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Research Article

FORMULATION AND EVALUATION OF ONCE DAILY OSMOTIC TABLET OF KETOPROFEN

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ABSTRACT

Objective: The aim of present investigation was to develop a controlled porosity osmotic pump (CPOP) based drug delivery of Ketoprofen to be taken once daily.

Methods: Unlike the elementary osmotic pump (EOP) which consists of an osmotic core with the drug surrounded by a semi permeable membrane drilled with a delivery orifice, controlled porosity of the membrane is accomplished by the use of channelling agent in the coat. Dextrose: fructose was used as an osmogent. Cellulose acetate (CA) was used as the semi permeable membrane and PEG 4000 was used as pore forming agent.

Results: The drug release profile of CPOP tablet increased with the amount of osmogent and increase in concentration of pore former whereas percent weight gain produced a significant effect on release profile. Optimization was done using 3^2 factorial design considering two independent factors at three levels. Data was evaluated statistically by Stat Ease Design Expert 7.1.4 software. Optimized formulation F5 exhibited zero order kinetics with a drug release of 99.85% in 24 hrs. SEM studies showed the formation of pores in the membrane. The optimized formulation F5 were subjected to stability studies as per ICH guidelines and was found to be stable.

Conclusions: This system is simple to prepare with no drilling required and has a potential to be used in the field of controlled delivery of Ketoprofen.

Keywords: Controlled porosity osmotic pump (CPOP); Ketoprofen; Osmogent; Cellulose acetate; pore former.

INTRODUCTION

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS). Once-daily controlled release preparation is often desirable. However, drug release from oral controlled release dosage forms may be affected by pH, gastric motility, and presence of food [1]. Osmotic devices are most promising strategy based system for controlled drug delivery. They are among the most reliable controlled drug delivery system and could be employed as oral drug delivery systems or implantable device. Osmosis is an aristocratic bio-phenomenon, which is exploited for the development of delivery systems with every desirable property of an ideal controlled drug delivery system.Osmotic drug delivery system provides greater effectiveness in the treatment of chronic conditions by providing zero order drug release and which may reduce side effects and also better patient compliance [2].

Recently, osmotic tablets have been developed the delivery orifice is formed by the incorporation of a leachable component in the coating [3].Once the tablet comes in contact with the aqueous environment, the water-soluble component dissolves, and an osmotic pumping system results. Subsequently, water diffuses into the core through micro porous membrane, setting up an osmotic gradient and thereby controlling the release of drug. The release rate from these types of systems dependents on the coating thickness, level of leach in the tablet core, and osmotic pressure difference across the membrane, but is independent of the pH and agitation of the release media [3].

Ketoprofen is used for the long term treatment and management of various conditions like acute and chronic rheumatoid arthritis, osteoarthritis, ankylosing spondylitis [4]. Dosing frequency is high, 3 times or 4 times in a day, Ketoprofen has a short biological half-life of 1-3 hr. Adverse and side effects which are the limitation of conventional dosage form due to fluctuation in drug absorption as the dosing frequency is high, Ketoprofen is devoid of hepatic first pass effect and extensively absorbed through GIT [4]. Thus delivery of Ketoprofen through osmotic tablets may be used as means to overcome the limitations encountered in Ketoprofen conventional dosage forms.

The objective of the study was to develop osmotically controlled release tablets of Ketoprofen to be taken once daily. Dextrose: fructose was used as the osmogent. The tablets were coated with cellulose acetate as the semi permeable membrane containing PEG 4000 as pore forming agent.

MATERIALS AND METHODS

Materials

Ketoprofen was obtained from Pell Tech Health Care Pvt. Ltd. Mumbai; PVP K-30 and Cellulose acetate with 39.8% acetylene content were obtained as a gift sample from Wockhardt Ltd., Aurangabad; microcrystalline cellulose PH 101, sodium lauryl sulphate, magnesium stearate, PEG-4000 were obtained from Research fine lab., Mumbai; dibutyl phthalate, acetone were obtained from Thermofisher Scientific Ind. Pvt. Ltd. Mumbai; dextrose and isopropyl alcohol were obtained from Universal Lab. Pvt. Ltd. Mumbai; fructose was obtained from Merck Specialities Pvt. Ltd. Mumbai, talc (Himedia lab. Pvt. Ltd. Mumbai).

