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RESEARCH ARTICLE

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A Path for Horizing Your Innovative Work

FORMULATION AND EVALUATION OF ENTERIC COATED CONTROLLED POROSITY OSMOTIC MATRIX TABLETS OF MODEL DRUG

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Abstract: It is a novel osmotically driven matrix system, which utilizes the property of hydrophilic polymers to swell and gel in aqueous medium forming a semi-permeable in situ. Release from such a matrix system containing an osmogent could, therefore, be modulated by the osmotic phenomenon. OMT thus judiciously combines both matrix and osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix systems. Diclofenac Sodium was prepared in the form of tablets and evaluating the various processing parameters including pre-compression and post-compression parameter with in vitro drug release studies in 0.1 N HCl (pH 1.2) and Phosphate buffer(pH 6.8). Ten formulations containing varying proportions of polymer Guar gum and release modifying agent used as NaCl,PEG-400.and fixed amount of PVPK30,SLS, Magnesium stearate & Lactose were used as binder, wetting agent, lubricant & glidant respectively. The tablets were prepared by Wet granulation Method, The different levels of enteric-coating membrane could prevent Eudragit L100-55 (containing PEG-400) from forming pore or rupture before contact with simulated colonic fluid, but had no effect on the drug release. Drug release rate from 1h-12h were taken as responses. The increase in concentration of osmotic agent with decrease in concentration of polymer after a limit, changes the release from zero order to Higuchi based release. The optimized formulation F8 follows osmosis release mechanism. The DSC and SEM studies revealed that no physicochemical interaction between excipients and drug and good pore form. Stability studies revealed that optimized formulation was stable.

Keywords: Diclofenac sodium, Controlled Porosity osmotic matrix pump, PEG 400, Sodium Chloride.

INTRODUCTION

By using oral controlled drug delivery system can provide continuous delivery of drugs at predictable and reproducible kinetics throughout the GI transit. Also the systems that target the drug delivery to a specific region within the GI tract for either local or systemic action1. To maintain drug concentration within the therapeutic window the drug dose and dosing interval are optimized, thus ensuring efficacy while minimizing toxic effects[1]. Oral controlled release system that provides greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule2. The drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. The oral osmotic pump tablets have many advantages, such as reducing risk of adverse reactions, zero-order delivery rate, a high degree of *in vitro in vivo* correlation and improving patient compliance[2].

Diclofenac sodium is a non steroidal anti-inflammatory analgesic with potent cyclooxygenase inhibition activity and also commonly used for pain control and the treatment of rheumatic diseases. Diclofenac sodium has biological half life of 2 h and it absorbs throughout the intestinal tract. The drug shows linear pharmacokinetics, is suitable for oral controlled release tablets and it would be advantageous to slow down its release in GI tract not only to prolong its therapeutic action but also minimize possible side effects of Diclofenac such as peptic ulcer, epigastric[3, 4]..

The various approaches developed for the purpose of achieving colonic targeting include time-controlled delivery systems (Steed et al., 1997; Hebden et al., 1999), pH-dependent delivery systems (Markus et al., 2001; Cole et al., 2002), pressure controlled delivery systems (Muraoka et al., 1998; Shibata et al., 2001), prodrug (Ahrabi et al., 2000; Maris et al., 2001) and micro flora-triggered delivery systems (Brondsted et al., 1998; Katsuma et al., 2002; Yano et al., 2002). Among these approaches, there appears more interest in pressure controlled

delivery systems achive the goal of delivery.

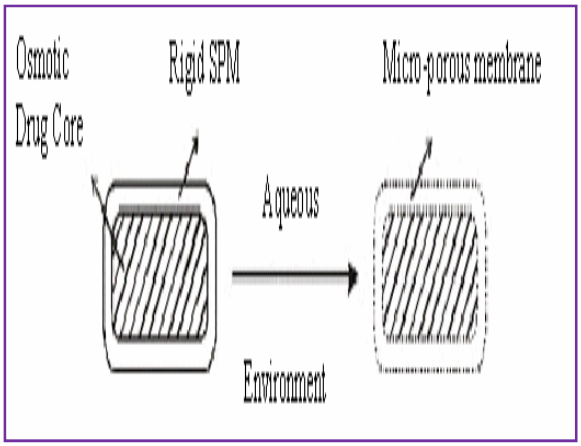

Figure 1. Schematic diagram of CPOMT.

