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DESIGN AND DEVELOPMENT OF MEBEVERINE COMPRESSION COATED TABLETS FOR COLONIC DELIVERY

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ABSTRACT

The main objective of this study was to develop mebeverine hydrochloride colon targeted drug delivery system using compression coating technique for effective treatment of irritable bowel syndrome. This work was mainly focused on the formulation & in-vitro evaluation of compression coated tablets of mebeverine hydrochloride with different pH dependent polymers like Eudragit L100-55, hydroxypropyl methyl cellulose phthalate (HPMC P55) & cellulose acetate phthalate. The fast disintegrating mebeverine core tablets were compression coated with different percentages of polymers in the outer coat. The prepared compression coated tablets were evaluated for invitro drug release studies using a change in pH method. A drug release was observed in the initial phases of dissolution in higher pH media like 7.4 upon erosion of pH dependent polymers. In order to avoid the drug release in the upper part of small intestine the formulations were further optimized with the help of different hydrophobic materials so that the lag time was prolonged and the drug release was started at lower part of intestine which can deliver maximum amount of drug to colon. Hydrophobic material ethyl cellulose was added to Eudragit L100-55, HPMC P55 and Magnesium stearate was added to cellulose acetate phthalate in the outer coat material. The addition of hydrophobic materials significantly increases the lag time and rapid drug release was observed after lag time.

Key words: mebeverine, compression coat, irritable bowel syndrome, pH dependent coat.

INTRODUCTION

Conventional oral dosage forms are ineffective in the treatment of colonic diseases like crohn's disease, ulcerative colitis, irritable bowel syndrome etc because most of the administered drugs were absorbed in the upper part of gastrointestinal tract (GIT) before reaching colon. Colon specific drug delivery systems have attracted researcher's interest in the last decade. Even though colon drug delivery can be achieved by both oral and rectal route, oral route is most preferred because rectal delivery to proximal colon cannot be achieved [1].

Colon specific drug delivery systems avoid the drug release in the upper part of GIT and deliver the drugs to lower part of intestine, thereby protecting the drug molecule from the harsh environment of stomach and reducing the systemic side effects of drugs. Colon drug delivery is widely useful in delivery of drugs to treat local diseases of colon [2]. Colon has less hostile environment for drug delivery because it has low intensity of enzymatic activity and nearly neutral pH. These conditions are very suitable for absorption of proteins, peptides and vaccines which can be delivered by colon drug delivery systems [3]. Colon drug delivery systems also useful in the treatment of rheumatoid arthritis, nocturnal asthma where a delay in absorption is needed which can be achieved by colon specific systems [4-6].

Various approaches employed for successful oral delivery of drugs to colon are pH dependent, time dependent and systems that use bacteria that colonize in colon [7]. pH, time response systems are easier to prepare but limitations of these systems are variable physiological and pathological conditions of GIT. The combination of pH and time controlled systems are prepared by enteric coating with high threshold pH materials, enteric coating on press coated tablets (ETP) and blends of extended release and enteric polymers [8]. Compression coating technique is an alternative technique to spray coating technique for the application of high molecular weight polymers. A thick coat can be applied on the core tablet and it is solvent free [9]. Various materials can be applied on the core tablet by compression coating technique like

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HPMC, hydroxypropyl cellulose, Eudragit [10-12] etc. Drug release modified systems can be prepared by this technique.

Irritable bowel syndrome is one of the most commonly encountered gastrointestinal disorder commonly causing constipation, crams, abdominal pain, bloating and diarrhoea. This condition is known to cause discomfort and distress among individuals where intestines are affected. Mebeverine hydrochloride is a smooth muscle relaxant and widely used in the treatment of irritable bowel syndrome. Mebeverine is a musculotrophic that acts directly at the smooth muscles of GIT, relieving spasm without affecting normal gut motility.

The main aim of present investigation was to develop colon targeted mebeverine compression coated tablets. These compression coated tablets contains inner core tablet surrounded by high thickness of polymeric material. The presence of high thickness pH dependent polymer coat around core tablet provides gastric resistance and retard the drug release in small intestine due to slower erosion of high thickness polymer coat.

