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DESIGN AND EVALUATION OF pH TRIGGERED OSMOTICALLY CONTROLLED SYSTEM FOR ILEO-COLONIC DRUG DELIVERY

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ABSTRACT

The aim of the present work is to formulate and evaluate pH triggered osmotic pump tablet of prednisolone to improve the bioavailability and target the drug to ileo-colonic, this will also increase patient compliance. Osmotic pump tablets of prednisolone were prepared by making molecular inclusion with beta cyclodextrin. These inclusion complexes were used in the formulation of controlled porosity osmotic pump with different concentrations of osmogens. Wet granulation technique was employed in making the granules. pH sensitive coating is done with mixture of Eudragit L100 and Eudragit S100, which dissolves at pH above 6.8. Formulated tablet were characterized by pre-compression and post compression parameters. The in-vitro drug release studies were performed in phosphate buffer pH 6.8. All the results were in the standard limits of I.P. Formulated dosage form can be effective alternative to conventional dosage form, which can be effectively used in the treatment of several, Bowel disease, Ulcerative colitis, Crohn's disease, Rheumatoid Arthritis, and Cancer, etc.

Key words: pH sensitive, Osmotic pump, Molecular inclusion, β-cyclodextrin, Osmogens, Zero order release.

INTRODUCTION

Oral controlled drug delivery system can provide a continuous delivery of drugs at predictable and reproducible kinetics throughout the Gastro-intestinal transit. Also the systems that targets the drug delivery to a specific region within the Gastro-intestinal tract for either local or systemic action. 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 schedule [2]. The drug release from the oral controlled release dosage forms may be affected by pH, gastro-intestinal motility and presence of food in the gastro-intestinal 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 released characteristics can be predicted easily form the known properties of the drug and the dosing form. The oral osmotic pump tablets have many advantages, such as reducing risk of adverse reaction, zero-order delivery rate, a high degree of in vitro in vivo correlation and improving patient compliance [2].

Various approaches developed for the purpose of achieving colonic targeting include time-controlled delivery systems, pH-dependent delivery systems, pressure controlled delivery systems, prodrug an micro flora-triggered delivery systems. Among these approaches, there appears more interest in pressure controlled delivery systems achieve the goal of delivery. The below figure shows schematic diagram of CPOMT, which consists of an osmotic core, an inner semipermeable membrane layer composed of the mixture of cellulose acetate powder, and an outer enteric- coating layer [3].

Prednisolone is a synthetic glucocorticoid, a derivative of cortisol, which is used to treat a variety of inflammatory and auto-immune conditions. Prednisolone has biological half-life of 1 to 2 hours 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 gastro-intestinal tract not only to prolong its therapeutic action [4].

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In the present research, controlled porosity osmotic pump was formulated by using different combination of osmogens. Beta cyclodextrin complexation was used to improve the solubility of the drug. Chitosan is natural polysaccharide serves dual functions, osmogens as well microbially degrading agent. Concentration of osmogens, chitosan, sodium chloride and mannitol on the dependent variable i.e. percentage cumulative drug release (%CDR) and disintegration time (DT).

MATERIAL AND METHODS

Materials

Prednisolone I.P. (Bal Pharma, Bangalore), Beta-cyclodextrin (Cydex pharmaceutical, Lenexa, Kanas), Microcrystalline cellulose (Shreeji Chemical, Mumbai), PVP K-30, Sodium chloride, Mannitol, Sorbitol, Eudragit L100 and Eudragit S100 (Shreeji Chemical, Mumbai)Tri acetin, Polyethylene glycol, Isopropyl alcohol, Methanol (S.D. Fine Pvt. Ltd. Mumbai), Chitosan, Starch, Triethyl citrate (S.D. Fine Pvt Ltd. Mumbai), Talc, Magnesium stearate (Himedia Laboratories Pvt Ltd, Mumbai) all other chemical uses were of LR grade.

Methods

Complexation of Prednisolone with Beta-cyclodextrin

Beta-cyclodextrin has been used to modify drug's physico-chemical properties. In the present study, drug-cyclodextrin complex were prepared in two different ratios 1:2 and 1:4.

Kneading method

The kneaded complex of Prednisolone and beta cyclodextrin was prepared by wetting the physical mixture in a mortar with a minimum volume of ethanol/water mixture (15/85, V/V) and kneading thoroughly with a pestle to obtain a paste, which was then dried under vacuum at room temperature, sieved through a 0.25 mm sieve (# 60) and stored in a dessicator until further evaluation [5].

