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Formulation and evaluation of colon specific matrix tablets of Esomeprazole

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Abstract: Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The present investigation is aimed to formulate the Eight formulations of Esemoprazole were developed by direct compression technique enteric coated by cellulose acetate pthalate. The F6 formulation was found to be best of all the trials showing that the drug release matches with the brand product. The best formulation F6 can successfully be employed as a controlled release of drug delivery system. The tablets can control the fluctuations in the plasma drug concentration, increase the gastric residence time and eventually improve the bioavailability of the drug.
Key words: Colon specific drug delivery system, CDDS, Esemoprazole, cellulose acetate phthalate, entric coated tablet.

Introduction

The goal of many of the original controlled release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile, in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. There are three primary mechanisms by which active agents can be released from a delivery" system which includes diffusion, degradation, and swelling followed by diffusion. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon.[3] The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability.[4] And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers. Oral route is the most convenient and preferred route but other routes for CDDS may be used. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal.[5] Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine.

Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity.[6] Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides.[7]

Criteria for Selection of Drug for CDDS

The best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery.[8] The criteria for selection of drugs for CDDS is summarized in Table 2.[9-10] Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule.[17] For example; aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems.[11]

Materials and Methods

Materials:

Esemoprazole obtained from Raaga pharmaceuticals, Micro crystalline cellulose, Magnesium stearate and Aerosil are purchased from Symchem Research Labs.

Chemicals:

Sodium bicarbonate and citric acid obtained from Sigma Chemicals.

METHOD:

The Esomeprazole floating tablets were prepared by direct compression method.

All the ingredients were first sieved and then blended in mortar with pestle to obtain uniform mixing. Then they were compressed by karnavati single punch machine by using 12 mm flat. The weight of tablet was adjusted to 500 mg and each tablet contained 200 mg Esomeprazole. The compressed tablets of each type of polymer were then evaluated for tablet characteristics such as thickness, weight variation and friability.

Results and Discussion

Esomeprazole compressed tablet formulations

Twelve batches of Esomeprazole compressed tablets were prepared by direct compression method with different drug-polymer ratios by using HPMC K 15 M, HPMC k 100 m, PEO, PVP K 30, Microcrystalline cellulose and Magnesium stearate according to formula mentioned in Table No 1 . These compressed tablets were evaluated with different physicochemical evaluation such as hardness, friability, average weight, and drug content and *in vitro* drug release behaviour. The results indicate the good physicochemical characteristics for compressed tablets.

Table No.1

Formulation code/Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)	F10(mg)	F11(mg)	F12(mg)
	20	20	20	20	20	20	20	20	20	20	20	20
Esomeprazole	5	10	15	20	25	30						
HPMC K 15 M							5	10	15	20	25	30
HPMC k100 m												
PEO	20	20	20	20	20	20	20	20	20	20	20	20
PVP K 30	5	5	5	5	5	5	5	5	5	5	5	5
microcrystalline cellulose	48.8	43.8	38.8	33.8	28.8	23.8	48.8	43.8	38.8	33.8	28.8	23.8
Magnesium stearate	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Aerosil	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Total	100	100	100	100	100	100	100	100	100	100	100	100

Physicochemical evaluation:

Bulk Density: Density is defined as weight per unit volume. Bulk density P_b is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. There are two types of bulk density.

The particles are pack in such a way so as to leave large gaps between their surfaces resulting up in light powder of low bulk density. Here the smaller particles shift between the large particles resulting in heavy powder of high bulk density. Bulk density is very important in the size of containers needed for handling, shipping and storage of raw material and blend. It is also important in size blending equipment. Apparent bulk density (P_b) was determined by pouring blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated by using the following formula and the values are mentioned in table No 2

$$\mathbf{P_b = M / V_b}$$

Where,

P_b = Bulk Density
M = Weight of sample in gm
V_b = Final volume of blend in cm^3

Tapped Density:

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. The tapped density was calculated by using the following formula and the values are mentioned in table no 3

$$\mathbf{P_t = M / V_t}$$

Where,

$\mathbf{P_t}$ = Tapped Density
M = Weight of the sample in gm
$\mathbf{V_t}$ = Tapped volume of blend in cm^3

Post compressionstudies

Tablet Dimensions:

Thickness and diameter were measured using a calibratedvernier calipers. Three tablets of each formulation were picked randomly and thickness was measured individually.