Above fig. shows schematic diagram of CPOMT, which consists of an osmotic core (containing drug, Guar gum, osmotic agent with other excipient), an inner semipermeable membrane layer composed of the mixture of cellulose acetate powder, and an outer enteric-coating layer[5].

MATERIALS AND METHODS

Materials

Diclofenac sodium was obtained as gift sample from AGO pharmaceutical Ltd (Pune, India). Cellulose acetate was purchased by S.D Fine Chem. Ltd (Mumbai, India). PEG 400, microcrystalline cellulose and povidone K30 was received as gift sample from Strides Arco labs LTD (Bangalore, India). Magnesium stearate and talc was purchased from S. D. fine Chem. LTD (Mumbai, India). The other entire ingredient are Analytical grade.

Fourier Transform Infrared Spectroscopy (FTIR)

Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FT-IR spectroscopy.

Differential Scanning Calorimetry (DSC)

DSC studies were carried out for the pure drug, physical mixtures of drug and excipients to study the compatibility.

Scanning Electron Microscopy

Coating membrane of formulation obtained before and after complete dissolution of core tablet was examined for their porous morphology by using SEM.

Preparation of porous osmotic pump tablet

Preparation core tablets

Core tablets of DS were prepared by wet granulation method. All the ingredients (Table 1) except povidone K30, magnesium stearate and talc were accurately weighted and mixed in mortar with a pestle for 5 minutes to get the uniform mix. The dry blend was granulated with sufficient quantity of PVP K30 which was dissolved in isopropyl alcohol. The powder mass was dried at 60 °C in hot air oven for 6 h and passed through sieve no.18. The dried granules were mixed with magnesium stearate and talc for 3 min. The blended powder was compressed in to round tablets by using 9 mm punch in JAGUAR,GMD-4-B[9][6].

Coating of core tablet

Enteric coating

Different weight gains (F1: 2%, F2: 4% and F3: 6%, F4:8% respectively, w/w) of enteric layer's materials (Table no 3) were coated on the surface of tablet. Operating conditions were as follows: stainless steel pan, 200 mm diameter; 4 baffles; rotation rate of the pan, 65 rpm; nozzle diameter of spray gun, 1 mm; spray rate, 2 mL/min; spray pressure, 1.5 bar; drying temperature, 50°C. The surface of MO tablet had a smooth and uniform appearance. Coated tablets were dried for 4 h at 40 ◦C.[6]

Influences of tablet formulation variables on drug release

To investigate the influences of tablet core formulation variables on drug release, tablets with different formulations were prepared, coated with the same coating solution[7].

RESULTS AND DISCUSSION

Influence of amount of NaCl

CPOMTs with different amounts of NaCl as an osmotic pressure accelerant and amylum pregelatinisatum as a loading agent in the core were prepared. The results are shown in Fig. 2. A significant influence was observed. With an increasing amount of NaCl, the release rate was accelerated, because the increasing osmotic pressure made more drug release from the core.

Figure 2.Influence of amount of NaCl

Influence of amount of Guar gum

Different amounts of Guar gum were added to the core for tabletting and coating. Fig. 3 indicates that the amount of Guar gum had a significant effect on the release rate. With increasing Guar gum the release rate clearly slowed. This is because, as Guar gum increased, the swelling rate and viscosity in the core increased, so that the water entry into the core was hindered.

