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Research Article

FORMULATION DEVELOPMENT AND OPTIMIZATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS OF DICLOFENAC SODIUM

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ABSTRACT

The porous osmotic pump tablets were designed using D-Optimal design and numerical optimization technique was applied to find out the best formulation. Osmotic agent sodium chloride and pore former PEG 400 was considered as independent variables. Drug release rate at 2 h, 4 h, 8 h, 12 h, $T_{50\%}$ and release exponent (n) were taken as responses. The increase in concentration of pore former and osmotic agent after a limit, changes the release from zero order to Higuchi based release. The optimized formulation follows non-Fickian release mechanism. The FT-IR and DSC studies revealed that no physicochemical interaction between excipients and drug. The influence of pH and agitation intensity on the release of drug was studied and the release mechanism was through osmosis. Stability studies revealed that optimized formulation was stable. The result of D- Optimal design and ANOVA studies reveals that osmotic agent and pore former have significant effect on the drug release up to 12 h. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demostrates the feasibility of the optimization procedure in successful development of porous osmotic pump tablets containing diclofenac sodium by using sodium chloride and PEG 400 as key excipients.

Keywords: Diclofenac sodium, Optimal optimization, Porous osmotic pump, Poly ethylene glycol 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 action[1].

To maintain drug concentration within the therapeutic window the drug dose and dosing interval are optimized, thus ensuring efficacy while minimizing toxic effects. 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 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[3].

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[4].

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[5].

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[6].

MATERIALS AND METHODS

Materials

Diclofenac sodium was obtained as gift sample from Novartis pharmaceutical Ltd (Mumbai, 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).

Experimental design

D-Optimal design was applied using the software Design-Expert software (Stat-Ease Inc, Minneapolis, USA). Factors taken as A & B. 'A' is the osmotic agent (Sodium chloride), 'B' is the pore former[7].

Fourier Transform Infrared Spectroscopy (FT-IR)

Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FT-IR spectroscopy[8].

Differential Scanning Calorimetry (DSC)

DSC studies were carried out for the pure drug, physical mixtures of drug and excipients and placebo of the porous osmotic pump tablets to study the compatibility. The analysis were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to eliminate oxidative and pyrolytic effects at a standard heating rate of 10 ºC/min over a temperature range of 50 ºC – 400 ºC using a Universal V4 5A TA instruments[9].

Preparation of porous osmotic pump tablet

Preparation of 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 10 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.20. 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 Rimek mini press-I compression machine[9].

Coating of the core tablets

Coating was performed by using spray pan coating machine. The cellulose acetate in acetone containing different levels of pore formers (PEG 400) was used as coating solution (Table 1). Total components in the coating solution were 4% w/v. The coating conditions were as follows: pan, 9 inch circular; speed of pan, 50 rev./min; nozzle diameter,1mm; spray rate, 1 ml/min; spray pressure, 40 lb/sq.in.; drying temperature, 55-60 °C. Weight gain of all the formulations was maintained to 3%[10].

Table 1: Master formula for porous osmotic pump tablets

Ingredients (Quantity in mg for 1 tablet)	OP1	OP2	OP3	OP4	OP5	OP6	OP7	OP8	OP9
Core tablets									
Sodium Chloride	60	60	60	80	80	80	100	100	100
Microcrystalline cellulose	105	105	105	85	85	85	65	65	65
Coating- Components in %w/w									
Cellulose acetate	80%	70%	60%	80%	70%	60%	80%	70%	60%
P.E.G -400	20%	30%	40%	20%	30%	40%	20%	30%	40%

Each formula also contains: Diclofenac sodium-100 mg; Povidone K30-15 mg; Sodium lauryl sulphate-15 mg; Magnesium stearate-2 mg; Talc-3 mg

Powder flow properties

Angle of repose

The angle of repose of the mixture of the drug and excipients was determined by fixed funnel method. The values are used in the following equation to get the angle of repose.

Tan θ = h/r Where, h, r and θ are the height, radius and angle of repose of the powder pile.