Phase solubility study

The phase solubility technique illustrates the evaluation of the affinity between Beta cyclodextrin and prednisolone in water. The solubility measurement of prednisolone with Beta cyclodextrin was performed according to Higuchi and Connors. An excess amount of drug (50 mg) was added to conical flasks containing an aqueous CD solution of concentration 0.014 M. The flasks were placed in orbital shaker for 3 days at 25°C. Aliquots of 2 ml were withdrawn and filtered suitably and analysed for prednisolone by measuring absorbance at 246 nm. The intrinsic solubility in water was determined form sample without CD. Study was carried out in triplicates [6].

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, and physical mixtures of drug and beta cyclodextrin complexes to study the compatibility.

Preparation of core tablets

Core tablets were manufactured by wet granulation of the dry blend of prednisolone and osmogens, microcrystalline cellulose, starch, PVP K-30, and magnesium stearate were passed through sieve #60. Granules were prepared by using starch paste as binder by sieve #16 according to the formula given in table no. dried at 54°C for about 3 hours. These granules were passed through sieve # 18/20 and lubricated with talc. Granules were compressed into tablets (each of 220 mg) were formulated on mini- rotary 6 point tablet press using 8mm standard concave punches. Two different batches were prepared with two different osmogens at varying concentrations. Formulations of different batches are shown batches are shown in Table no 1.

Coating of Tablets

The core tablets of Prednisolone were coated with cellulose acetate in an automated perforated pan. The compositions of the coating solution used for coating solution used for coating tablets are given in Table 2. All the tablets were coated with coating solution A.

Various components of the coating solution were added to the solvent mixture in s sequential manner. The component added first was allowed to dissolve before the next component was added. Core tablets of prednisolone were placed along with 500 gm of filler tablets. The rotating speed of the pan was kept 20 rev/min. The coating was performed using spray gun with nozzle diameter 1 mm and the spray rate of 3-5 ml/min atomization pressure was kept 1kg/cm^2 while outlet temperature was kept 45°C [7].

Enteric Coating

The enteric coating of tablets was performed by pan coating. The enteric coating solution was prepared by dissolving Eudragit S100 and Eudragit L100 in ratio of 3:1 in acetone at 12%w/v. Tablets were coated until the weight of the tablets were increase to 10% w/v. Evaporation of the solvent was performed by using a hot air gun [8].

Evaluation of Tablets

The prepared tablets were evaluated for the following parameters Hardness (Pfizer hardness tester),

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Weight Variation (Electronic balance), Friability (Roche friabilator) and Drug content (Assay, UV- analysis).

Disintegration Test

Disintegration test was performed on each formulation for checking intactness of coating. Disintegration apparatus (Electro lab Ltd. ED-2L) was used and I.P. method was followed. Six tablets of each formulation were tested for disintegration. Tablets were firstly tested for disintegration. Tablets were firstly tested in water for 5 minutes then in 0.5N Hcl for 2 hours to see the damage to the coat.

***In-vitro* release studies**

The in-vitro dissolution studies were carried out using USP dissolution apparatus type-II in different medium. Buffer stage: Two hours in 900ml of 1.2 pH buffer, three hours in 900ml of 7.4 pH buffer and seven hours in 900ml of 6.8 pH buffer solution at 100 rpm. Dissolution test was carried out for a total period of 12 hours. Analysis for prednisolone was done by UV-spectrophotometer at 246 nm.

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 [9].

RESULT AND DISCUSSION

Phase-solubility Study

The phase solubility diagram of the prednisolone with β-Cyclodextrin is shown in figure 2. The intrinsic solubility in water was determined from sample without β-Cyclodextrin. Study was carried out in duplicates. The intrinsic solubility was found to be 252 mg/l, slightly higher than the reported value 200 mg/l. The phase solubility diagram for prednisolone β-Cyclodextrin showed A_L type curve according to Higuchi and Connors. The aqueous solubility of drug was increased linearly as a function of the concentration of β-Cyclodextrin. Straight line was fitted to the A_L type diagrams with regression coefficient 0.9849.

Phase solubility diagram of prednisolone and cyclodextrin indicated a liner increase in solubility of prednisolone as the concentration of cyclodextrin increases. Straight line was fitted according to A_L type diagram with the R^2 0.9849.

Influence of amount of Sodium Chloride

CPOMTs with different amounts of Nacl as an osmotic pressure accelerant 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 form the core.