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester .It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability Test:

The friability of tablets was determined by using vergofriabilator. It is expressed in percentage (%). It is expressed in percentage (%). Ten tablets were initially weighed (wI) and transferred into friabilator .The friabilator was operated at 25rpm or run up to 100 revolutions.The tablets were weighed again(wF).The friability was then calculated by ---

% F=100(1-W I/W F)

% Friability of tablets less than 1% was considered acceptable.

Weight variation Test :

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to U.S. Pharmacopeia. The following percentage deviation in weight variation was allowed.

Floating Time Studies:

The buoyancy lag- time of the tablets was studied at 37±0.5 c, in 100 mlof 0.1N Hcl. The time required for the tablet to rise to the surface and float was taken as the buoyancy lag- time.The duration of floating is known as floating time.

In Vitro Dissolution studies:

The released rate of Esomeprazole from floating matrix tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900ml of 0.1N Hcl at 37 ± 0.5 c and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 16 hrs, and the samples was replaced with fresh dissolution medium. The samples were passed through Whatmann filter paper and absorbance of the solution was measured at 252nm.The values are mentioned in table no 4.

Method of Analysis:

In Vitro dissolution studies for Esomeprazole

Apparatus : Dissolution apparatus IP Type II(paddle)

Speed : 50 rpm

Min. temp : 37±0.5 0c

Sample preparation:
One tablet each were placed in 6 – dissolution bowl. Then the apparatus was runned and the sample was withdrawn from each bowl at regular intervals and the solution was filtered through 0.45 micron memebrane filter. The filterate was collected after discarding first few ml of the filterate.
Buffer: 0.1N Hcl
Preparation of 0.1N Hcl: Dissolve 8.5 ml of Hcl in 1000 ml of water .
FTIR studies:
From the infrared spectra it is clearly evident that there were no interactions of the drug. IR Spectrum of the pure drug shows the characteristic peaks at 3490cm^{-1} , 1696cm^{-1} 1480cm^{-1} 3320cm^{-1}, 2930cm^{-1} 2840cm^{-1} and 1605cm^{-1} The IR Spectrum of Drug and polymer exhibited peaks at 3490cm^{-1}, 3320cm^{-1}, 2840cm^{-1}, 1696cm^{-1}, 1605cm^{-1}, and 1480cm^{-1}. This confirms the undisturbed structure of the drug in the formulation. This proves the fact that there is no potential incompatibility of the drug with the polymers used in the formulation. Hence, the formula for preparing Esomeprazole can be reproduced in the industrial scale without any apprehension of possible drug-polymer interactions.

Bulk density Results:

Table no 2

Formulation code	Bulk Density
F1	0.49
F2	0.48
F3	0.46
F4	0.43
F5	0.41
F6	0.39
F7	0.55
F8	0.53
F9	0.5
	0.49
F11	0.47