Bulk density

Accurately weighed 3 g of the sample was transferred to the measuring cylinder of bulk density apparatus. The apparatus was adjusted for 100 tapping and noted the final volume as tapped volume.

$$\text{Tapped density } (\rho_t) = \frac{\text{Weight of the powder}}{\text{Tapped volume of the powder}}$$

Porosity

Porosity of the powder was determined by using formula:

Porosity = $[(V_b - V_p)/ V_b] \times 100$. Where V_b is the bulk volume and V_p is the true volume

Carr's index

The carr's index of the powder was determined by using formula:

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Where, TBD is the total bulk density and LBD is the loose bulk density[11].

Evaluation of Porous osmotic pump Tablets

Thickness

Thickness of the core tablets and coated tablets were measured by using screw gauge. Ten tablets from each formulation were randomly selected and used. Thickness is expressed in millimeters.

Hardness

The hardness of the core tablets and coated tables were measured using the Pfizer hardness tester. Six tablets from each formulation were randomly selected and used. The average hardness and the standard deviation were calculated. It is expressed in Kg/cm^2.

Friability

Friability of the matrix tablets and core tablets of porous osmotic pump tablets were determined. 10 tablets were randomly selected, weighed and placed in the Roche Friabilator. The apparatus was rotated at 25 rpm for 4 min. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% \text{ Friability} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Weight uniformity

Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated[11].

Determination of drug content

Ten tablets were accurately weighed and powdered. A quantity of the powder equivalent to 100 mg of Diclofenac sodium was weighed accurately and extracted in 100 ml methanol by shaking for 20 min. After filtration through whatmann filter paper no.1 and sufficient dilution with methanol, samples were analyzed spectrophotometrically at 283 nm. Amount of drug present was determined from the calibration curve of Diclofenac sodium in methanol[12].

***In vitro* dissolution studies**

Drug release studies were carried out using USP dissolution test apparatus (Apparatus I basket type). The dissolution medium was 900 ml of phosphate buffer pH 7.5. The release was performed at 37 ± 0.5°C, with a rotation speed of 100 rpm. 10 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by UV spectrophotometer[3].

Curve fitting Analysis

For the determination of the drug release kinetics from the porous osmotic pump tablet, the *in vitro* release data were analyzed by zero order, first order, Higuchi and Korsmeyer and Peppas equations.

Zero order release kinetic

To study the zero order release kinetics the release data was fitted into the following equation:

$$dQ/dt = K_0$$

Where, 'Q' is the amount of drug release, 'K_0' is the zero order release rate constant and 't' is the release time. The graph is plotted percentage cumulative drug release (% CDR) verse time.

First order release kinetic

To study the first order release kinetics the release rate data are fitted into the following equation:

$$dQ/dt = K_1 Q$$

Where, 'Q' is the fraction of drug release, 'K_1' is the first order release rate constant and 't' is the release time. The graph is plotted log % CDR remaining verse time.

Higuchi release model

To study the Higuchi release model the release rate data are fitted into the following equation:

$$Q = K_H t^{½}$$

Where, 'Q' is the fraction of drug release, 'KH' is the release rate constant and't' is the release time. The graph is plotted % CDR verses square root of time.

Korsmeyer and Peppas kinetics

To study the Korsmeyer and Peppas release kinetics the release rate data are fitted in to following equation:

$$Mt/M\infty = K_{KP} t^n$$

Where, $Mt/M\infty$ is the fraction of drug release, 'K_{KP}' is the release rate constant and't' is the release time and 'n' is the diffusion exponent related to mechanism of drug release. The graph is plotted log %CDR verses log time[13].

Optimization

In the numerical optimization techniques, the desirability approch was used to generate the optimum settings for the formulation. For the optimized formulation, the drug release at 2 h, 4 h, 8 h, 12 h, $T_{50\%}$, release exponent(n) were kept in target. The drug release target was kept according to the USP standards (Table 10).

Effect of pH on drug release

The optimized formulation of porous osmotic pump tablets is tested for the effect of pH on drug release. The best formulations are undergone dissolution studies in 0.1N HCl, 6.8 pH phosphate buffer, 7.5 pH phosphate buffer and distilled water in rotation speed of 100 rpm and 37 ± 0.5°C using USP dissolution test apparatus (type 1) and compared[9].