Influence of amount of Mannitol

CPOMTs with different amounts of Mannitol as an osmotic pressure accelerant in the core were prepared. The results are shown in Fig 3. A significant influence was observed with an increasing amount of Mannitol, the release rate was accelerated, because the increasing osmotic pressure made more drug release form the core.

Influence of amount of pore forming agent (Sorbitol)

In order to assess the effects of concentration of pore former on in vitro drug release, the optimized formulations was coated with a coating solutions (A, B, C) containing varying amount of pore formers (Sorbitol) i.e. 10%, 12.5%, and 15% as per the procedure described earlier. The influence of increasing concentration of pore former on in vitro drug release was studied.

Influence of different coating weights

To study the influence of weight gain of the coating on drug release, optimum batch of prednisolone were coated as per procedure describe earlier, so as to get tablets with different weight gains (10, 12, and 14% w/w). The tablets with different weight gain were evaluated for drug release and effect of weight gain on in vitro release of prednisolone was studied [10].

Compatibility studies

Differential Scanning Calorimetry (DSC Analysis)

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

Fourier Transform Infrared Spectroscopy

IR spectra of pure drug prednisolone and combination of prednisolone and excipient were obtained, which are shown in Fig 9, 10. All the characteristic peaks of prednisolone were present in spectra thus indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug.

EVALATION OF POWDER BLENDS

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 3.[11]

Pre-compression parameter

Angle of repose

Angle of repose was determined by using fixed funnel method. The blend was poured through a funnel

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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 (θ) was calculated using the formula.

$$\theta = tan^{-1}\left(\frac{h}{r}\right)$$

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;

$$Bulk\ Density = \frac{Mass\ of\ powder\ blend}{Bulk\ volume\ of\ blend\ powder}$$

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;

$$Tapped\ Density = \frac{Mass\ of\ powder\ blend}{Tapped\ volume\ of\ powder\ blend}$$

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 Carr's index which is calculated as follows. The value below 16% indicates a powder with usually good flow characteristics, whereas above 23% indicate poor flowability.

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} X\ 100$$

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 combination of functional excipients are given in table no 5.

Thickness

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

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.

Tablet friability

The friability of the tablets was measured in a Roche friabilator. Tablet sample of a known weight (Wo) 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.

$$\%\ friability = \frac{Wo - W}{Wo} X\ 100$$

Drug content uniformity

Five tablets from each were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing from this equivalent to 20mg of Prednisolone was taken in 100 ml volumetric flask and diluted with methanol to 100ml. Further appropriate dilution was made and absorbance was measured at 246 nm.

***In vitro* drug release of micro-porous membrane osmotic tablet**

The release studies were conducted in dissolution medium with 0.1N Hcl pH 1.2; phosphate buffer pH 6.8 with a rotation speed of 100 rpm at a 37±0.5°C. Samples of 10 ml were withdrawn at specified time points (0, 1, 2, 3, 4, 5, 6, 8, 10, 12hr) and replaced with fresh dissolution medium. Obtained samples were properly diluted and analysed by UV absorption measurement at 246 nm.

STABILITY STUDY

Accelerated stability studies (AST) was carried for optimized batch F4 exposing it to 40°C/75% RH for 15, 30, 45, and 60 days. The sample was analysed for colour, hardness, Drug Content and in-vitro dissolution studies [12].

FUTURE SCOPE

Future possibility for improvement in pH triggered controlled porosity osmotic pump tablet and drug delivery are very bright, but they are still relatively new technologies. Several drug delivery technologies that can be leveraged on improving drug therapy form controlled porosity osmotic pump tablets have yet to be fully realized. In future the conventional dosage forms can be well replaced by CPOMT because of the greater advantages over the other conventional dosage forms and more patient compliance.

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Fig 1. Schematic diagram of CPOP before and during operation

