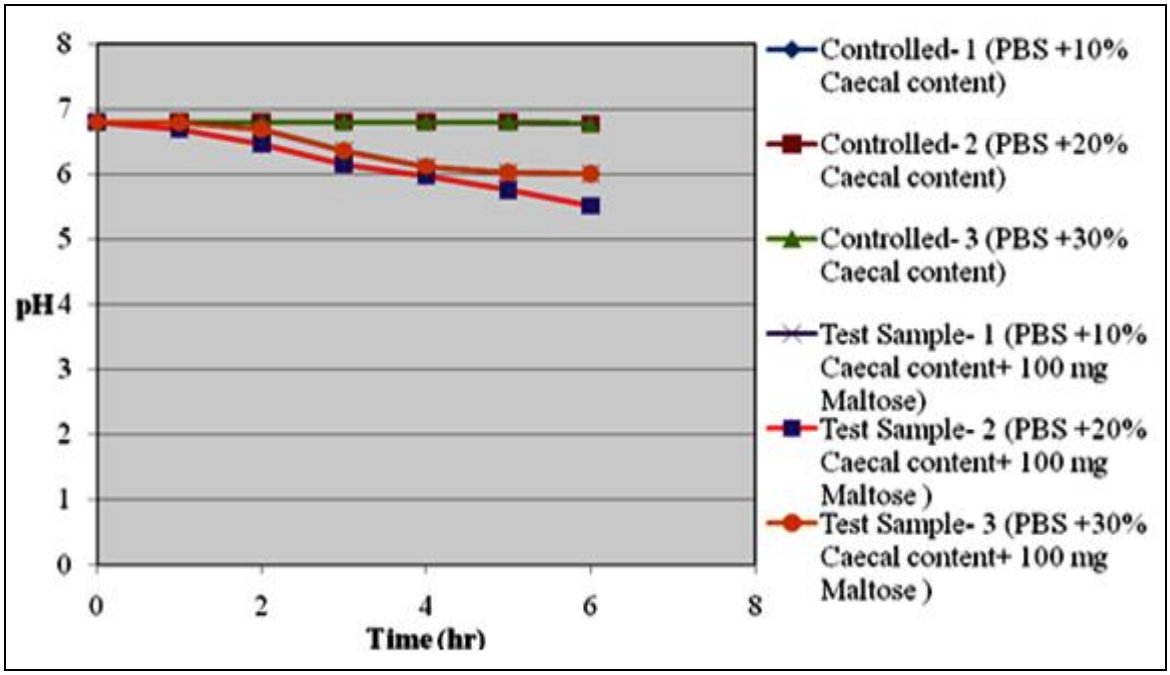

FIG. 2: *IN-VITRO* PH CHANGE STUDY OF POLYSACCHARIDES IN PRESENCE OF CEACAL CONTENT (PH VS TIME HR)

The polysaccharide (maltose) was further studied for pH measurement of rat ceacal contents after dosing maltose solution by oral route to the rats. The maltose solution were administered orally to rats and pH of ceacal content was measured by scarifying the rats the pH of ceacal content in this study was not changed may be due to absorption of maltose in the upper GI tract.

To bypass absorption of maltose in upper G. I. Tract the maltose spheres were developed by extrusion and spheronisation technique and further coated with different polymers. The developed and coated maltose spheres were administered to rats orally. The pH of rat ceacal content were measured the pH was dropped off from pH 7.00 to 5.5 at the end of eighth hr (**Fig. 3**).