Effect of agitation intensity on drug release

The optimized formulation of matrix and porous osmotic pump tables are tested for the effect of agitation intensity on drug release. The best formulations are undergone dissolution studies by maintaining different rotation speed of 50, 100, 150 rpm and at 37 ± 0.5 °C in 7.5 pH phosphate buffer for 8 h using USP dissolution test apparatus (type 1) and compared[9].

Effect of osmotic pressure

The release studies of the optimized formulation were conducted in media of different osmotic pressure for confirming the mechanism of drug release. To increase the osmotic pressure of the release media osmotic agent mannitol was added in 7.5 pH phosphate buffer at 37 °C±1 °C). Release studies were performed in 900 mL of media using USP-I dissolution apparatus (100 rpm). To avoid any interference in the analysis by mannitol, the samples were analyzed to determine the residual amount remaining in each formulation. At the end of 8 h formulations were withdrawn from each vessel and cut open, and the contents were dissolved in sufficient volume of phosphate buffer. The results after direct measurement of drug in to the release media were similar to the results of residual drug analysis method. The osmotic pressure of the medium was determined using Van't Hoff and Morse equation[9].

$$\pi V = nRT$$

Were, π – Osmotic pressure, V- Volume of the solution in liter, n- Number of moles of solute, T- Absolute temperature, R- Gas constant which is equal to 0.082 lit atm/mol deg.

Membrane morphology of porous osmotic pump tablet

Scanning Electron Microscopy

Coating membranes of formulation obtained before and after complete dissolution of core contents were examined for their porous morphology by scanning electron microscope (JEOL JSM-6300, Japan). Membranes were dried at 45 °C for 12 h and stored between sheets of wax paper in a dessicator until examination. The membrane were coated under an argon atmosphere with gold-palladium, and observed with a scanning electron microscope[14].

Stability

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The most satisfactory formulation was sealed in an aluminum foil and stored at 30 ± 2ºC, 65 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 6 months. Tablets were periodically removed and evaluated for physical characteristics, in-vitro drug release[9].

RESULT AND DISCUSSION

Drug polymer compatibility studies using FT-IR

In order to investigate the possible chemical interaction between drug and selected polymers, FTIR studies were carried out. IR spectrum for pure drug and physical mixture of drug- polymers were obtained and analyzed for principle peaks at 3380 cm^{-1} (NH stretch), 1647 cm^{-1} (C=O), 3081 cm^{-1} (Aromatic CH), 750 cm^{-1} (-Cl stretch), 1453 cm^{-1} (CH bend), 1564 cm^{-1} (NH bend). The FTIR characteristic of Diclofenac sodium with polymers resembles almost with the spectra of authentic sample of Diclofenac sodium. The studies suggest that there is no incompatibility between drug and polymer. Results are given in Table 2.

Table 2: FT-IR spectrum of DS alone and excipients

IR absorption bands	Interpretation					
	NH stretch (cm^{-1})	C=O (cm^{-1})	Aromatic CH (cm^{-1})	-Cl stretch (cm^{-1})	CH bend (cm^{-1})	NH bend (cm^{-1})
Diclofenac sodium	3380	1647	3081	750	1453	1564
Drug + MCC	3339	1637	3080	756	1456	1550
Drug + CA	3350	1645	3085	757	1457	1550
Drug + PVP	3397	1648	3080	756	1455	1558
Drug + SC	3231	1650	3085	752	1456	1562

Drug polymer compatibility studies using DSC

In order to investigate the possible physical interaction between drug and excipients, DSC studies were carried out. The drug exhibited a sharp melting endotherm at 281.35°C. The DSC thermograms of Diclofenac sodium, porous osmotic pump tablet and placebo of porous osmotic pump tablets are depicted in Fig. 1. No change in the endotherm of the drug was observed in coated porous osmotic pump tablets. From this it was inferred that there was no interaction between the drug and excipients.