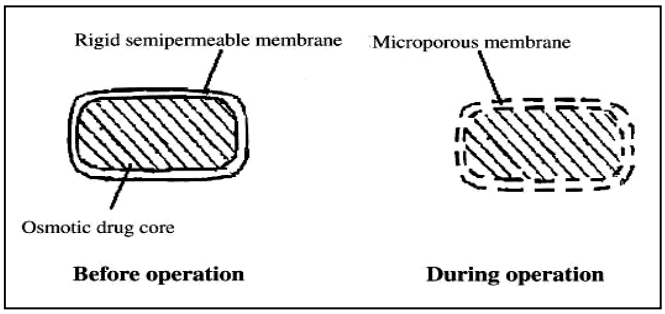

Fig 2. Phase solubility graph of Prednisolone with beta cyclodextrin

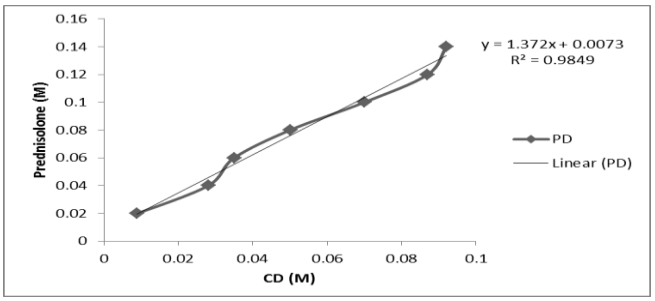

Fig 3. Influence of amount of Sodium chloride

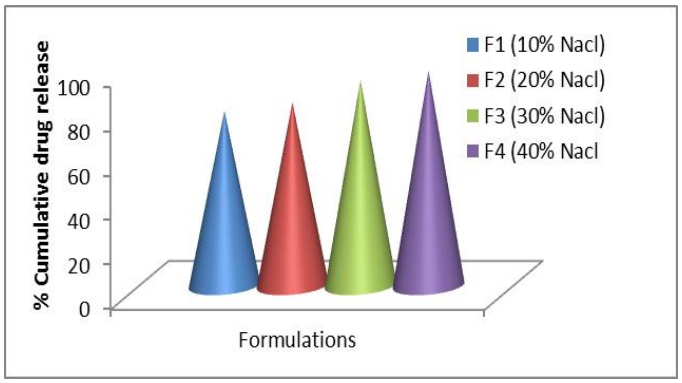

Fig 4. Influence of amount of Mannitol

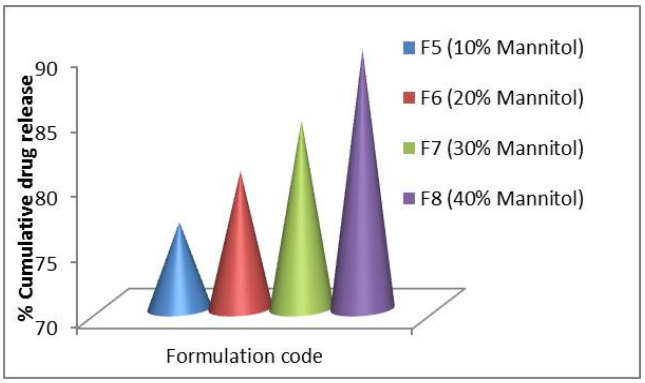

Fig 5. Influence of pore former on drug release

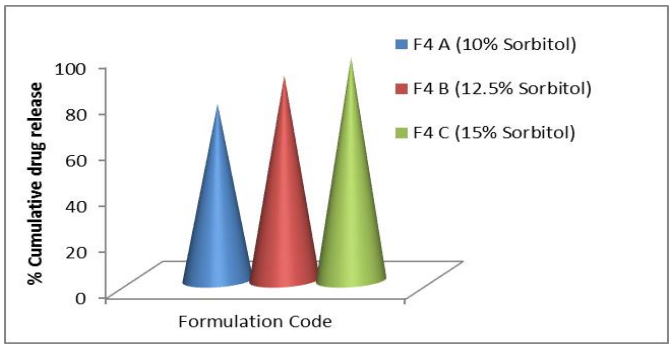

Fig 6. Influence of different coating weights

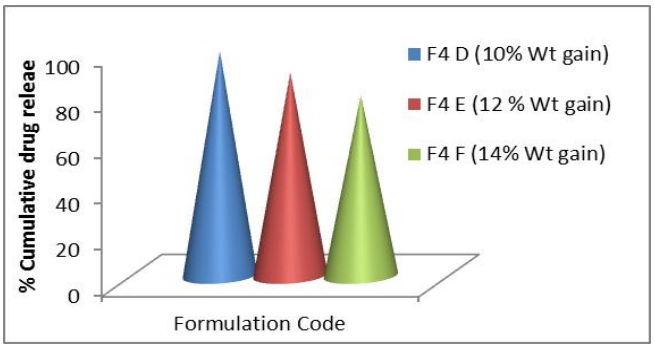

Fig 7. DSC of pure prednisolone

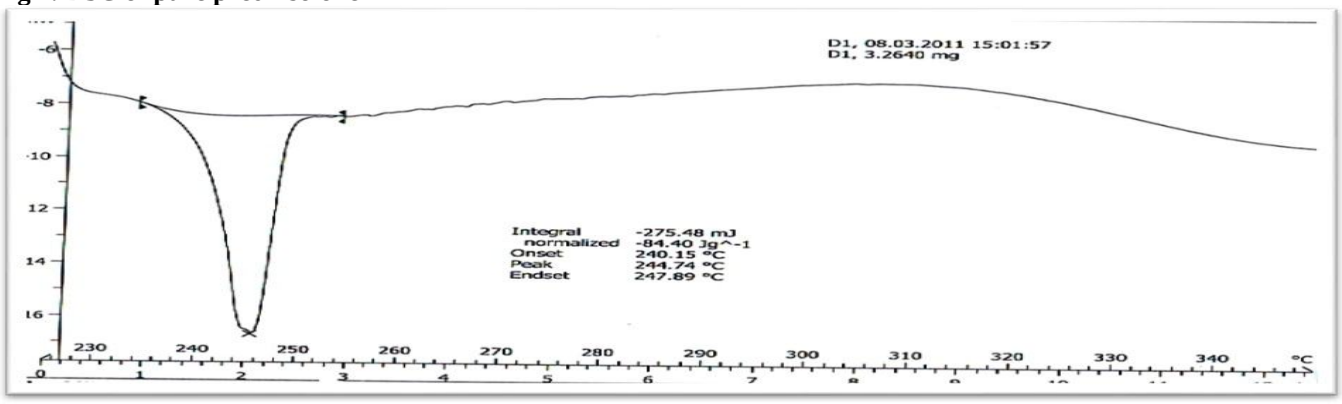

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Fig 8. DSC Thermogram of prednisolone-CD Kneading complex (1:4)