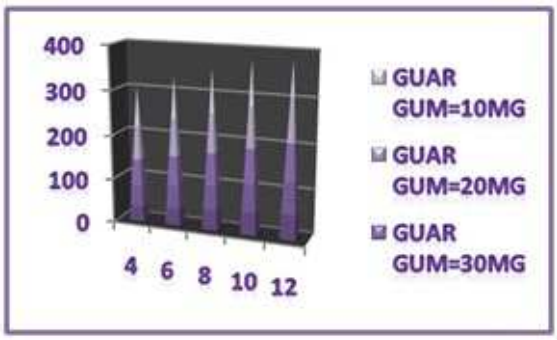

Figure 3.Influence of amount of Guar gum

Influence of amount of MCC

Tablets with different amounts of MCC were prepared. The results are shown in Fig. 4. The results showed that the amount of MCC had a significant effect on the release rate. This can be accounted for by the fact that after extramembranous water was imbibed into the intramembrane, the swelling of MCC would lead to increasing static pressure inside the membrane, which would accelerate drug release from the core.

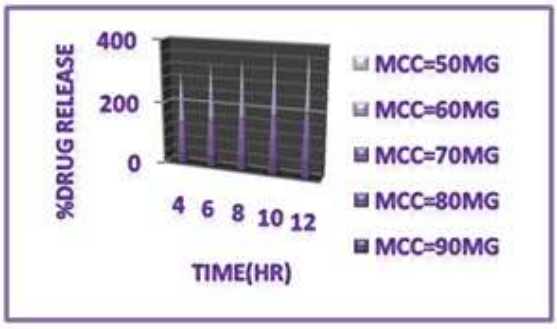

Figure 4.Influence of amount of MCC

Influences of coating formulation on drug release [6, 7]

Influence of coating solution concentration

EudrigitL100-55 solutions of 2%, 4%, 6% and 8% (g/100 ml) with the DBP and PEG-400 were prepared. Then, the cores of tablets coated by using the above-mentioned coating solution. From Fig. 5, it can be observed that the concentration of the coating solution didn't significantly affect drug release. But, in practical use, when the concentration of coating solution was above 6%, the viscosity of the coating solution would be too great to finish the coating process. When the concentration of the coating solution is lower than 2%, the coating membrane would be difficult to form. So, 4-6% EudragitL100-55 solution was chosen as the coating solution.

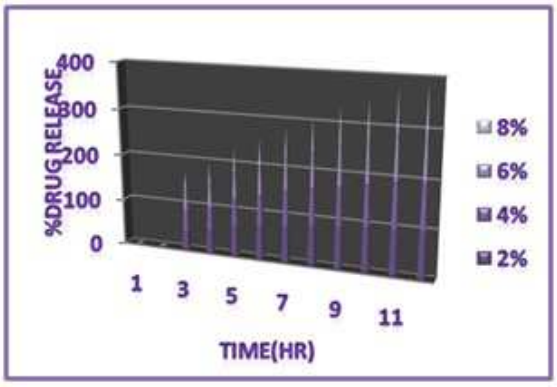

Figure 5.Influence of coating solution concentration

Influence of amount of DBP

DBP was chosen as the plasticizer. CA acetone solutions with different amounts of DBP were used to coat the cores of tablets with the same lot number. Fig. 6 shows that an increase in the amount of DBP led to a increased in the drug release rate but finally decrease. If EudragitL100-55 solution alone is used for coating, the coating membrane will be easily ruptured over the course of drug release. Plasticizer is good for improving the nature of the coating membrane and plasticity of the coating material. Meanwhile, it can improve the membrane's adherence to the core and mechanical character.