MATERIALS AND METHODS

Materials

Mebeverine hydrochloride was obtained as a gift sample from Synthokem labs, Hyderabad. Ethylcellulose FP was received as a gift sample from Colorcon Asia Pvt Ltd. Eudragit L100-55 was received as a gift sample from Corel Pharma Pvt Ltd. Other excipients used in tablet formulation and coating process were of standard pharmaceutical grade and all chemical reagents, solvents were of analytical grade.

Methods

Preparation of Mebeverine core tablets

The core tablets for compression coating with different pH dependent polymers were prepared by direct compression as shown in table 1. Each core tablet of 200 mg consisted of 135 mg mebeverine, microcrystalline cellulose as diluents and a mixture of talc and magnesium stearate. Sodium starch glycolate was incorporated at 5% concentration level to obtain fast disintegration characteristics. Mebeverine and other excipients were thoroughly mixed and passed through sieve 16. The mixture was compressed into tablets using 8-mm round flat punches on rotary tablet press (Cemach). These tablets were tested for weight variation, hardness, content uniformity, friability.

Preparation of compression coated tablets

The core tablets were compression coated with 200 mg of different coat mixture as shown in table 2. About 50% of coat material was placed in the die cavity (diameter 10 mm). The core tablet was carefully placed in the centre of die cavity, which was filled with remaining coat material. Then it was compressed around the core tablet using 10-mm concave punch. The prepared compression coated tablets were tested for weight variation, hardness, friability etc.

Determination of drug content in the tablet formulation

Twenty tablets of each prepared formula were weighed and transformed into powder form. Accurately weigh a quantity of the powdered tablet which is equivalent to 0.135 g of mebeverine HCl Was mixed with 100 mL of 0.1 M HCl and heated for 10 Min in a water bath 40°C and cooled and add a sufficient amount of 0.1 M HCl to produce 250 mL solution which was then filtered. To the 10 ml filtrate add a sufficient amount of 0.1N HCl to produce 100 ml. 10 ml of the resulting solution was diluted to 100 ml with 0.1 N HCl. The absorbance of this solution was measured at a maximum wave length (λ max) of 263 nm. The content of mebeverine HCl was calculated by taking the maximum value at 263 as the value of A (1%, 1 cm).

Acid uptake studies

All enteric coating formulations at each coating level were evaluated for acid resistance and uptake. Six coated tablets of each formulation were weighed and subjected to dissolution conditions in 0.1 M HCl. After 2 h, the tablets were removed and excess medium was drained and blotted with filter paper from around the tablets. The tablets were weighed again, and the acid uptake by the tablet was calculated according to Eq. (1). Formulations were chosen for dissolution testing at the minimum coating level that met the criteria for acid protection, i.e., no more than 10% acid uptake and no visible signs of coat disruption after two hours acid treatment.

$$\text{Acid uptake} = \frac{wf - wi}{wi} \times 100$$

Where Wf is the final weight of tablet, Wi is the initial weight of tablet.

In vitro drug release studies

In-vitro dissolution studies were preformed for mebeverine compression coated tablets by using a change in pH method. Dissolution studies were carried out using USP dissolution apparatus II (paddle method, Electrolab) at 50 rpm, $37^0 \pm 0.5^0$ c using 900 ml dissolution medium. The prepared tablets were tested for drug release initially using 900 ml of 0.1 N HCl (pH 1.2) for 2h (average gastric emptying time).Then replaced with pH 7.4 buffer and dissolution was carried out for 3h. Later replaced with pH 6.8 dissolution medium and continued till the end. Aliquot samples were collected at predetermined intervals, filtered through Whatman filter paper and analysed using double beam UV-visible spectrophotometer (Schimadzu) at 263 nm. The cumulative percentage release for mebeverine was calculating using beer's-lamberts curve generated in respective medium. The drug release studies were performed in triplicate, the mean cumulative percentage of drug calculated (±SD) was plotted against time.

Stability studies

The optimized formulations of mebeverine compression coated tablets were stored at accelerated stability conditions 40^0 C±2^0 C/ 75%±5% RH for 6

months. After a specified period of time tablets were observed for change in physical appearance, colour, and drug content. Then dissolution was performed for these tablets, subjected to stability testing and were compared by calculating the similarity factor (f2) [14-15].