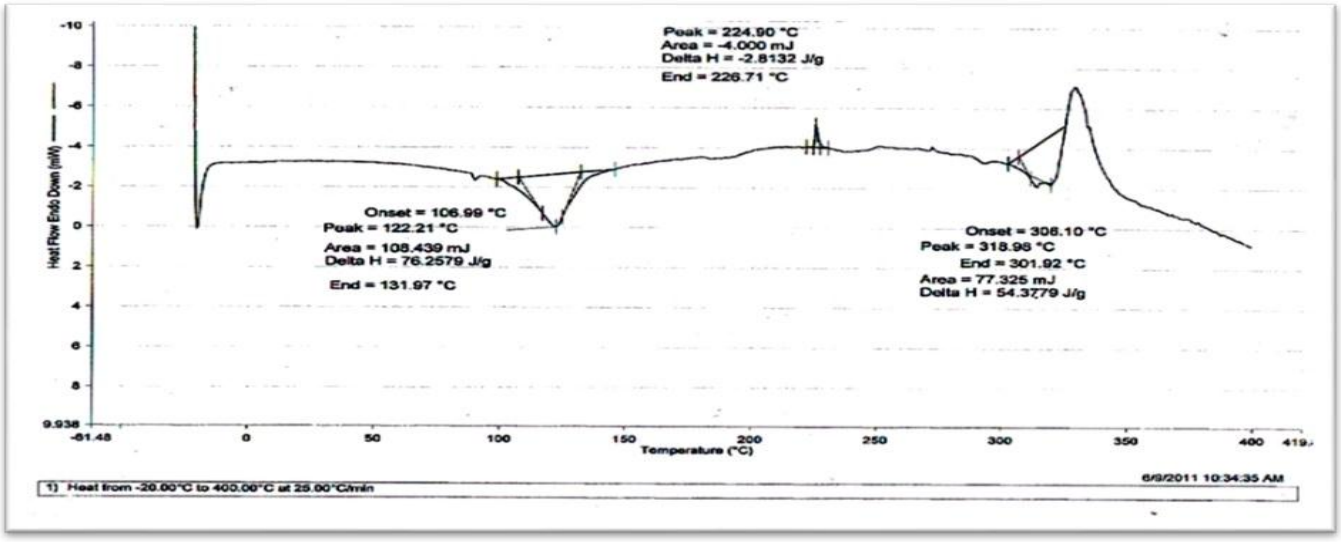

Fig 9. FTIR of pure prednisolone

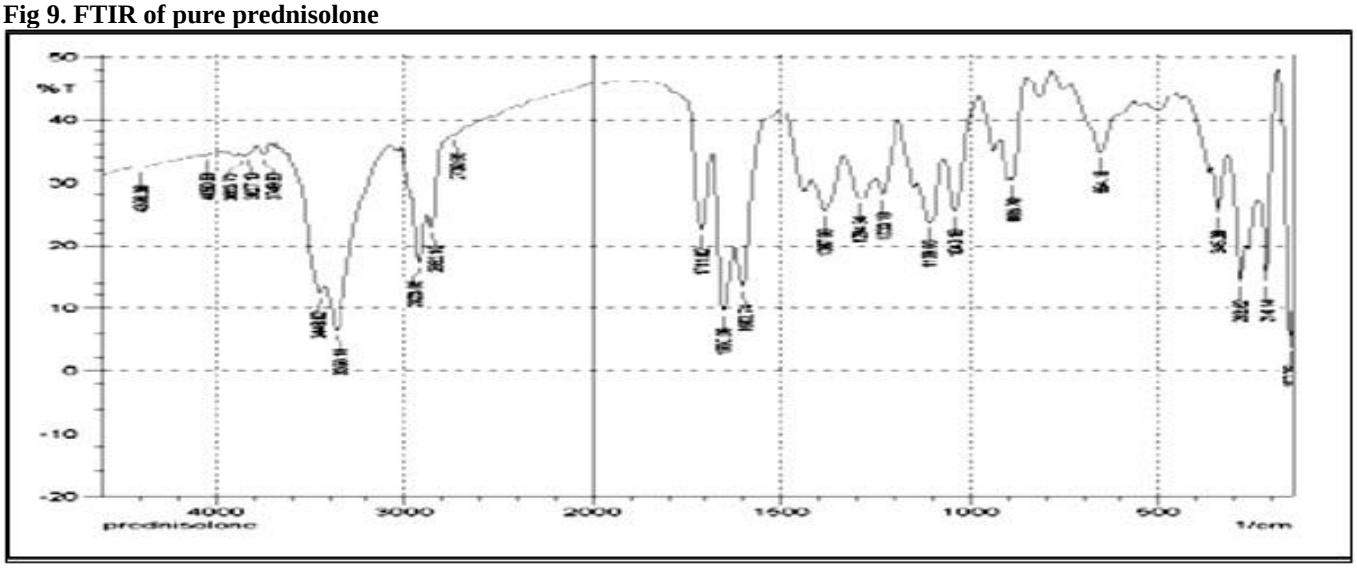

Fig 10. FTIR of prednisolone-CD Kneading complex (1:4)