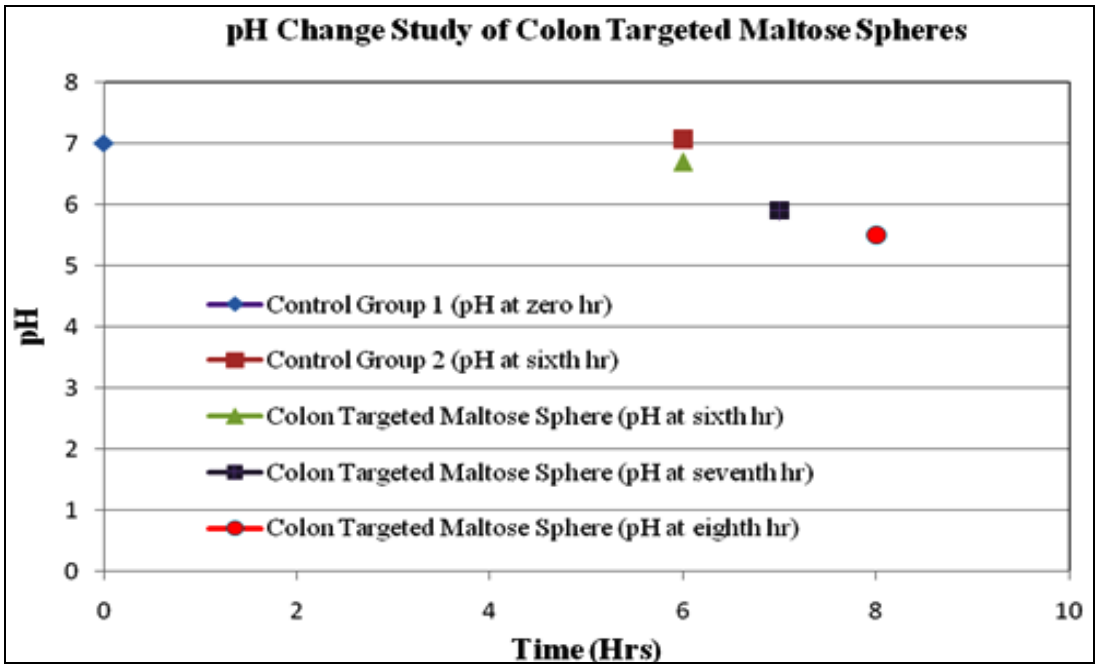

FIG. 3: PH CHANGE STUDY OF COLON TARGETED MALTOSE SPHERE

To developed colon specific drug delivery system of Prednisolone by using polysaccharide as minitab firstly the FT-IR study for compatibility study of drug and excipients were carried out. The FT-IR of pure Prednisolone and in combination of maltose was done and did not show any possibility of interaction between Prednisolone and maltose used to develop the formulation (**Fig. 4, 5 and 6**).