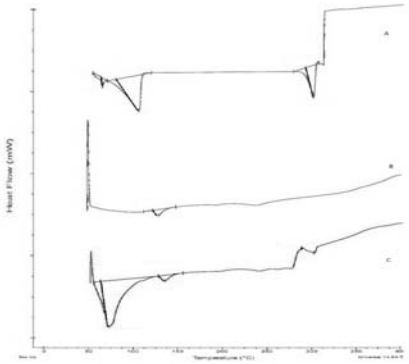

Fig. 1: DSC spectra of drug and excipients

A- Diclofenac sodium (DS), Placebo of porous osmotic pump tablets, Physical mixture of drug and excipients

Powder flow properties

The results of preformulation parameters for formulated physical mixtures of all batches are shown in table 3. The flowability of the polymers was found to be quite good according to the flow properties. Angle of repose ranges from 26.89 to 28.50°, bulk density ranges from 0.353 to 0.361 g/cm^3, % Compressibility ranges from 13.21 to 14.54%.

Physicochemical properties

The mean values of hardness, friability, thickness, weight and drug content of prepared matrix tablets and core tablet of porous osmotic pump tablets is recorded in the table 4. The thickness, diameter, hardness, weight of the coated porous osmotic pump tablets is recorded in the table 5.

Table 3: Powder flow properties for formulated physical mixtures

Formulation Code	Angle of Repose* (°)	Bulk Density* (g/cm^3)	Tapped Density* (g/cm^3)	Porosity* (%)	Compressibility* (%)
OP1,OP2,OP3	26.89±0.23	0.358±0.002	0.413±0.003	13.15±0.09	13.21±0.16
OP4,OP5,OP6	27.18±0.53	0.353±0.004	0.411±0.006	14.01±0.10	14.11±0.28
OP7,OP8,OP9	28.50±0.49	0.361±0.005	0.423±0.006	14.47±0.17	14.54±0.15

Note: (*****) All values are the mean of three readings

Table 4: Physicochemical parameters of developed core tablets of porous osmotic pump

Formulation code	Hardness* (kg/cm^2)	Friability (%)	Thickness* (mm)	Weight* (mg)	Drug con- tent* (%)
OP1,OP2,OP3	8.13±0.15	0.389	3.91±0.009	300.6±1.855	99.11±0.615
OP4,OP5,OP6	8.23±0.137	0.521	3.78±0.007	301.7±2.099	98.54±0.735
OP7,OP8,OP9	8.267±0.07	0.445	3.67±0.012	301±1.66	99.19±0.372

Note: (*****) All values are the mean of three readings

Table 5: Physicochemical parameters of developed porous osmotic pump tablets

Formulation Code	Thickness* (mm)	Diameter* (mm)	Hardness* (kg/cm^2)	Weight* (mg)
OP1	4.011 ± 0.13	9.109±0.014	8.5 ± 0.11	310.2 ± 1.03
OP2	4.010±0.02	9.106 ± 0.017	8.47 ± 0.16	309.8 ± 1.03
OP3	4.006±0.017	9.108 ± 0.018	8.43 ± 0.15	310.4 ± 0.966
OP4	3.896±0.019	9.103 ± 0.015	8.4 ± 0.126	310.3 ± 1.49
OP5	3.89±0.015	9.112 ± 0.015	8.47 ± 0.10	309.7 ± 1.337
OP6	3.889±0.013	9.117 ± 0.011	8.5 ± 0.11	309.6 ± 1.174
OP7	3.780±0.017	9.103 ± 0.022	8.43 ± 0.15	309.7 ± 1.159
OP8	3.770±0.015	9.128 ± 0.014	8.43 ± 0.234	310.5 ± 1.08
OP9	3.770±0.016	9.122 ± 0.015	8.47 ± 0.16	311 ± 1.247

Note: (*****) All values are the mean of three readings

***In vitro* dissolution study**

In porous osmotic pump tablets the drug release rate is depends on the concentration of the osmotic agent and the pore former used. The osmotic agent concentration increases then the osmotic pressure created inside the tablet also increases, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug so the release of the drug also will increase. The pore former concentration increases then the number of pore formed or the pore size also increases it will cause easy leaching out of the drug from the formulation. The concentration of the pore former or the osmotic agent on increase beyond a limit, it will cause the release of the drug in a diffusion manner. Results are shown in Fig. 2A, 2B, 2C.