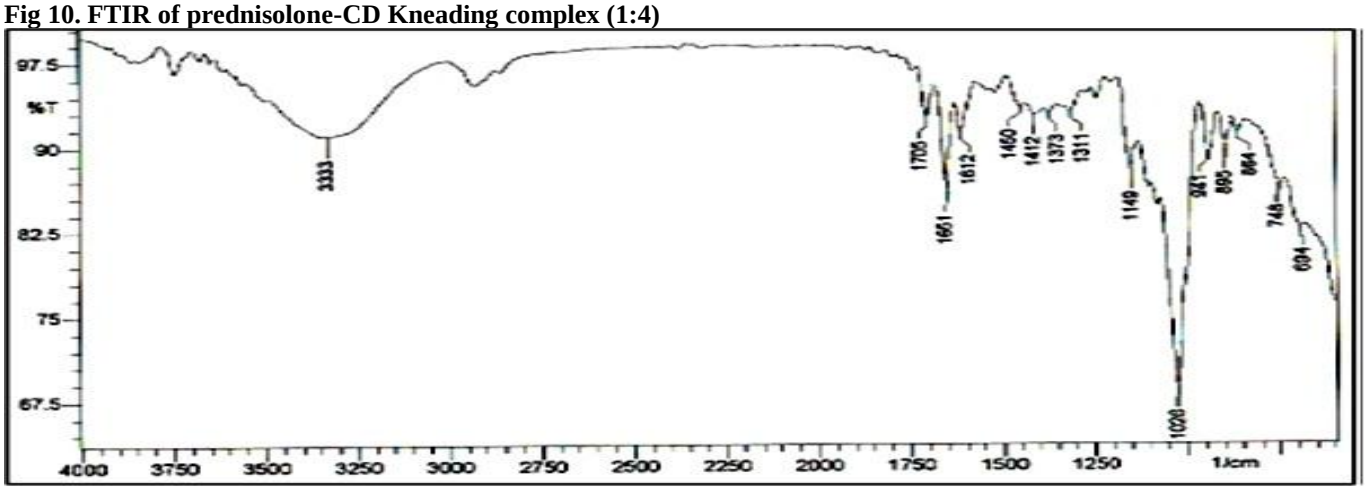

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Fig 11. Cumulative % drug release of coated tablets