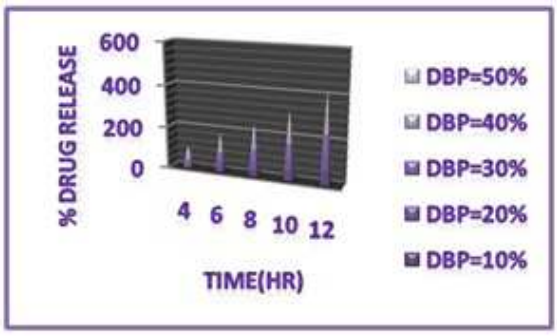

Figure 6. Influence of the amount of DBP

Influence of the amount of PEG-400

In this study PEG-400 was used as a plasticizers. Different amounts of PEG-400 were added to 6% EudragitL100-55 coating solution to coat the cores of tablets with the

same lot number. The influence of PEG-400 on release was investigated. The results are shown in Fig. 7. It was observed that PEG-400 had a marked influence on drug release. With the increase in the amount of PEG-400, the drug release rate increased but finally decrease. This may be explained as follows: porous channels in the surface of the coating membrane increased with the increasing amount of PEG-400. Therefore, water could be imbibed into the membrane very quickly, accelerating the release rate of the drug.

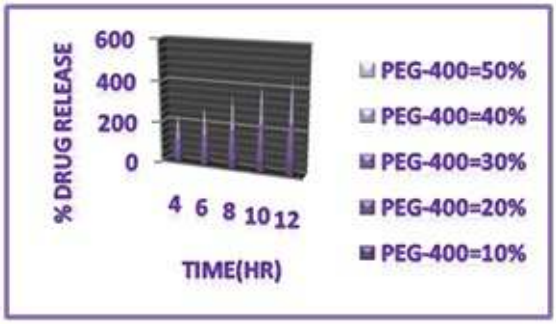

Figure 7.Influence of the amount of PEG-400

Differential Scanning Calorimetry (DSC Analysis):

DSC thermo gram of the optimized formulation showed that there is was no any major difference in onset temperature and peak temperature, when compared with pure drug thermo gram. The DSC thermo gram optimized batch is shown in following figure;

Influence of different coating weights

The same core tablets were coated with different coating weights (2%, 4%, 6%, and 8%). The influence of different coating weights is shown in Fig. 8. The result shows that the release rate slowed following the increase of the coating membrane thickness.

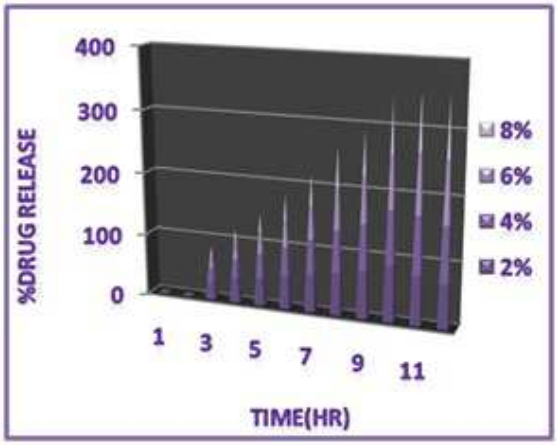

Figure 8. Influence of different coating weight

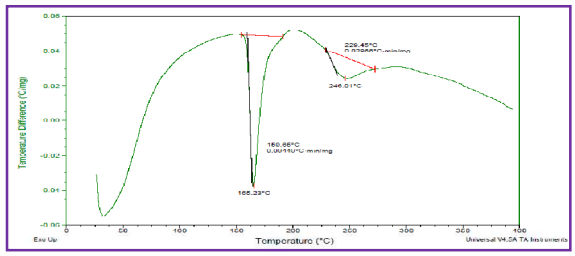

Figure 9. DSC thermo grams of optimized batch

Scanning Electron Microscopy

Coating layer of formulation obtained before and after complete dissolution of core tablet was examined for their porous morphology by using SEM (JEOL JSM-6300, JAPAN). Membrane were dried at 45°C for 12hr and stored between sheet of wax paper in desiccators until examination. The membrane were coated under an argon atmosphere with gold-palladium and observed with a SEM.