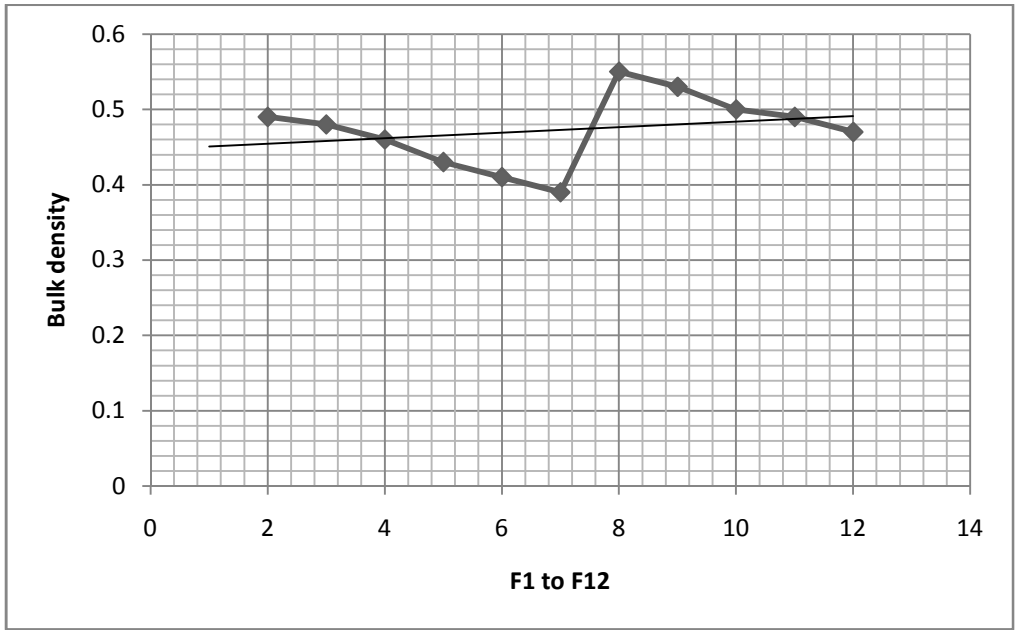


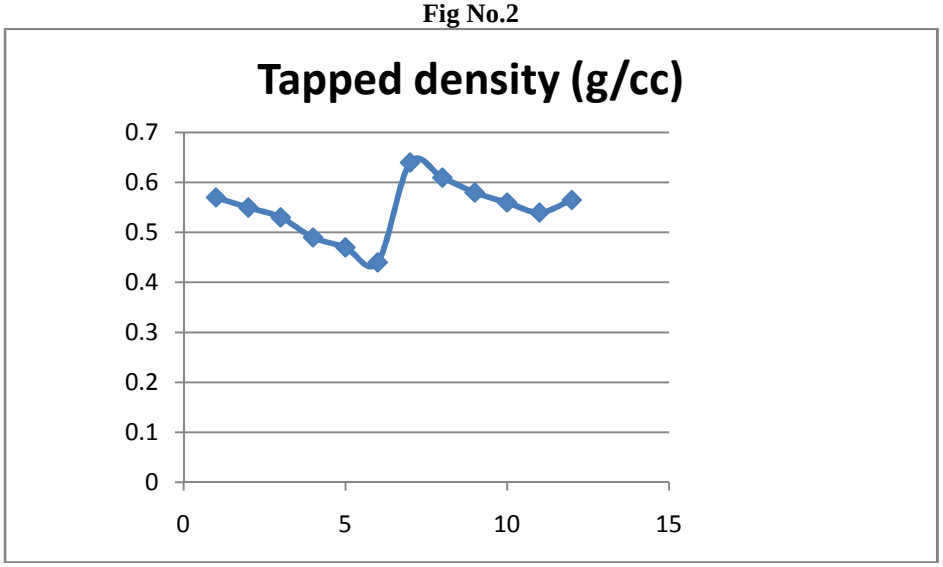
Fig No.1

Tapped density Results:

Table No 3

Formulation code/Parameter	**Tapped density (g/cc)**
F1	0.57
F2	0.55
F3	0.53
F4	0.49
F5	0.47
F6	0.44
F7	0.64
F8	0.61
F9	0.58
F10	0.56
F11	0.54
F12	0.565