RESULTS AND DISCUSSION

Core tablets of mebeverine

The core tablets used in the preparation of mebeverine compression coated tablets were prepared by direct compression coating technique and the post compression and pre compression parameters are explained in the tables 3 and 4. The incorporation of sodium starch glycolate in the core tablet aids in fast disintegration. The core tablets were disintegrated in less than 3 min. The weight of core tablet was fixed to 200 mg and the test for weight variation passed. The drug content of mebeverine core tablets was found to be 132.54±1.822 (98.18 ±0.23%). The mean hardness of the core tablet was found to be 3.5 kg/cm^{2}and friability test was performed and weight loss was found to be 0.29%.

Compression coated mebeverine tablets

Different pH dependent polymers were compression coated on mebeverine core tablets. The mean hardness of these tablets was in the range of 5.0-5.5 kg/cm^2

In vitro drug release

Eudragit L100-55

Mebeverine compression coated tablets with Eudragit L100-55 shows no drug release in 0.1N HCl as shown in figure 1. After replacing with phosphate buffer pH 7.4, F2 with 100% Eudragit L100-55 in the compression coat releases 30.58±3.04% of drug in pH 7.4 buffer by the end of 5h. Formulation F1 having 90% polymer in the outer coat shows a drug release of 44.24±2.62 % in 7.4 pH buffer. On the other hand F3 containing 95% of polymer and 5% of ethyl cellulose, shows a decrease in drug release when compared to F1 & F2. F4 containing 10% of ethyl cellulose and 90% of polymer shows further decrease in drug release compared to F2 and F3. The drug release in the pH 7.4 buffer was 21.15±2.73%, 13.12±2.2% for F3, F4 respectively. The lag time for F2, F3, F4 formulations were found to be nearly 4, 4.5 and 4.5-5 h respectively.

Eudragit L100-55 was soluble at a pH greater than 5.5. There was no drug release was observed in pH 1.2 medium because of pH dependent solubility of Eudragit. Eudragit L100-55 experienced pH controlled erosion in pH 7.4 buffer. After complete erosion of outer coat, a rapid release of drug was observed from the core tablet.

Ethyl cellulose was hydrophobic in nature and the addition of ethyl cellulose in the outer coat further decreases the drug release from F3, F4 when compared to F2. The decrease in the drug release was due to presence of ethyl cellulose in the outer coat which decreases the acid uptake and penetration of dissolution medium into the coat. An increase in the concentration of ethyl cellulose in the outer coat decreases the drug release and increase the lag time of drug release and decrease the acid uptake values. A 5% addition of ethyl cellulose in F3 prolong the lag time to nearly 4.5h and release nearly 80% of drug in pH 6.8 buffer and 10% of ethyl cellulose in F3 shows lag time of nearly 4.5-5h and more than 85% of drug released in 6.8pH buffer.

HPMC P55

Mebeverine compression coated tablets were prepared using HPMC P55 alone in outer shell with various concentrations as explained in figure 2. HPMC P55 is an enteric coating material which cannot be dissolved in pH 1.2 buffer. F5 containing 90% polymer in the outer coat shows a drug release of 41.12±2.61% in pH 7.4 buffer with a lag time of 1.5h in pH 7.4 buffer. A rapid drug release was observed with in 2.5 h after a lag time. F6 and F7 formulations containing 100% and 95% polymer (5% EC) in the outer coat respectively releases 34.72±2.13%, 30.18±1.18% drug by the end of 5h. A decrease in the amount of polymer in the outer coat, a rapid drug release was observed in pH 7.4 buffer with a decrease in lag time.

F7 containing ethyl cellulose in a concentration of 5% shows a decrease in drug release in pH 7.4 buffer when compared to F6. A further increase in concentration of ethyl cellulose to 10% in F8 results in increase in lag time and decrease in the cumulative amount of drug release in pH 7.4 buffer. Nearly 70% and 75% of drug release was found in pH 6.8 buffer for F7 and F8 respectively. The hydrophobic material in the outer coat prevents the entry of dissolution medium into the coat which suppresses the drug release in pH 7.4 buffer.