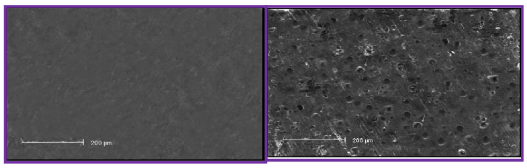

Fig. 10A: Before dissolution

Fig. 10B: After dissolution

Fig. 10: Coating layer morphology of formulation F08 by scanning electron microscopy

EVALUATION OF POWDER BLEND

The prepared granules were evaluated for the blend property like angle of repose, bulk density, tapped density, Carr's index. Results obtained are shown in Table 5.[8]

Pre-compression parameters

Angle of repose

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (_) was calculated using the formula.

$$\theta = \tan^{-1} (h / r)$$

Bulk density (BD)

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume and Mass of the powder was determined. The bulk density was calculated by using below mentioned formula

$$\text{Bulk density} = \frac{\text{Mass of powder blend}}{\text{Bulk Volume of blend powder}}$$

Tapped density (TD)

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the Mass of the blend was measured. The tapped density was calculated using the following formula,

$$\text{Tapped Density} = \frac{\text{Mass of powder blend}}{\text{Bulk Volume of blend powder}}$$

Carr's Index

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by carrs' index which is calculated as follows, The value below 16% indicates a powder with usually give rise to good flow characteristics, whereas above 23 % indicate poor flowability.

$$\text{Carr's Index} = \frac{\text{TD-BD}}{\text{TD}} 100$$

EVALUATION OF CORE TABLETS

Physicochemical Evaluation

All the preparations were evaluated for physical parameters and content uniformity before proceeding further. Includes the values (mean ± SD) of Thickness, Hardness, Weight Variation, Friability and Content Uniformity of tablet batches prepared using different combinations of functional excipients Table no:5.[8, 9]

Weight variation test

Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with average weight. The

Comparison variation within the I.P limits, it passes the weight variation test.

Tablet hardness

Tablet crushing strength or hardness, the force required to break a tablet in a diametric compression, was measured using Monsanto tablet hardness tester.

Thickness

The thickness of individual tablets was measured using Vernier caliper, which permits accurate measurements and provides information of the variation between tablets.

Tablet friability

The friability of the tablets was measured in a Roche friabilator. Tablets sample of a known weight (W0) were deducted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ friability} = \frac{W0 - W}{W0} \times 100$$

Drug content uniformity

Five tablets from each formulation were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing from this equivalent to 20 mg of Diclofenac Sodium was taken in 100 ml methanol. Further appropriate dilution was made &absorbance was measured at nm 283 nm.

Evaluation of Enteric Coated Microporos Membrane Osmotic Matrix Tablets

***In Vitro* Drug Release of Enteric Coated Microporous Membrane Osmotic matrix Tablet**

To release studies were conducted in dissolution medium with 0.1NHCL pH 1.2; phosphate buffer, pH 6.8 with a rotation speed of 100 rpm at a 37±0.5^{0}C. Samples of 10 mL were withdrawn at specified time points (0, 1, 2, 4, 6, 8, 10, 12hr) and replaced with fresh dissolution medium. Obtained samples were properly diluted and analyzed by UV-absorption measurement [9, 10].

STABILITY STUDY:-

Accelerated stability studies (AST) was carried for optimized batch F 08 exposing it to 40°C/75% RH for 15, 30, 45 and 60 days. The sample was analyzed for Colour, Hardness, Drug Content and *In vitro* dissolution studies.[10]