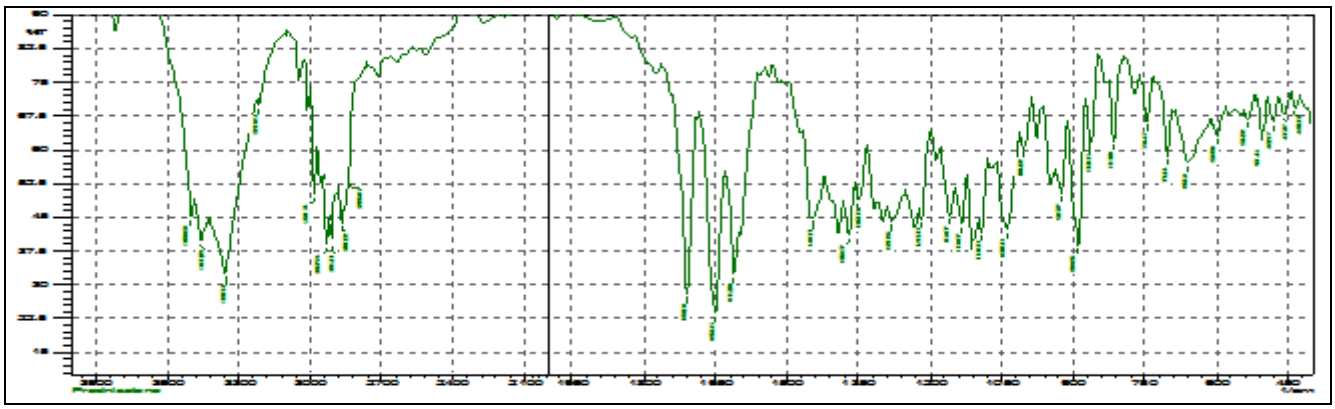

FIG. 4: FT-IR SPECTRA OF PREDNISOLONE

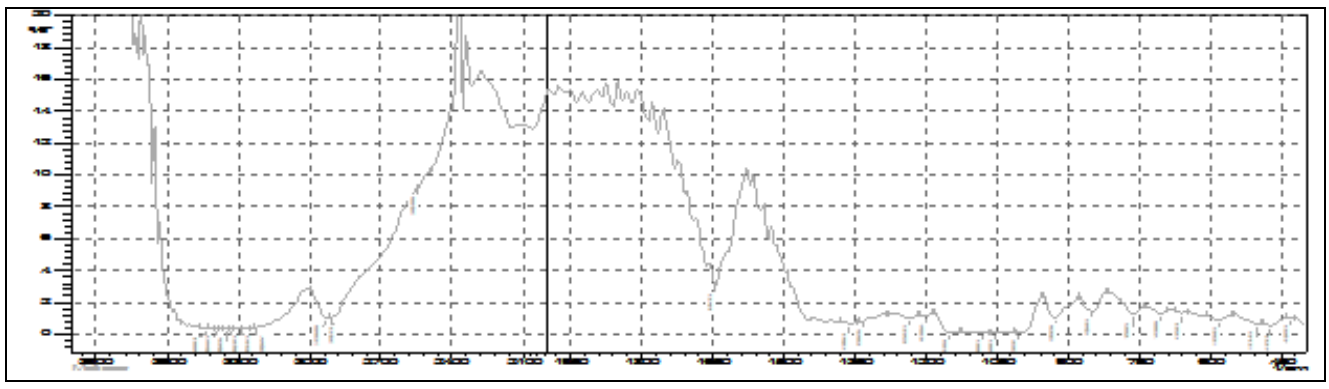

FIG. 5: FT-IR SPECTRA OF MALTOSE

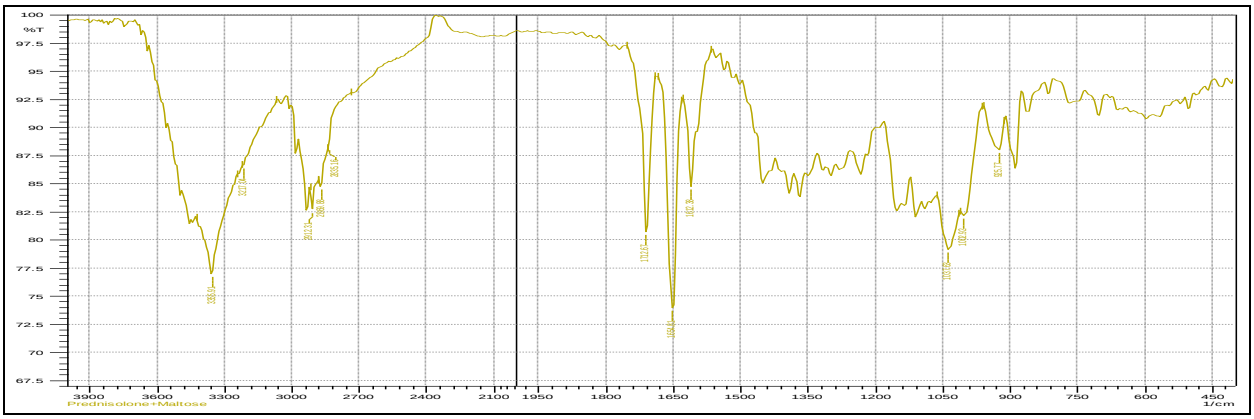

FIG. 6: FT-IR SPECTRA OF MIXTURE OF PREDNISOLONE AND MALTOSE

The core minitabs of Prednisolone consisting maltose as a polysaccharide and various additives were prepared by direct compression method and evaluated (**Table 1 and 7**).

The *in-vitro* dissolution of batch P-1 was showed 96.36 % drug release in 30 minutes (**Table 4 and Fig. 7**).

TABLE 4: DISSOLUTION PROFILE OF BATCH P-1 (CORE MINITAB)

Sr. No.	Time in (min)	Cumulative % release
1	00	00
2	10	35.9 (± 0.52)
3	20	67.1 (± 0.48)
4	30	96.4 (± 0.44)