Methods

Drug excipient interaction studies

DSC is a very quick and accurate method to test and select the best candidates for stable dosage forms. In the present study the drug and excipient mixtures were prepared in the ratio 1:1 and kept in the stability chamber (Thermolab) maintained at 40°C and 70 % RH for 10 days. After 10 days the samples were analyzed for chemical interaction by using Shimadzu DSC-60.

Formulation of porous osmotic pump tablet

The core tablets for primary batches were formulated using Dextrose: Fructose as an osmogent, microcrystalline cellulose used as diluent, magnesium stearate as a lubricant and talc used as glidant, three formulations were made using different level of osmogent as shown in Table 1. The core tablets were coated with 2% w/w of cellulose acetate using different level of pore formers, drug release profile and disintegration time of uncoated tablets were evaluated. The drug, osmogent and diluent were weighed accurately, passed through 40 mesh sieve and blended. This mass was granulated using IPA as granulating solvent. The resulting wet mass was passed through a sieve no. #10 and the granules were dried at 50°Cfor 15 min to get a loss on drying (LOD) value between 1% and

1.2%, after which they were passed through sieve no #16. Dried granules were blended with magnesium stearate and talc. The prepared granules were evaluated for parameters like bulk density, tapped density, Carr's index, angle of repose, and Hausner's ratio [5].

Table 1: Formulations of tablets with Dextrose: Fructose (Osmogent)

Ingredients (mg)	P1	P2	P3
Ketoprofen	200	200	200
Dextrose:Fructose	75:75	100:100	125:125
Microcrystalline cellulose	50	56	34
SLS	15	25	35
PVPK-30	13	15	20
IPA	q.s	q.s	q.s
Magnesium stearate	2	2	3
Talc	2	2	3
Total	432	500	545

Coating of tablet

Cellulose acetate (2% w/v) in acetone: isopropylalcohol (80:20) containing dibutypthalate 2% w/v, different levels of PEG 4000 i.e. 35, 40, 45 % w/w was used as coating formulation. Talc and titanium dioxide were used as antiadherant and opacifier, respectively, in concentration of 1%. The tablets were coated in a conventional pharma R & D coater (Ideal cures Pvt. Ltd), 4 inches with 3 baffled stainless steel pan by spray coating process. Initially the tablets were kept at 40°C for 10 min while the pan rotated at 20 rpm. The rotating speed was then increased to 20-45 rpm and the coating solution was sprayed at a rate of approximately 1-2 ml/min. The atomizing pressure was adjusted to 1-2 kg/cm^2, and the inlet and outlet temperatures were varied from 35-55°C. The process was continued until the whole solution was sprayed onto the tablets. The coated tablets were rotated for a further 15 min under blower.

Formulation of factorial batches

Based on the of evaluation of primary batches, formulation P3 was optimized using 3^{2}factorial design (Table 2) for two factors i.e. pore former (PEG 4000) and % weight gain to obtain nine formulations as shown in Table 3. Coated tablets were evaluated for % weight gain and thickness of film. Thickness of film was calculated using the following equation,

Wall thickness (h) = r (1-p) d_1/3[pd_2 + (1-p) d_1]

Where, r = Arithmetic mean radius of the tablet, d_1 = density of the core material (tablet), d_2 = density of the coating material, p = proportion of the medicament.

Table 2: Factorial Design

Level	-1	0	+1
Pore former (PEG 4000)	35 %	40 %	45 %
% weight gain	2 %	4 %	6 %

Table 3: Formula for factorial batches

Batch code	% weight gain [X1]	Level of Pore former[X2]
F1	-1	-1
F2	0	-1
F3	+1	-1
F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1

Drug content

For determining the drug content, 20 tablets were taken and crushed; powder equivalent to 25 mg of ketoprofen was accurately weighed and transferred to 250 ml volumetric flask. 150 ml of methanol was added and shaken for 10 min and further volume made up to 250 ml by using methanol. 10 ml of this solution was further diluted to 100 ml with methanol and the absorbance of resulting solution was measured at about 258 nm (Shimadzu UV-1800, Japan) using 662 as value of A (1% 1cm) [6].