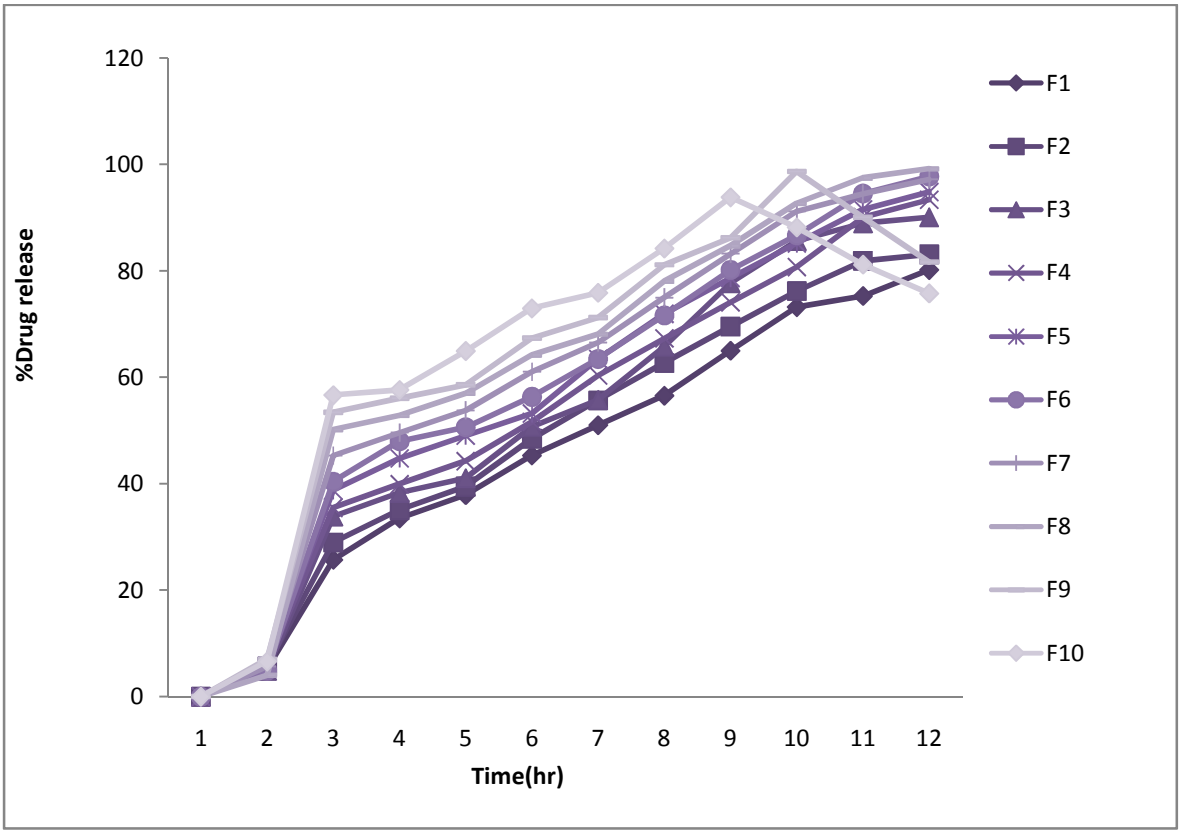

Figure No 11. Cumulative % Drug Release of Coated Tablet

CONCLUSION

The study conclusively demonstrated significant results of Diclofenac Sodium and dissolution of entric coated controlled porosity osmotic tablet(CPOMT). The CPOMT can be so designed that delivery of its drug would follow zero order kinetics and thus better control over the drug's *in vivo* performance is possible. It is possible to attain better release rates than those obtained with conventional diffusion based drug delivery systems. Drug release from the CPOMT exhibits significant *in vitro-in vivo* correlation within specific limits. Hence, at the end of this investigation it can be cocluded that entric coated controlled porosity osmotic matrix tablet of Diclofenac Sodium was successfully prepared by conventional wet granulation method using

different concentration of NaCl and polymer with the objectives of this study are achieved and optimize batch 08.

FUTURE SCOPE

Future possibilities for improvements in entric coated CPOMTand drug delivery are bright but technology is still relatively new. Several drug delivery technologies that can be leveraged on improving drug therapy from entric CPOMT have yet to be fully realized.

ACKNOWLEDGEMENT

The generosity of AGO pharmaceutical Ltd (Pune, India), Merk Specialties Private Ltd., (Mumbai), Loba Chemie Pvt. Ltd.,(Mumbai), Pure Chem Lab,(Mumbai) is gratefully acknowledged for providing the gift samples of Diclofenac Sodium, Sodium Chloride, Microcrystalline Cellulose, Guar gum respectively. All other chemicals employed were of analytical grade. The authors are also thankful to the guide and management of Faizpur College of Pharmacy, for providing all the necessary laboratory facilities.