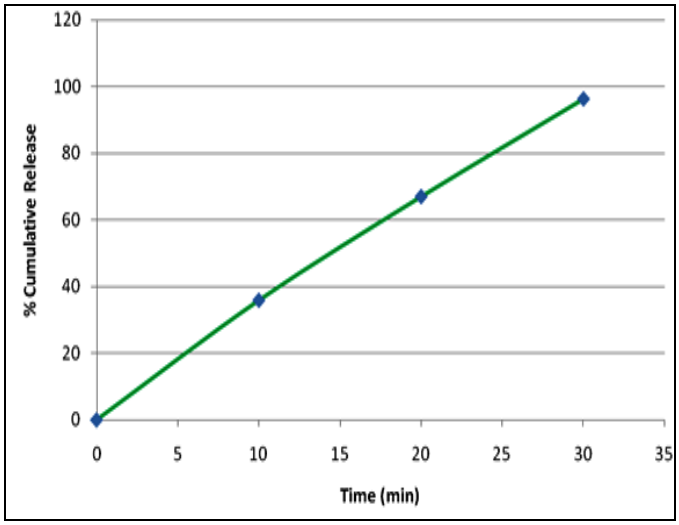

FIG. 7: RELEASE OF PREDNISOLONE FROM CORE MINITABS IN PHOSPHATE BUFFER SOLUTION PH 7.4

The core minitabs (P-1) were further studied for optimization of the coating level of various polymers like Acid soluble polymer Eudragit E-100, HPMC barrier layer and Enteric coating layer (Eudragit L-100) (**Table 5**).

The average weight of core minitab was 40 ± 0.5 mg. After coating with a first coating layer of acid soluble polymer Eudragit E-100 at coating levels of 4%, 6%, 8% , 10% and 12%. The 12% coating layer of Eudragit E-100 showed negligible release at the end of 4th hour in pH 6.8 buffer solution and the weight of minitab after coating were 44.8 ± 0.5mg (**Fig. 8**).

Afterwards minitabs were coated with 2% of the HPMC barrier layer coating to reduce possible interaction between Eudragit E-100 and final coat of Eudragit L-100. Eudragit L-100 as an enteric coat was used in various concentrations to optimize the coating level and evaluated during optimization. The *in-vitro* dissolution study showed that 10% coating layer of Eudragit L-100 provide better protection and no release up to 2 hours in pH 1.2 buffer solutions (**Fig. 9**). The weight of the minitab after coating with enteric coating polymer Eudragit L-100 (10% coating layer) was 49.6 ± 0.5 mg. The optimize formulation (Batch M-12) was evaluated for various physicochemical properties (Table 7) and *In-vitro* dissolution study were performed without ceacal content and with ceacal content in dissolution media at changing pH (**Fig. 10 and 11**).

TABLE 6: OPTIMIZATION OF VARIOUS COATING LAYERS

Coating Formulation	Formulations										
	P-2	P-3	P-4	P-5	P-6	P-7	P-8	P-9	P-10	P-11	P-12
Eudragit E-100 (%)	4	6	8	10	12	--	--	--	--	--	--
HPMC Barrier Layer (%)	--	--	--	--	--	2	2	2	2	2	2
Eudragit L-100 (%)	--	--	--	--	--	--	2	4	6	8	10