Scanning electron microscopy (SEM)

Coating membranes of formulation obtained before and after complete *in-vitro* dissolution of core contents were examined for their porous morphology by scanning electron microscope (SEM). Before dissolution, the tablets were cut with a sharp blade and coating membrane was taken out. This membrane was cleaned with dried cloth to remove any adherent particles and was used for SEM. Similarly, coating membrane was taken out from the tablets after 24 hr of dissolution study and was used for SEM. The coating membrane was carefully washed 3-4 times with water to remove any adherent solid particles. Coating membranes were dried at 45°C for 12 hours and stored between sheets of wax paper in a dessicator until examination. The small pieces of coating membranes were placed on a spherical brass stub (12 mm diameter) with a double backed adhesive tape in such a way that the outer portion of coating membrane comes in front of electronic beam and was examined under scanning electron microscope.

Dissolution studies

The release rate of Ketoprofen from CPOP (n=3) was determined from primary batches and factorial batches. Batches were evaluated by studying the release study for first 2 hr in 900 ml 0.1 N HCl as dissolution medium, then remaining 24 hrs in 900 ml dissolution medium of phosphate buffer pH 7.4 using USP type II (Paddle) dissolution apparatus with 100 rpm at 37°C ± 0.5°C. The samples

(10 ml) were withdrawn every hour for 12 hrs than the sample is withdrawn after every 2 hrs up to 24 hrs. The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through whatman filter paper and analyzed spectrophotometrically at 258 nm (Shimadzu UV-1800, Japan).

Kinetics of drug release

The dissolution profile of all the batches were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model [7].

Accelarated stability studies

On the basis of *in-vitro* evaluation, the batch F5 formulations were packed in strips of 0.04 mm thick aluminium foil laminated with polyvinyl chloride (PVC) and stored in ICH certified stability chamber for the accelerated stability studies. The tablets were stored in the stability chamber at the controlled conditions of temperature and relative humidity. The stability of the tablets was studied for the duration of 90 days at temperature 40°C ± 2°C and 75% ± 5% relative humidity [8]. The tablets was then evaluated for various parameters viz. thickness, hardness, drug content and release studies.

RESULTS AND DISSCUSSION

Drug excipient interaction studies

DSC was carried out for drug and physical mixture of drug and excipient which are directly in contact with drug. Physical mixture was made in 1:1 combination of drug and excipient, in Figure 1 and 2, it indicates a sharp melting endothermic peak at 96.81°C and for physical mixture it is found to be 96.23°C. DSC analysis shows slight change in endothermic peak (melting point) of Ketoprofen because of presence of other excipients, or it may be due to change in geometry.

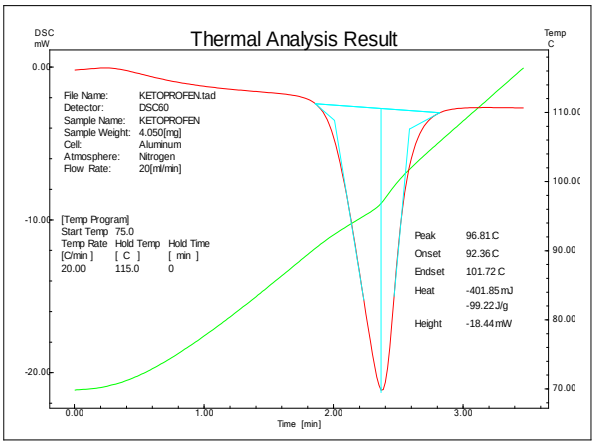

Fig. 1: DSC thermograph of Ketoprofen

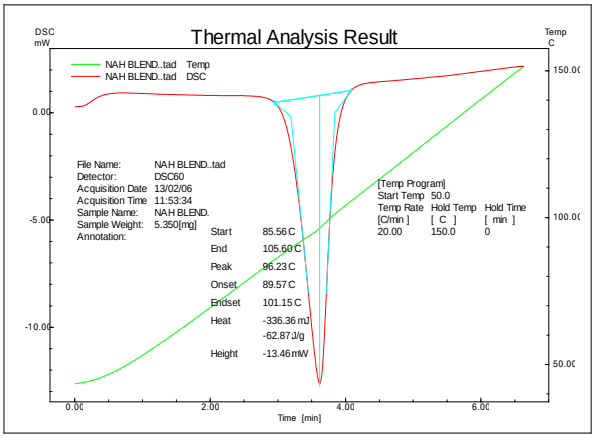

Fig. 2: DSC thermograph of Ketoprofen physical mixture

Formulation of porous osmotic pump tablet

Disintegration time and drug release profile of primary batches is as shown in Table 4 and 5 respectively. Formulation P3 shows optimum release containing Dextrose: Fructose mixture (125:125) as an osmotic agent and 25 % PEG 4000 as pore former.