Table 1.

Formulation of core tablets

Sr.no	Ingredient	Qty.taken(mg)
1	Diclofenac Sodium	100
2	Sodium Chloride	60-140
3	Microcrytalline Cellulose	50-90
4	Guar Gum	10-50
5	Povidone K-30	20
6	Sodium Laury Sulphate	15
7	Magnesium Stearate	2
8	Talc	3
	Total weight/tab	335

Table 2.

Composition of enteric coating

Sr.no	Ingredient	Qty. Taken
1	Eudragit L100-55	2-8mg
2	PEG-400	4ml
3	Glycerin	3ml
4	TEC	0.6mg
5	Talc	1.5mg
	95% ethanol	Upto 100ml

Table No 3.

Influences of coating formulation on drug release

Sr.no	Parameters	Concentration (%)
1	Coating Solution Conc.(Eudragitl100-55)	2-8
2	Different Coating Weights	2-8
3	Dibutly Phalate(DBP)	10-50
4	PEG-400	10-50

Table No 4.

Optimize coating formula

Sr.No	Parameters	Concentration (%)
1	Coating Solution Conc.(Eudragitl100-55)	4- 6
2	Different Coating Weights	4
3	Dibutly Phalate(DBP)	40
4	PEG-400	40

Table no 5.

Physical Properties of Powder Blend

Parameters Formulations	Angle of Repose (^{0}) ±SD	Bulk Density (g/ml) ±SD	Tapped Density (g/ml) ±SD	Carr's index (%)	Carr's Index (%)±SD
F 01	25.45±0.50	0.42±0.031	0.60±0.040	13.67±0.73	12.67±0.73
F 02	24.87±0.64	0.44±0.032	0.63±0.022	11.87±0.60	14.87±0.60
F 03	26.69±0.55	0.47±0.018	0.64±0.020	15.72±0.27	12.72±0.27
F 04	27.65±0.39	0.38±0.024	0.62±0.024	17.71±0.71	15.71±0.71
F 05	23.32±0.78	0.49±0.037	0.67±0.051	19.31±0.99	17.31±0.99
F 06	25.71±0.59	0.54±0.025	0.65±0.036	21.81±0.77	16.81±0.77
F 07	30.93±0.46	0.50±0.024	0.69±0.032	23.96±0.49	17.96±0.49
F 08	27.53±0.32	0.53±0.012	0.72±0.012	17.20±0.34	19.20±0.34
F 09	26.90±0.46	0.55±0.024	0.77±0.032	20.98±0.49	21.95±0.49
F 10	23.55±0.32	0.53±0.012	0.65±0.012	18.23±0.34	19.27±0.34

All these results indicated that, the powder blends possess satisfactory flow and compressibility properties.

Tablet No 6.

Evaluation of Formulated Core Tablets

Parameters / Formulations	Thickness (mm) ± SD	Hardness (kg/cm^2)	Weight Variation (mg)	% Friability ± SD	Drug Content (%)
F 01	4.34±0.03	10.83±0.2	336±5	0.83±0.2	98.61±0.03
F 02	4.45±0.03	10.98±0.2	336±5	0.98±0.2	97.78±0.03
F 03	4.23±0.03	10.10±0.3	334±5	0.51±0.3	99.64±0.03
F 04	4.18±0.03	10.27±0.3	338±5	0.42±0.3	100.0±0.03
F 05	4.56±0.03	11.74±0.6	335±5	0.37±0.6	96.99±0.03
F 06	4.74±0.03	10.43±0.5	340±5	0.34±0.5	98.87±0.03
F 07	4.35±0.03	10.50±0.3	329±5	0.25±0.3	102.0±0.03
F 08	4.60±0.03	10.05±0.3	335±5	0.15±0.3	99.84±0.03
F09	4.39±0.03	10.50±0.3	330±5	0.25±0.3	98.56±0.03
F10	4.62±0.03	11.05±0.3	337±5	0.65±0.3	99.97±0.03

Table No 7.