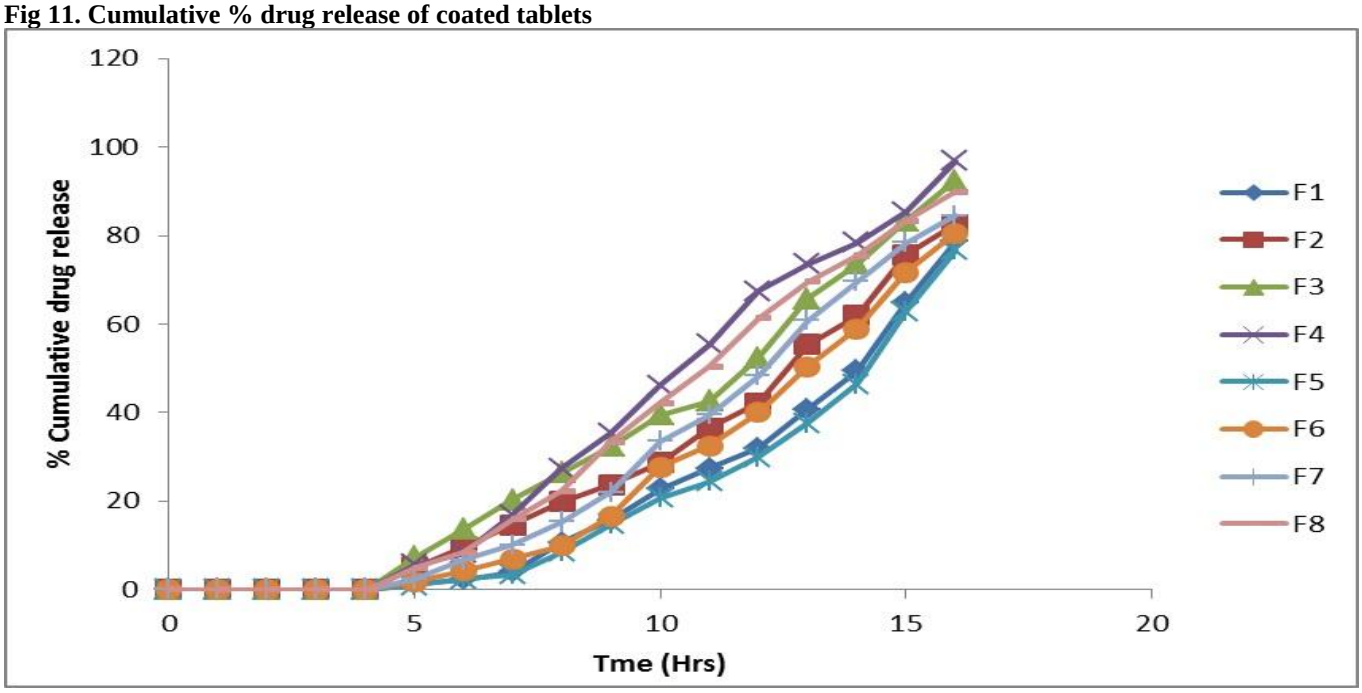

Table 1. Composition of the controlled porosity osmotic pump tablets of Prednisolone.

Formulation Ingredients	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Binary complex (1:4, 20mg prednisolone)	100	100	100	100	100	100	100	100
PVP K-30	40	40	40	40	40	40	40	40
Sodium Chloride	10	20	30	40	--	--	--	--
Mannitol	--	--	--	--	10	20	30	40
Microcrystalline cellulose	60	50	40	30	60	50	40	30
Starch Paste (10% w/v)	2	2	2	2	2	2	2	2
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3
Total Weight	220	220	220	220	220	220	220	220

Table 2. Composition of coating solution

Ingredients	Coat code A	Coat code B	Coat code C
Cellulose acetate	2.8 (70%)	2.7 (67.5%)	2.6 (65%)
Sorbitol	0.4 (10%)	0.5 (12.5%)	0.6 (15%)
Tri-acetin	0.2 (5%)	0.2 (5%)	0.2 (5%)
PEG 400	0.6 (15%)	0.6 (15%)	0.6 (15%)
Dichloromethane : Methanol	Up to 100 ml	Up to 100 ml	Up to 100 ml