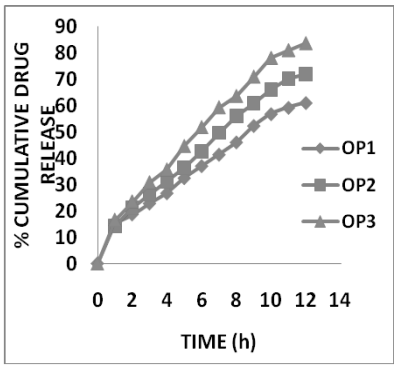

Fig. 2A

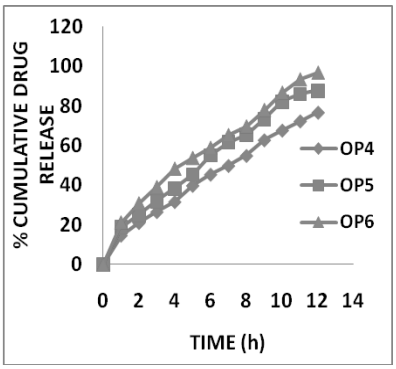

Fig. 2B

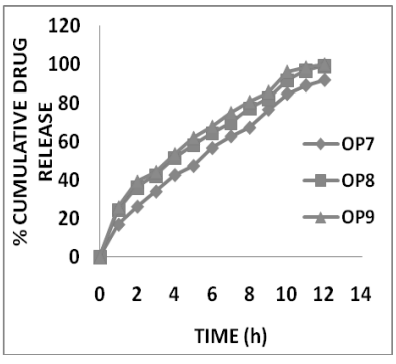

Fig. 2C

Fig. 2: Dissolution profile of porous osmotic pump tablets

***In vitro* drug release study after 2 hour (h)**

Total amount of Diclofenac sodium released from all formulations ranges from 18.68% to 39.42% in 2 h (Table 6). Increased rate of drug release was observed after 2 h with increase of the concentration of osmogent and pore former. When the tablets contact with dissolution media the pore formation on membrane will takes place. The porous membrane and concentration of osmogent in the core tablet acts as rate controlling for the release of drug. In this case, effect of both osmogent and pore former can be explained by mathematical equation in terms of actual factors:

$$R1 = + 26.97 + 6.42 * A + 4.63 * B$$

The linear model is selected for this response with Model F-value 15.92 and p value is 0.0101. p value less than 0.0500 indicate model terms are significant. In this case A, sodium chloride and B, PEG 400 are significant model terms. Both the factor A, sodium chloride and B, PEG 400 increases drug release from the tablets (positive effect). The effect of A and B can be further elucidated with the help of 3D surface plot (Fig. 3A). Higher release of Diclofenac sodium was found after 2 h in higher concentrations of both factors. At high level of A and B percentage release has high value which indicates factor A and B helps more release of drug.

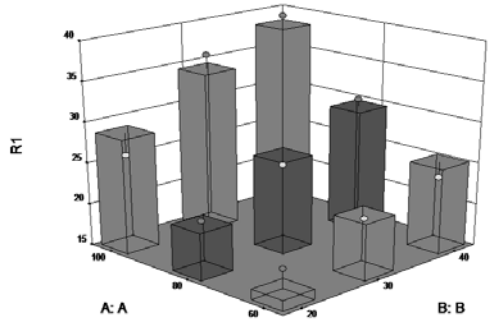

Fig. 3A: 3D surface plot showing the effect of factor A and factor B on drug release after 2 h

***In vitro* drug release study after 4 hour**

Total amount of Diclofenac sodium released from all formulations ranges from 26.71% to 53.68% in 4 h (Table 6). Increased rate of drug release was observed after 4 h with increase of the concentration of osmogent and pore former. The effect of both osmogent and pore former can be explained by mathematical equation in terms of actual factors:

$$R2 = + 40.77 + 10.19 * A + 6.10 * B$$

The linear model is selected for this response with Model F-value 12.46 and p value is 0.0157 indicate the model is significant. The Equation shows both factors A and B have significant positive effect on the response. The effect of A and B can be further elucidated with the help of 3D surface plot (Fig. 3B).