Cumulative % Drug release of CPOM

Formulation	F01	F02	F03	F04	F05	F06	F07	F08	F09	F10
Time (hr)										
0	0	0	0	0	0	0	0	0	0	0
1	9.74 ±0.82	15.11 ±1.00	18.49 ±0.63	21.43 ±1.67	23.89 ±1.20	27.36 ±0.87	30.79 ±0.55	32.49 ±1.12	35.49 ±0.68	37.49 ±0.68
2	15.61 ±0.65	25.94 ±1.25	26.37 ±0.90	28.40 ±0.79	27.75 ±0.98	29.64 ±0.92	31.95 ±0.26	34.93 ±1.01	38.13 ±0.57	40.13 ±0.57
3	21.49 ±0.55	35.32 ±0.66	39.02 ±0.88	42.61 ±1.75	45.93 ±0.57	46.45 ±0.63	47.31 ±0.48	48.34 ±1.15	52.85 ±0.97	54.85 ±0.97
4	29.24 ±1.64	43.30 ±1.10	46.44 ±1.01	49.82 ±0.98	50.92 ±0.79	52.44 ±1.03	53.80 ±0.39	56.16 ±0.93	60.66 ±1.02	63.66 ±1.02
5	37.64 ±1.18	48.90 ±0.69	50.55 ±0.65	54.91 ±1.08	56.57 ±0.83	57.38 ±1.04	59.34 ±1.26	63.17 ±0.71	65.43 ±1.26	68.43 ±1.26
6	45.11 ±1.89	56.23 ±1.67	58.57 ±0.63	60.20 ±1.45	62.02 ±0.97	63.95 ±1.66	64.44 ±1.08	68.54 ±0.56	71.81 ±0.58	74.81 ±0.58
7	57.25 ±1.78	60.80 ±0.38	63.25 ±0.63	66.45 ±1.04	68.83 ±1.04	69.55 ±0.82	71.25 ±1.09	73.55 ±0.75	77.44 ±0.59	79.25 ±1.09
8	65.59 ±1.06	69.43 ±1.08	74.41 ±1.38	75.44 ±1.45	78.10 ±0.67	77.42 ±0.97	78.16 ±0.39	80.13 ±0.99	83.92 ±0.25	84.92 ±0.25
9	73.14 ±0.99	83.00 ±2.63	84.57 ±1.40	88.03 ±0.30	90.62 ±1.33	93.02 ±0.82	94.17 ±0.66	87.44 ±0.95	89.64 ±0.66	92.64 ±0.66
10	90.51 ±0.81	97.36 ±1.47	98.08 ±1.11	95.12 ±1.39	93.59 ±1.30	95.30 ±1.00	96.64 ±0.76	95.24 ±1.89	95.77 ±0.68	95.77 ±0.68
11	95.43 ±1.08	91.27 ±1.26	91.72 ±1.33	97.28 ±1.25	98.93 ±1.61	97.89 ±0.73	98.47 ±0.56	98.08 ±0.87	90.90 ±0.99	98.90 ±0.99
12	80.14 ±0.99	96.00 ±2.63	74.57 ±1.40	78.03 ±0.30	80.62 ±1.33	81.02 ±0.82	69.17 ±0.66	99.94 ±0.95	86.64 ±0.66	88.64 ±0.66

Table No 8.

Stability Studies

Parameters	Days			
	15	**30**	**45**	**60**
Colour	No change	No change	No change	No change
Hardness(Kg/cm^2)	10.24 ± 0.47	10.90 ± 0.59	10.67 ± 0.3	10.41 ± 0.74
Drug Content (%)	98.24 ± 0.4	97.90 ± 0.59	99.67 ± 0.3	98.41 ± 0.74
***In-vitro* diso studies (in 12hr)**	97.94 ± 0.9	99.51 ± 0.75	99.22 ± 0.3	98.01± 0.47

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