Table 4: Disintegration time for primary batches

Batch code	Disintegration time
P1	3 hrs
P2	1 hr 24 min
P3	58 min

Table 5: Drug release profiles of primary batches.

Time	% Drug release (n ± SD)*		
(hr)	P 1	P 2	P 3
1	01 ± 0.21	2 ± 0.95	3.43 ± 0.92
2	02 ± 0.82	2.87 ± 0.74	6.22 ± 0.56
3	2.7 ± 0.55	4 ± 0.56	9.00 ± 0.52
4	4 ± 0.85	6.12 ± 0.31	12.02 ± 0.40
5	4.8 ± 0.92	9.11 ± 0.60	18.00 ± 0.68
6	6 ± 0.42	11 ± 0.35	26.02 ± 0.71
7	8 ± 0.65	13.21 ± 0.52	32.22 ± 0.53
8	9 ± 0.50	18 ± 0.50	34.43 ± 0.85
9	11 ± 0.65	19.32 ± 0.62	48.11 ± 0.15
10	12.5 ± 0.6 0	24.04 ± 0.70	52.14 ± 0.32
11	14.2 ± 0.35	25.78 ± 0.55	54.98 ± 0.35
12	15.8± 0.55	27.60 ± 0.35	57.32 ± 0.42
16	18.66 ± 0.88	34.25 ± 0.55	62.99 ±1.20
20	22.58 ± 0.98	43.78 ± 1.02	69.33 ±1.04
24	24.98 ± 0.98	48.22 ± 0.87	74.67 ± 0.43

(*SD- Standard deviation, n=3)

Formulation of factorial batches

The granules were investigated for their various derived properties as shown in Table 6. All formulated osmotic core tablet batches were dull white with smooth surface, circular curved faced with good texture. The thickness of the tablet was found to be 4.3 to 4.5 mm, due to constant tablet press setting across all batches irrespective of weight variation. Thickness depended on punch size (13 mm) and tablet weight (545 mg); coefficient of variation (based on 20 tablets/ batch) for each batch was less than ± 6 %, which indicates good thickness uniformity. Diameter of core tablet was 13 mm for each formulation. The hardness of the tablet was found to be in the range of 3.5 to 4 kg/cm^2. This ensured good mechanical strength. Drug content was uniform within each batch and ranged from 92-110% of the theoretical value (Table 7).

Table 6: Physical properties of the Granules for batch F 1 to F9

Batch Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio (%)	Angle of repose θ
F1	0.74 ± 0.00	0.81 ± 0.00	13.78 ± 0.01	1.12 ± 0.06	18.1±0.08
F2	0.73 ± 0.01	0.82 ± 0.02	12.50 ± 0.28	1.12 ± 0.01	18.17±0.1
F3	0.73 ± 0.04	0.79 ± 0.02	14.2 ± 0.62	1.18 ± 0.02	17.21±0.14
F4	0.73 ± 0.09	0.82 ± 0.00	10.75 ± 0.00	1.12 ± 0.03	18.10±0.24
F5	0.74 ± 0.02	0.82 ± 0.12	13.20 ± 0.47	1.17 ± 0.07	17.44±0.52
F6	0.72 ± 0.07	0.81 ± 0.20	14.50 ± 0.78	1.20 ± 0.08	19.21 ±0.35
F7	0.73 ± 0.04	0.80 ± 0.07	12.44 ± 0.64	1.12 ± 0.04	17.56 ±0.03
F8	0.75 ± 0.02	0.82 ± 0.02	15.94 ± 0.62	1.16 ± 0.02	16.49 ±0.35
F9	0.74 ± 0.08	0.81 ± 0.02	14.80± 0.35	1.12 ± 0.01	18.98 ±0.37