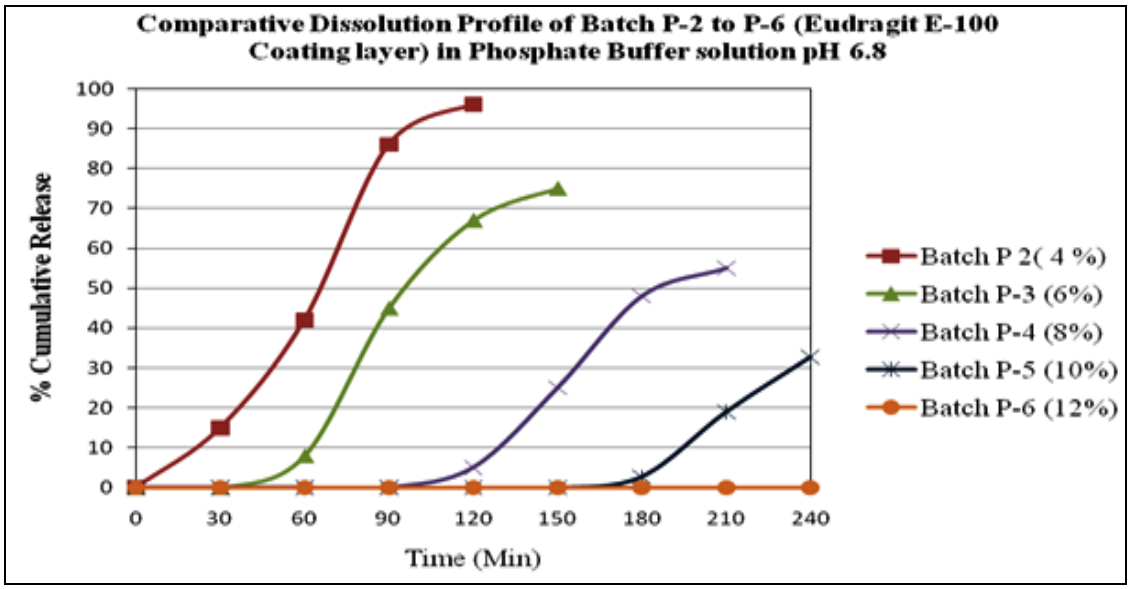

FIG. 8: COMPARATIVE DISSOLUTION PROFILE OF EUDRAGIT E-100 COATING LAYER

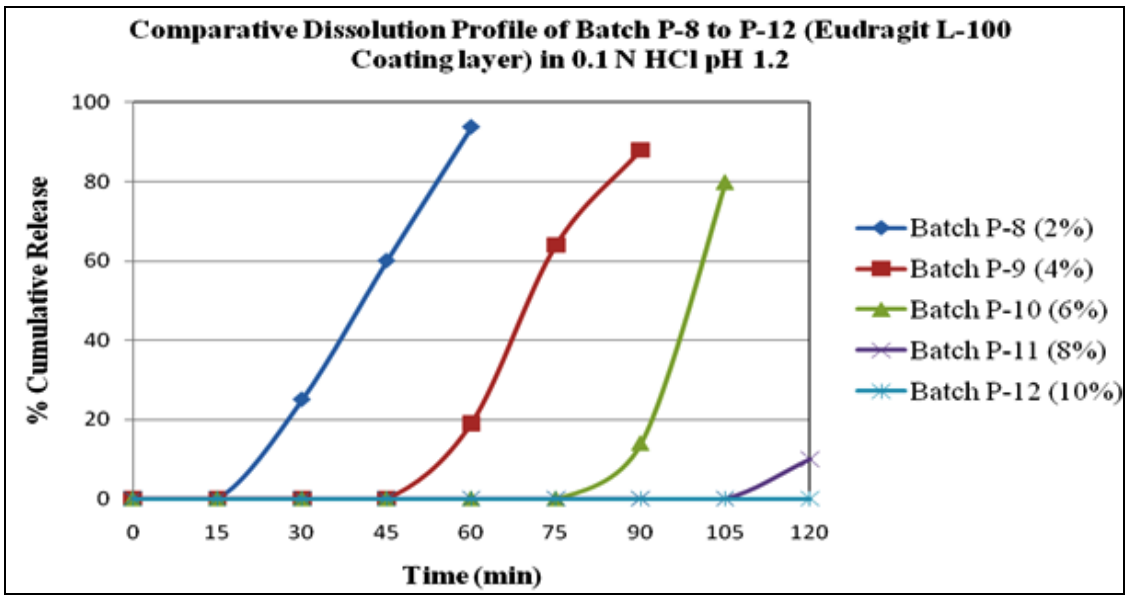

FIG. 9: COMPARATIVE DISSOLUTION PROFILE OF EUDRAGIT L-100 COATING LAYER

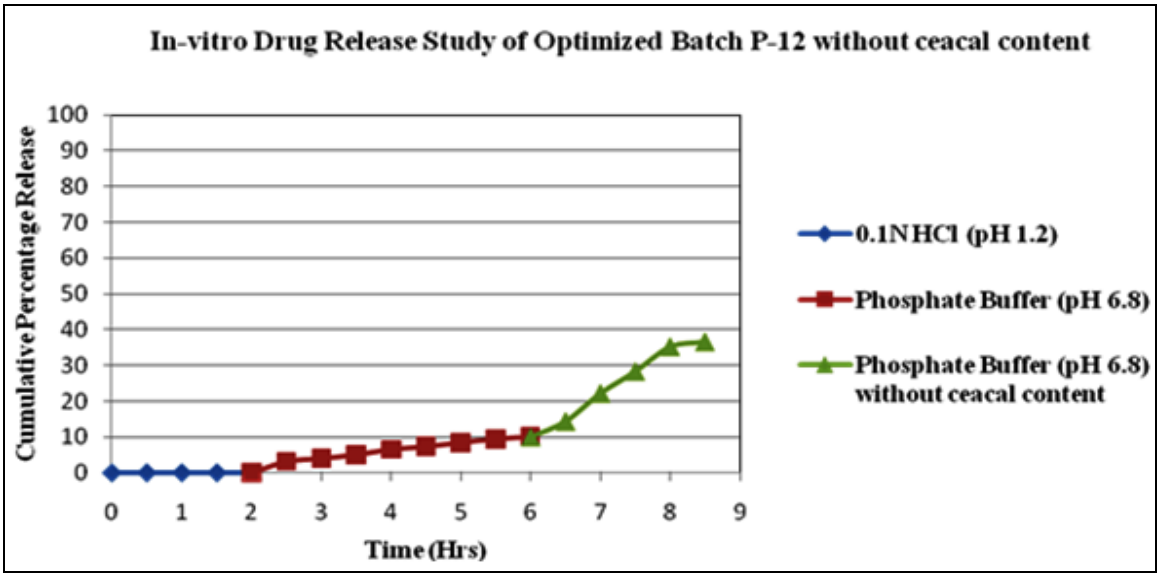

FIG. 10: IN-VITRO DRUG RELEASE STUDY OF OPTIMIZED BATCH WITHOUT CEACAL CONTENT

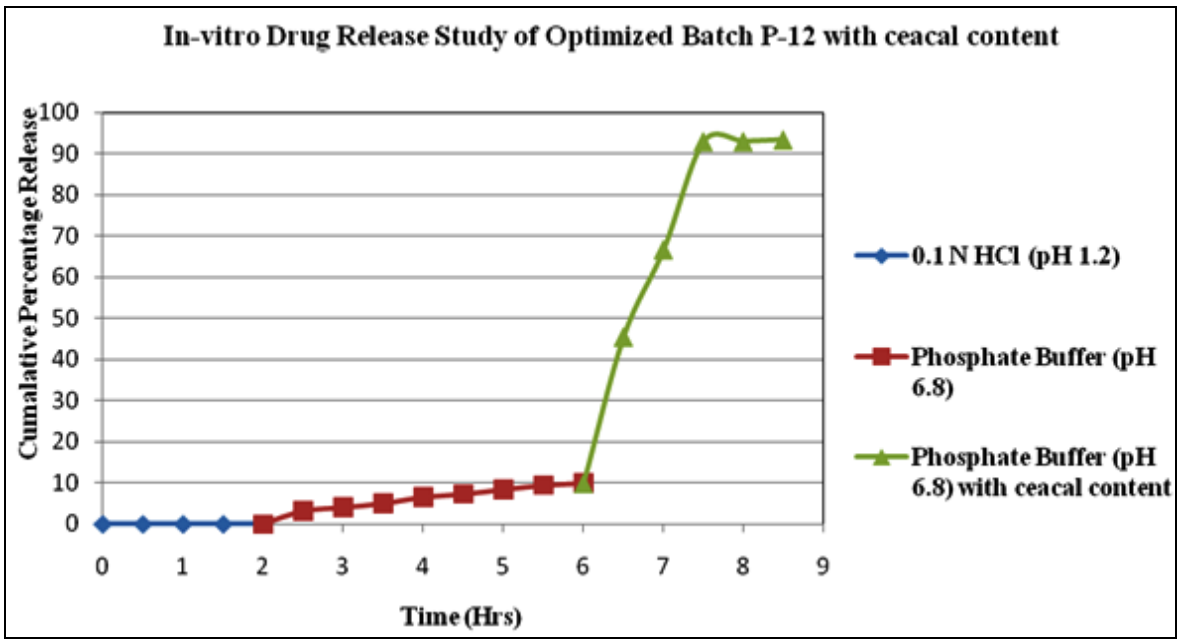

FIG.11. IN-VITRO DRUG RELEASE STUDY OF OPTIMIZED BATCH WITH CEACAL CONTENT

TABLE 7: PHYSICOCHEMICAL PARAMETERS OF MINITABS

Formulation Code	Thickness (mm)	Diameter (mm)	Weight Variation	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec.)	Drug Content (%)
M-1 (Core Minitab)	2.51	4.04	39.8	3.02	0.87	40	99.85
M-12 (Optimized)	2.69	4.09	49.6	--	--	--	99.79

The drug release of developed colon specific drug delivery system without ceacal content shows only 36.59 % (CPR) drug release at the end of 8.5 hours (Fig. 10). The drug release of same optimized formulation with ceacal content shows 93.45 % (CPR) at the end of 8.5 hours (Fig. 11).