Cellulose Acetate Phthalate (CAP)

Cellulose acetate phthalate is dissolved at pH greater than 6. Cellulose acetate phthalate provide good gastric protection in 0.1N HCl. The compression coated tablets remained intact in 0.1N HCl and no drug release was observed from these formulations. The press coated tablets were prepared using various concentrations of Cellulose acetate phthalate and Magnesium stearate in the outer shell and explained in figure 3. F9 with Cellulose acetate phthalate alone in outer coat releases 34.47±3.15% of drug pH 7.4 buffer by the end of 5h. F11and F12 contains 5%, 10% magnesium stearate in outer coat respectively. The drug release profile of F12 was less when compared to F10 and F11 and release only 18.14±3.12% of drug in pH 7.4 buffer. F11 containing 5% of magnesium stearate release 23.24±2.40% of drug. A further increase in the concentration of magnesium stearate in the outer shell to 10% in F12 shows a decrease in the amount of drug release in pH 7.4 buffer when compared to F11.The presence of magnesium stearate in outer shell suppresses the drug release by preventing the entry of medium into the coat. F11 and F12 with 5% and 10% of magnesium stearate respectively in their outer coat can effectively deliver the maximum amount of drug to colon. A rapid drug release was observed in pH 6.8 buffer after erosion of outer Cellulose acetate phthalate coat.

Table 1. Composition of Mebeverine Hydrochloride Core Tablet

Ingredients	Quantity (mg)
Mebeverine	135
SSG	10
MCC	43
PVP K30	6
Talc	4
Mg. Stearate	2
Total	200

Table 2. Compression Coat Composition of the Different Prepared Formulas

Formulation code	Eudragit L100-55 (%)	HPMCP-55 (%)	CAP (%)	Ethyl cellulose (%)	Mg. Stearate (%)	DCP (%)
F1	90					10
F2	100					
F3	95			5		
F4	90			10		
F5		90				10
F6		100				
F7		95		5		5
F8		90		10		
F9			90			10
F10			100			
F11			95		5	5
F12			90		10	

Table 3. Flow Properties of the Different Powder Blends Used In Compression-Coated Tablets

Formulation	Bulk density	Tapped density	Hausner's ratio	Carre's index	Angle of repose (Ɵ)
Core Tablet	0.55	0.64	1.163636	14.0625	26.23
F1	0.52	0.58	1.115385	10.34483	17.29
F2	0.53	0.60	1.132075	11.66667	19.29
F3	0.53	0.59	1.113208	10.16949	18.49
F4	0.52	0.58	1.135385	10.34483	17.06
F5	0.58	0.67	1.155172	13.43284	21.45
F6	0.57	0.65	1.140351	12.30769	24.64
F7	0.58	0.66	1.137931	12.12121	23.16
F8	0.64	0.74	1.15625	13.51351	29.05
F9	0.64	0.74	1.1625	13.97849	28.12
F10	0.66	0.76	1.151515	13.15789	27.64
F11	0.64	0.73	1.140625	12.32877	27.08
F12	0.65	0.73	1.123077	10.9589	26.45

Table 4. Characteristics of Different Mebeverine Compression Coated Tablets

Formulation	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (mg)	Acid uptake
Core tablet	200.47±2.12	3.04±0.088	3.5	0.29	131.07±1.822	-
F1	401.98±2.66	5.31±.104	5.5	0.49	129.67±2.8	6.10
F2	394.98±1.64	5.45±1.04	5.5	0.46	130.57±0.82	5.97
F3	398.98±0.19	5.34±1.12	5.5	0.44	129.17±1.64	4.23
F4	402.34±1.37	5.41±1.62	5.5	0.41	130.84±1.64	2.62
F5	403.98±1.61	6.07±1.04	5.5	0.39	128.07±2.722	6.69
F6	396.25±0.86	6.14±2.31	5.5	0.36	130.07±0.12	6.40
F7	404.91±1.06	6.21±0.94	6.0	0.40	129.07±2.22	5.25
F8	405.28±2.54	5.86±0.17	5.5	0.41	128.07±3.02	3.97
F9	397.60±0.96	5.74±0.94	5.5	0.39	134.07±1.29	6.11
F10	404.12±1.46	5.88±1.78	5.5	0.42	131.07±0.92	6.08
F11	402.98±1.76	5.72±2.45	5.5	0.42	128.07±3.08	4.19