Table 7: Evaluation of Ketoprofen uncoated tablet

Batch Code	Thickness (mm)	Friability (%)	Hardness (Kg/ cm^2)	Uniformity of weight (mg)	Drug content (%)	Disintegr-ation time (min)
F1	4.3± 0.01	0.52 ± 0.03	3.8 ± 0.57	545 ± 2.09	99.23±1.10	62±3
F2	4.3 ± 0.04	0.55 ± 0.02	3.6 ± 0.76	543 ± 1.48	100.05±1.12	58±2
F3	4.3 ± 0.03	0.76 ± 0.01	3.8 ± 0.88	543 ± 2.47	99.45±0.64	61±2
F4	4.3 ± 0.05	0.49 ± 0.04	3.9 ± 0.54	545 ± 1.98	101.02±1.08	60±3
F5	4.3 ± 0.08	0.63 ± 0.02	3.5 ± 0.58	546 ± 2.86	99.48±0.19	59±2
F6	4.3 ± 0.04	0.55 ± 0.03	3.7 ± 0.76	543 ± 1.48	99.33±1.10	57±3
F7	4.3 ± 0.03	0.52 ± 0.01	3.7 ± 0.54	544 ± 1.98	99.98±0.52	61±4
F8	4.3± 0.01	0.34 ± 0.03	4.6 ± 0.88	544 ± 2.47	101.91±0.64	58±2
F 9	4.3 ± 0.02	0.22 ± 0.50	5.3 ± 0.43	545 ± 2.06	102.78±1.54	60±1

Scanning electron microscopy (SEM)

Cellulose acetate (CA) membranes of primary formulation (F5) obtained before and after dissolution were studied by SEM. Membranes obtained before dissolution clearly showed nonporous region (Figure 3). After 24-hour dissolution, the exhausted membrane contained plasticizer (DBT 2%) and pore former (PEG-4000, 40 %) clearly showed a micro-porous region (pores) in range of 5 to 5000 µm (Figure 4). Since PEG-4000 was present in coating membrane, the leaching of it from the membrane lead to formation of pores, and thus causes the release of drug from the core.

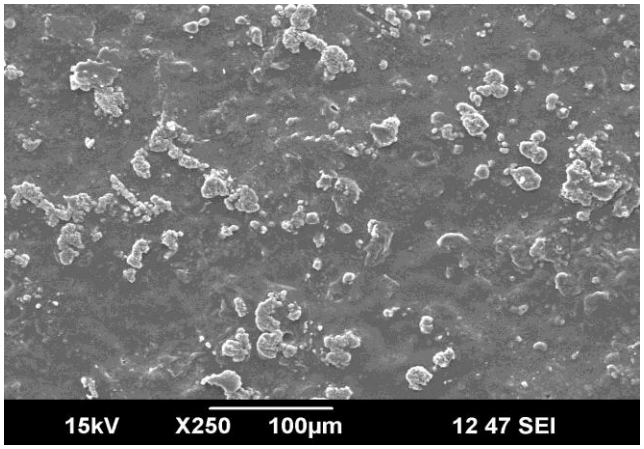

Fig. 3: SEM micrograph of coating membranes of F5 formulation before dissolution

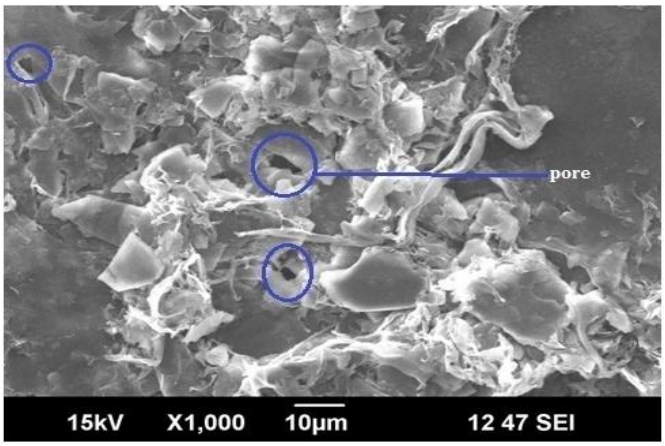

Fig. 4: SEM micrograph of coating membranes F5 formulation after dissolution

Dissolution studies

It was evident that with an increase in concentration of pore former the drug release from the system increased (Table 8 and Figure 5). Percent weight gain produces a significant effect on release profile. Decrease pore former concentration in the coat of the osmotic system inhibited drug release. Dextrose: Fructose mixture was used as osmotic agent in the formulation of CPOP tablet and to study the effect of concentration of osmogent, core formulations were prepared by using varying concentration of osmogent i.e. 30 %, 34 % and 45 % of tablet weight, from the release profile of primary batches, it was clear that more the increase in the concentration of osmotic agent, greater is the driving force, thus enhances the release

of drug and showed a direct effect on drug release. To study the effect of pore forming agent, core formulations of Ketoprofen were coated with varying coating compositions of PEG-4000 as a pore former. PEG-4000 was added 35%, 40%, and 45% w/w of coating polymer. It is clearly evident that the level of PEG-4000 had a direct effect on drug release. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release. Formulation F3 shows less release as compared to F1 and F2 as F3 has 6 % weight gain while F1 contains high level of pore former and less % weight gain hence it shows greater release. Similarly F6 and F9 showed less drug release due to 6 % weight gain whereas F4 and F7 contains high level of pore former and less % weight gain hence it showed greater release.