DISCUSSION: To develop the site specific drug delivery for colon, firstly maltose was investigated as a potential carrier to deliver drug more specifically to colon to treat various colonic diseases. The maltose was evaluated for pH change study by incubating with ceacal content as well as oral administration of maltose solution to Wistar rats. The maltose incubated with ceacal content showed dropped off pH while maltose solution after oral administration fails to show the same. This may due to absorption of maltose in upper GI tract.

Furthermore, maltose sphere was prepared by extrusion and spheronisation technique and coated with various polymers *viz*. acid soluble layer, barrier layer and enteric coating layer and optimized as per gastric residence time.

The coated maltose spheres were administered to rats via oral route and pH of ceacal content were measured after six hrs. The administered coated maltose spheres were dropped off the pH of colonic content of rats.

The FT-IR spectra for compatibility study of drug and excipients did not show any possibility of interaction between Prednisolone and various excipients used for the development of the formulation. The Prednisolone core minitabs consisting maltose as a multiparticulate drug delivery system for colon targeting was formulated by using direct compression method.

The developed core minitabs were evaluated for their *in-vitro* drug release studies and various physical properties like thickness, diameter, weight variation, hardness, friability, disintegration time and drug content. All these parameters for batch P-1were found in the range, therefore it was thought worthwhile, to evaluate batch P-1 formulation for further studies. The optimized core minitab formulation was further coated with an acid soluble coating layer.

The dissolution study was performed after 4%, 6%, 8%, 10% and 12% coating layer of Eudragit E-100 in pH 6.8 phosphate buffer solution to optimize the coating level. The 12% coating level of Eudragit E-100 showed minimum drug release at the end of 4th hr in pH 6.8 buffer solution. The formulation with an optimized coating layer of Eudragit E-100 were auxiliary coated with an HPMC barrier (2%) to overcome the possible interaction between Eudragit E-100 and Eudragit L-100, which may arises due to difference in their charges.

Then, this formulation was finally coated with different concentration of Eudragit-L100 (2%, 4%, 6%, 8% and 10%) as an enteric coating layer and evaluated in pH 1.2 buffer solution for optimization of Eudragit L-100 coating layer. The 10% coating layer of Eudragit L-100 showed no release up to 2 hrs in pH 1.2 buffer solution. The optimized formulation after coating with various layers (M-12) were evaluated for its lag phase and drug release studies in different pH solution like pH 1.2 for 2 hrs, pH 6.8 for 4 hrs and pH 6.8 without rat ceacal content and with rat ceacal content for 2.5 hrs. The designed formulation showed better protection in terms of release in pH 1.2 buffer solution up to 2 hours due to optimized coating layer of Eudragit L-100.

As formulation switched to pH 6.8 buffer solution minimum drug release was obtained at the end of the 6th hr showing that Eudragit E-100 layer was optimized. The dissolution study was further continued in pH 6.8 buffer solution without ceacal content up to 2.5 hrs. The drug release at the end of 8.5 hrs without ceacal content was very less i.e. 36.59 % (CPR). Simultaneously the dissolution study was performed by including ceacal content after completion of sixth hrs in pH 6.8 buffer solution. At the end of 6th hr the Eudragit E- 100 coat was slightly soluble and permeable as the system reaches to the colon the maltose leaches from acid soluble coat.

The interaction between maltose and colonic content the acid was released and it's responsible to form microenvironment to dissolved acid soluble coat. The formulation triggered the release due to solubilisation of acid soluble coat. The developed formulation completed its release up to 93% at the end of 8.5 hrs.

The developed system was exceedingly capable for impending targeting of Prednisolone to the colon and with no release in the stomach and small intestine and showed fast release in colon after a controllable lag phase in upper GIT.

CONCLUSION: In the present study, maltose was investigated as a potential carrier to deliver drug to the colon more specifically. Eudragit E-100 is an acid soluble polymer which was protects the system up to four hrs in the small intestinal environment. The Solubilization of the acid soluble coat in the colon was triggered by maltose when it interacts with colonic bacteria. The developed system may prove its feasibility and site specific action to deliver drug to colon to treat various diseases of the colon.

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