Fig 1. Cumulative drug release profile of Eudragit L100-55 compression coated tablets

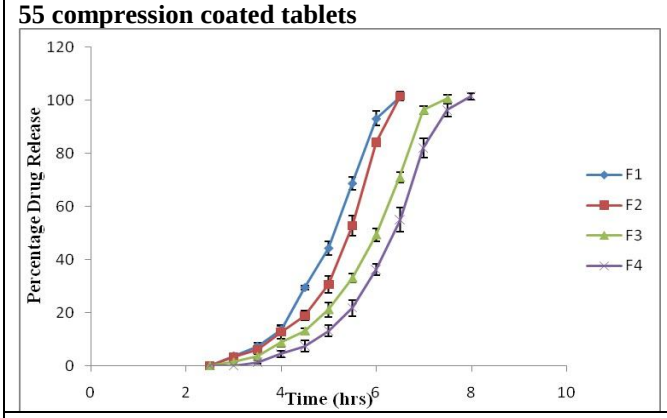


Fig 2. Cumulative drug release profile of HPMCP-55 compression coated tablets

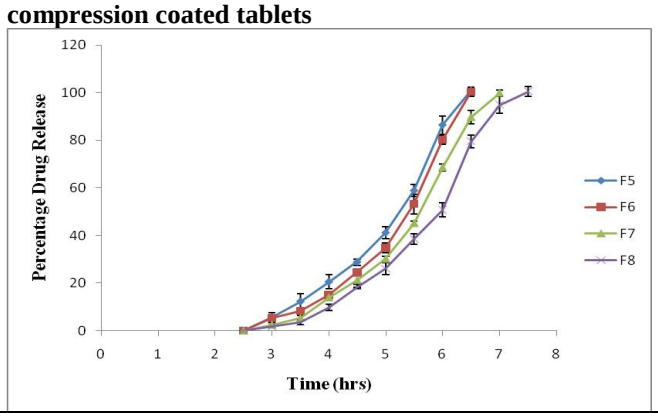
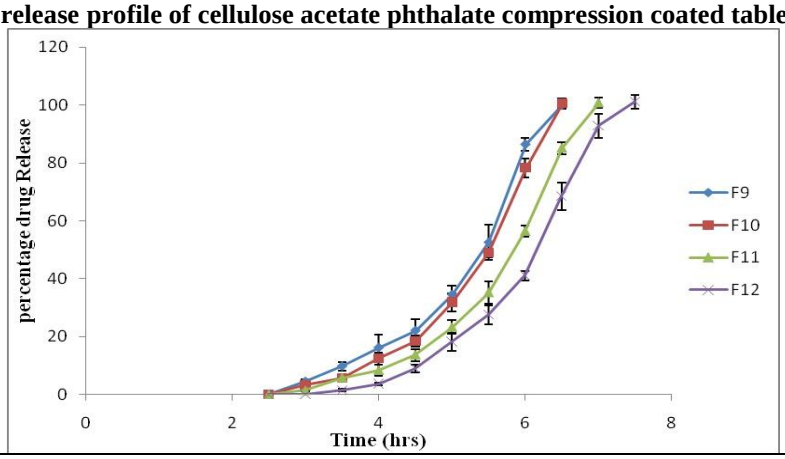


Fig 3. Cumulative drug release profile of cellulose acetate phthalate compression coated tablets



CONCLUSION

The mebeverine compression coated tablets prepared by using various pH dependent polymers can effectively deliver the drug to colon. The presence of high thickness coat on the core tablet prevents the drug release in the initial stages of dissolution. After erosion of the outer coat a rapid drug release from the core tablets was observed. The drug release was after a controllable lag time was achieved by the addition of hydrophobic material to the outer coat. The presence of ethyl cellulose in the Eudragit L100, HPMC P-55 and magnesium stearate in the cellulose acetate phthalate outer coat shows an increase in the lag time was observed.

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