Table 3. Phase solubility diagram of prednisolone-cyclodextrin system

Conc. Of Prednisolone (M)	Conc. of Cyclodextrin (M)
0.009	0.02
0.028	0.04
0.035	0.06
0.050	0.08
0.070	0.10
0.087	0.12
0.092	0.14

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Table 4. *In vitro* dissolution

Sr. No	Time (hours)	% Cummulative Drug Release							
		F1	F2	F3	F4	F5	F6	F7	F8
1	4	0	0	0	0	0	0	0	0
2	5	1.44	5.1	7.36	5.62	1.04	1.8	2.36	4.92
3	6	2.30	9.6	13.64	8.27	2.34	4.3	6.71	8.33
4	7	4.0	14.6	20.34	16.84	3.4	6.96	10.14	15.84
5	8	10.64	19.9	26.37	27.34	8.46	9.92	15.34	22.34
6	9	15.7	23.64	32.4	35.31	14.7	16.61	22.04	33.31
7	10	22.76	28.65	39.54	46.21	20.76	27.75	33.54	42.21
8	11	27.41	36.48	42.57	55.37	24.41	32.58	39.51	50.37
9	12	31.99	42.1	52.42	67.39	29.99	40.1	48.22	61.39
10	13	40.69	55.37	65.79	73.51	37.69	50.37	60.79	69.51
11	14	49.47	61.87	73.62	78.35	46.47	58.87	69.62	75.35
12	15	64.85	75.64	83.42	85.35	62.85	71.64	78.42	83.32

Table 5. Pre compression evaluation of the osmotic pump tablets

Formulation Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner's Ratio	Carr's Index	Angle of Repose
F1	0.59	0.70	1.22	15.71	25.23
F2	0.58	0.69	1.18	15.94	26.36
F3	0.59	0.65	1.1	9.23	24.55
F4	0.56	0.66	1.17	15.15	23.36
F5	0.58	0.68	1.17	14.70	26.34
F6	0.62	0.71	1.14	12.67	24.32
F7	0.57	0.69	1.21	17.36	26.21
F8	0.59	0.70	1.18	15.71	25.36

Table 6. Evaluation of the core and coated tablets

Formulation Code	Thickness (mm) (n=3) (Mean ± SD)		Average weight (mg) (n=10) (Mean ± SD)		Hardness (Kg/cm^2) (n=10) (Mean ± SD)		Friability (%) (n=10)	Content uniformity (%) (n=5)
	Before coating	After coating	Before coating	After coating	Before coating	After coating		
F1	**4.12±0.052**	**4.68±0.077**	**222.70±0.986**	**252.06±0.653**	**6.78±0.291**	**9.36±0.181**	**0.0623**	**102.6±2.44**
F2	**4.16±0.074**	**4.59±0.058**	**219.52±0.455**	**258.61±4.881**	**7.36±0.294**	**9.98±0.216**	**0.0645**	**104.82±3.08**
F3	**4.13±0.133**	**4.63±0.091**	**220.86±0.152**	**260.52±3.851**	**6.97±0.254**	**9.21±0.122**	**0.0506**	**99.87±2.96**
F4	**4.09±0.071**	**4.58±0.113**	**223.66±1.422**	**257.85±4.057**	**6.53±0.227**	**9.75±0.113**	**0.0401**	**101.57±1.93**
F5	**4.14±0.084**	**4.61±0.054**	**219.85±0.305**	**259.28±3.607**	**7.06±0.352**	**9.56±0.307**	**0.0482**	**104.18±2.45**
F6	**4.12±0.114**	**4.62±0.091**	**219.19±0.604**	**242.45±2.878**	**7.25±0.268**	**9.36±0.215**	**0.0771**	**97.51±3.18**
F7	**4.14±0.067**	**4.61±0.126**	**218.59±0.877**	**256.67±1.071**	**6.98±0.297**	**9.52±0.236**	**0.0718**	**99.67±2.35**
F8	**4.12±0.039**	**4.64±0.078**	**223.28±1.249**	**245.74±1.198**	**7.22±0.329**	**9.28±0.298**	**0.0685**	**102.47±2.49**

CONCLUSION

The study conclusively demonstrated significant results of Prednisolone and dissolution of 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 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 with specific limits. Hence, at the end of this investigation it can be concluded that controlled porosity osmotic tablet of prednisolone was successfully prepared by conventional wet granulation method using different concentration of osmogens and polymer with the objectives of this study are achieved and the optimized batch was F4.

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