Table 8: Drug Release Profiles of Factorial Batches of CPOP tablet of Ketoprofen

Time (Hr)	% Dissolution (n ± SD)*								
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F8	F9
1	7.86 ±0.08	4.74 ±0.22	4.27 ±0.66	10.28 ±0.25	9.01 ±0.35	4.39 ±0.87	10.86 ±0.03	8.55 ±0.65	5.78 ±1.22
2	11.41 ±0.05	8.60 ±0.32	8.25 ±0.58	14.21 ±0.27	11.89 ±58	9.06 ±1.08	13.29 ±0.55	12.69 ±0.25	10.93 ±1.05
3	13.85 ±0.02	12.16 ±0.45	10.31 ±0.35	17.49 ±0.55	15.02 ±0.54	14.13 ±1.25	15.40 ±0.24	14.56 ±0.35	14.86 ±1.04
4	17.47 ±1.05	16.00 ±1.02	12.85 ±0.47	21.15 ±0.21	17.15 ±0.12	16.14 ±1.24	23.20 ±0.24	19.11 ±0.14	19.30 ±1.23
5	19.28 ±0.65	18.48 ±1.52	15.99 ±0.45	24.73 ±0.58	19.76 ±0.23	21.63 ±2.11	28.77 ±1.08	23.14 ±0.25	22.86 ±1.54
6	22.37±1.22	21.11 ±0.65	19.98 ±0.21	29.97 ±0.57	26.22 ±0.25	23.60 ±1.62	34.17 ±1.35	29.63 ±0.36	26.00 ±1.36
7	26.89 ±0.84	26.42 ±0.25	21.35 ±1.20	34.68 ±0.65	31.01 ±0.65	26.62 ±1.32	39.85 ±1.05	34.46 ±1.05	30.44 ±0.58
8	34.11 ±0.36	32.60 ±0.32	25.74 ±1.42	40.72 ±0.85	35.85 ±0.48	30.96 ±0.88	46.64 ±1.04	40.14 ±0.68	35.85 ±0.24
9	39.91 ±0.55	36.65 ±0.66	29.94 ±1.14	48.08 ±0.25	41.66 ±0.75	36.02±0.35	53.03 ±0.65	44.50 ±0.25	41.32 ±0.35
10	44.96 ±0.47	41.43 ±0.32	35.81 ±0.35	53.22 ±0.24	47.31 ±0.72	41.15 ±0.65	57.87 ±0.15	51.91 ±1.02	46.38 ±0.12
11	52.14 ±0.88	49.02 ±0.36	39.43 ±0.24	63.72 ±0.52	54.74 ±1.02	46.09 ±0.36	63.92 ±0.66	56.74 ±0.68	50.69 ±0.22
12	57.66 ±0.22	53.72 ±0.54	42.39 ±1.20	72.95 ±0.12	58.55±0. 65	52.43 ±0.58	72.68 ±0.85	67.39 ±0.56	57.81 ±0.12
14	65.20 ±0.85	57.87 ±1.23	46.41 ±1.05	78.80 ±0.02	67.30 ±0.35	57.53±0.68	80.26 ±0.35	73.53 ±1.02	63.38 ±0.14
16	71.08 ±1.22	61.36 ±1.22	48.63 ±0.36	84.94 ±1.02	78.41 ±0.98	64.37 ±0.69	87.57 ±0.66	81.7 ±1.06	68.67 ±0.85
18	78.18 ±2.10	64.08 ±1.20	52.60 ±0.58	92.81 ±1.14	83.04 ±0.35	71.98 ±0.86	97.49 ±0.56	88.44 ±1.45	72.97 ±0.65
20	82.00 ±0.65	67.97 ±0.88	55.34 ±0.98	99.04 ±0.23	87.72 ±0.66	75.73±0.26		94.12 ±0.87	77.99 ±0.85
22	87.58 ±0.56	74.8 ±0.47	58.33 ±0.57		91.51 ±0.35	79.17 ±0.35		99.69 ±0.32	81.80 ±0.14
24	92.76 ±0.66	78.56 ±0.39	60.43 ±0.24		99.85 ±0.88				87.49 ±1.23