Fig No.2

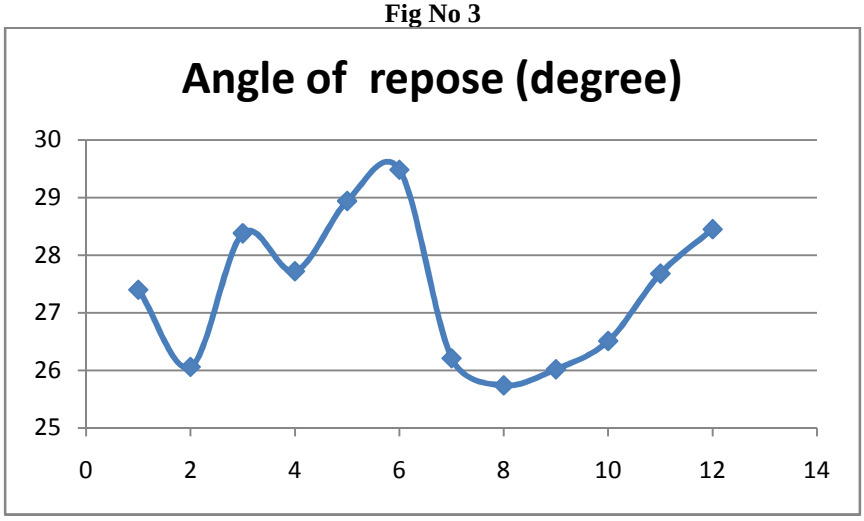


Angle of Repose Results:

Table No 4

Formulation code/Parameter	**Angle of repose (degree)**
F1	27.4
F2	26.06
F3	28.38
F4	27.72
F5	28.94
F6	29.48
F7	26.21
F8	25.74
F9	26.02
F10	26.51
F11	27.68
F12	28.45

Fig No 3

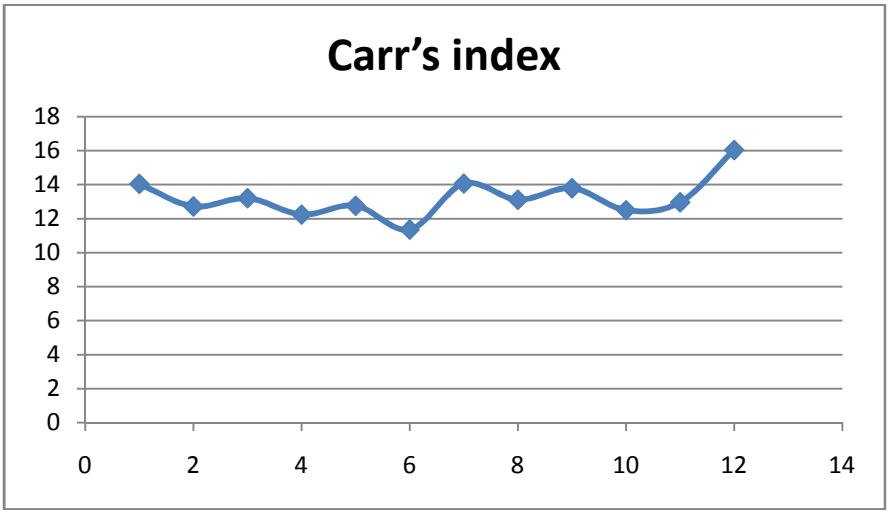


Carr's index Results:

Table No 5

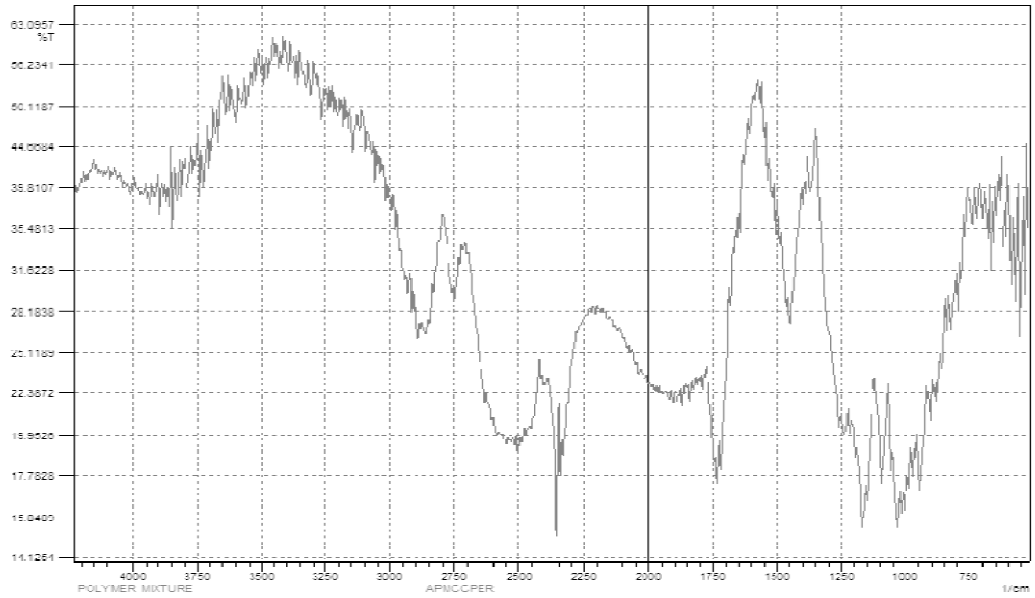
Formulation code/Parameter	**Carr's index**
F1	14.04
F2	12.72
F3	13.2
F4	12.24
F5	12.76
F6	11.36
F7	14.06
F8	13.11
F9	13.79
F10	12.5
F11	12.96
F12	16.03