(*SD- Standard deviation, n=3)

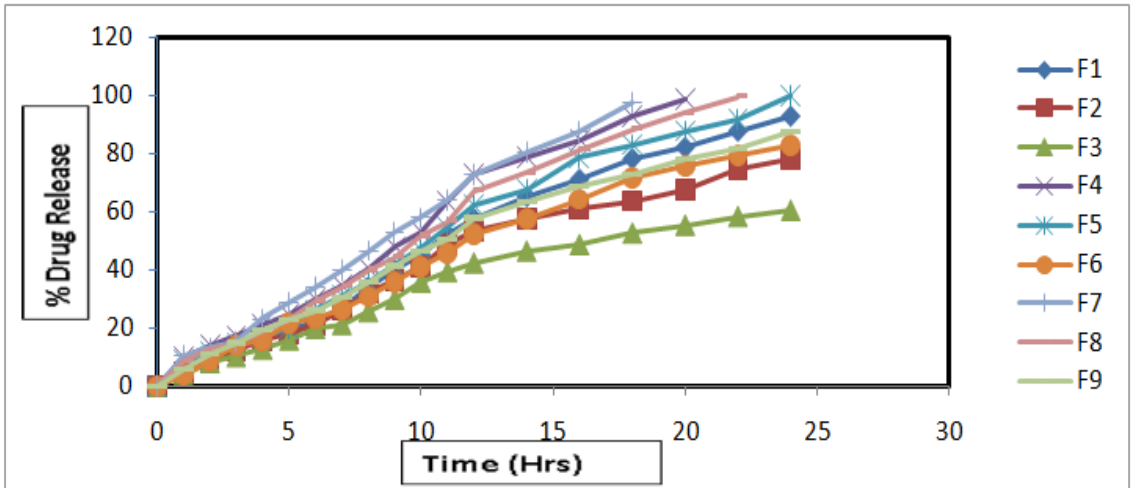

Fig. 5: *In-vitro* release profile of factorial batches of CPOP tablet

Drug release kineticsr

In order to understand the mechanism of drug release from the formulation the dissolution data was analyzed by PCP Disso Version 2.08 software. Considering the correlation coefficient (R^2) values as obtained from the different kinetic equations, the drug release from most of the batches of CPOP tablets were found to follow zero order and Peppas dissolution kinetic. The release exponent "n" value for the different formulation ranged from 0.85 to 0.93. The R^2value of all batches is as per observed in Table 9. The value of n i.e. release exponent was found to be less than 1, which shows release of drug from system as anomalous transport.

Accelerated stability studies

Optimized formulation (F5) was subjected to stability studies for a duration of 90 days at temperature 40°C ± 2°C and 75% ± 5% relative humidity. The tablets were evaluated at specific time period for various parameters viz. thickness, hardness, drug content and release studies. From Table 10 it can be seen that there is no change in the evaluation parameter of the tablet during the 1 month. Table 11 showed, that a slight decrease in drug release. Hence, stability data revealed that formulation F5 was stable for 3 month.

Table 9: Drug release kinetics of the formulated batches CPOP tablet of Ketoprofen

Batch code	R value					Best fit model	Parameters for Korsemeyer Peppas equation	
	Zero order	First order	Matrix	Peppas	Hixson Crowell		n value	K value
F1	0.9918	0.9735	0.9654	0.9854	0.9910	Zero	0.8879	5.9746
F2	0.9848	0.9934	0.9733	0.9946	0.9746	Peppas	0.9275	4.5597
F3	0.9818	0.9939	0.9770	0.9942	0.9911	Peppas	0.8751	4.2227
F4	0.9926	0.8939	0.9575	0.9830	0.9666	Zero	0.8405	7.7162
F5	0.9920	0.8221	0.9656	0.9835	0.9587	Zero	0.8594	6.4392
F6	0.9939	0.9904	0.9721	0.9976	0.9969	Peppas	0.9376	4.6229
F7	0.9972	0.9097	0.9624	0.9838	0.9695	Zero	0.8542	7.971
F8	0.9941	0.8615	0.9650	0.9892	0.9953	Zero	0.8819	6.6035
F9	0.9893	0.9902	0.9780	0.9974	0.9974	Peppas	0.8795	5.7879

Table 10: Stability evaluation

Batch Code	Thickness, Diameter (mm)	Hardness (Kg/ cm²)	Uniformity of weight (mg)	Drug content %
F 5	4.3 ± 0.08 mm Thickness, 13 mm diameter	3.42± 0.58	551 ± 2.86	99.45±0.19

Table 11: Drug release profile of F5

Time (hr)	% Dissolution (n ± SD)*	
	Initial	After 90 Days
1	9.01 ±0.35	8.98±0.87
2	11.89 ±58	11.42±0.15
3	15.02 ±0.54	13.68±1.20
4	17.15 ±0.12	17.11±0.89
5	19.76 ±0.23	19.02±0.58
6	26.22 ±0.25	25.14±0.88
7	31.01 ±0.65	31.10±0.74
8	35.85 ±0.48	35.00±1.65
9	41.66 ±0.75	42.07±0.65
10	47.31 ±0.72	46.88±1.25
11	54.74 ±1.02	54.68±1.5
12	58.55 ± 65	57.65±0.48
14	67.30 ±0.35	66.01±1.02
16	78.41 ±0.98	78.44±1.25
18	83.04 ±0.35	82.98±1.11
20	87.72 ±0.66	86.55±0.76
22	91.51 ±0.35	90.87±1.24
24	99.85 ±0.88	99.34±0.83

(*SD- Standard deviation, n=3)

Surface response plot

Stat Ease Design Expert 7.1.4 software was used for statistical analysis. Factor A (pore former) shows positive coefficient it estimates that increase in concentration of factor A have a direct effect on drug release i.e. as concentration of A increases drug release also increases (Figure 6). The % weight gain has opposite effect means as factor B concentration increases it decreases drug release. The value of F < 0.05 indicates model is significant and F> 0.1 indicates model is not significant (Table 12).

Table 12: ANOVA for surface response 2FI model

Source	Sum of squares	df	Mean square	F-value	P value prob>F	Significant
Model	1361.51	5	272.30	31.06	0.00087	
A-Pore Former	568.21	1	568.21	64.80	0.00040	
B-Wt gain	4781.53	1	471.53	53.78	0.00052	
Residual	26.30	3	8.77			
Core total	1387.81	8				

Equation:

% Drug release(Y) = +98.02-9.7A + 8.87B + 5.58AB- 6.09A²-7.84B²

Std.dev=2.961 R^2=0.9810 Adjusted R^2=0.9494 Predicted R^2=0.7946

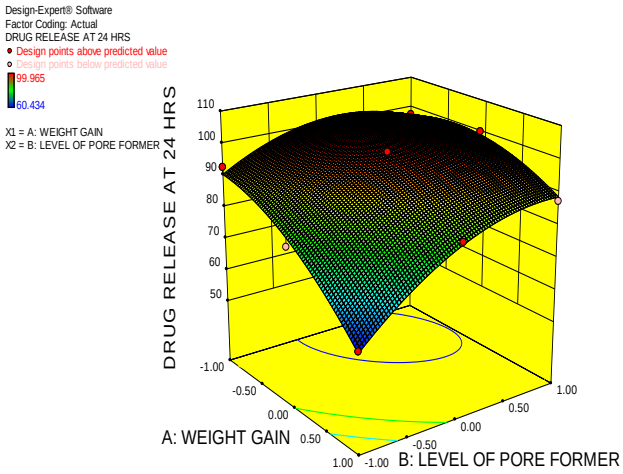

Fig. 6: Surface Response plot at 24 hrs

CONCLUSIONS

An osmotic system comprising a monolithic tablet coated with cellulose acetate as a semi permeable membrane containing PEG 6000 as pore forming agent has been developed for Ketoprofen. The desired zero order release profile was obtained by optimizing drug: osmogent ratio, pore former concentration and % weight gain. Drug release was directly proportional to the initial level of pore former, but inversely related to the membrane weight. Results of SEM studies showed the formation of pores in the membranes after coming into contact with the aqueous environment. Developed optimized formulation F5 showed zero order release kinetics and was found to be stable after 3 months of storage at accelerated stability conditions. This system is simple to prepare with no drilling required and has a potential to be used in the field of controlled delivery of Ketoprofen.

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