Fig No 4

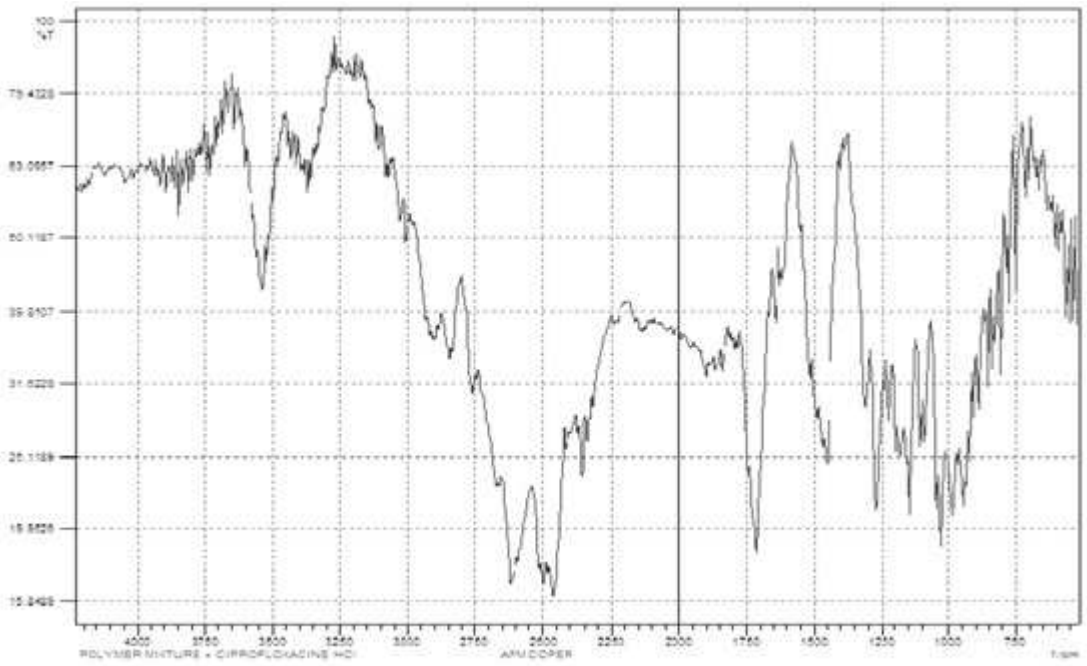


FTIR spectras:

Fig No 5



FT-IR spectrum of polymer mixture (Microcrystalline cellulose, sodium starch glycolate, povidone, aerosil and other excipients. Fig No: 5



FT-IR spectrum of polymer mixture + Esomeprazole.Fig No:6

Conclusion

Twelve formulations of Esemoprazole were developed by direct compression technique enteric coated by cellulose acetate pthalate. The F6 formulation was found to be best of all the trials showing that the drug release matches with the brand product. The best formulation F6 can successfully be employed as a controlled release of drug delivery system. The tablets can control the fluctuations in the plasma drug concentration, increase the gastric residence time and eventually improve the bioavailability of the drug.

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