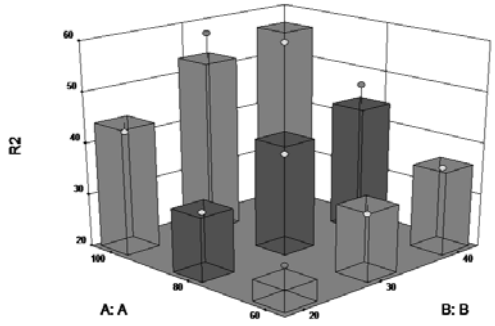

Fig. 3B: 3D surface plot showing the effect of factor A and factor B on drug release after 4 h

***In vitro* drug release study after 8 hour**

Total amount of Diclofenac sodium released from all formulations ranges from 46.07% to 80.69% in 8 h (Table 6). Increased rate of drug release was observed after 8 h with increase of the concentration of osmogent and pore former (positive effect). The effect of both osmogent and pore former can be explained by mathematical equation in terms of actual factors:

$$R3 = + 64.56 + 9.97 * A + 7.56 * B$$

The linear model is selected for this response with Model F-value 156.75 and p value is 0.0001 indicate the model is significant. The effect of A and B can be further elucidated with the help of 3D surface plot (Fig. 3C).

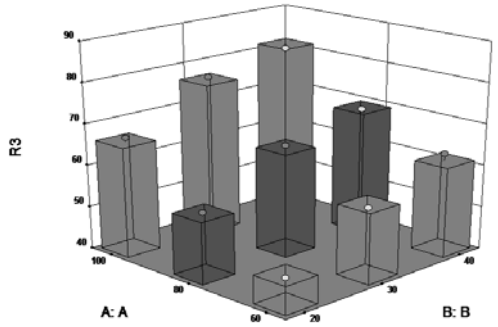

Fig. 3C: 3D surface plot showing the effect of factor A and factor B on drug release after 8 h

***In vitro* drug release study after 12 hour**

Total amount of Diclofenac sodium released from all formulations ranges from 61.06% to 99.87% in 12 h (Table 6). Increased rate of drug release was observed with increase of the concentration of osmogent and pore former (Positive effect). The effect of both osmogent and pore former can be explained by mathematical equation in terms of actual factors:

$$R4 = + 85.38 + 12.36 * A + 8.42 * B$$

The linear model is selected for this response with Model F-value 21.81 and p value is 0.0056 indicate the model is significant. The effect of A and B can be further elucidated with the help of 3D surface plot (Fig. 3D).

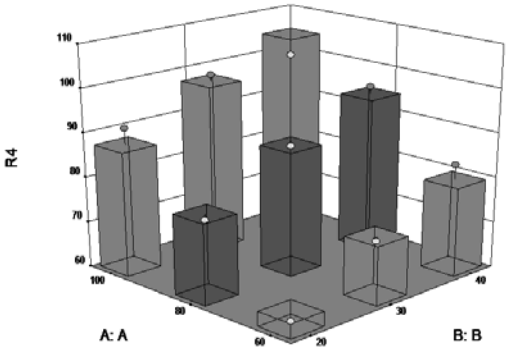

Fig. 3D: 3D surface plot showing the effect of factor A and factor B on drug release after 12 h

Effect of formulation variables on $T_{50\%}$

The value of $T_{50\%}$ ranges from the 3.7 to 8.6 h (Table 6). The increased $T_{50\%}$ was observed at low concentrations of osmogent and pore former (negative effect). The effect of both osmogent and pore former can be explained by mathematical equation in terms of actual factors:

$$R5 = + 5.69 - 1.45 * A - 1.20 * B$$

The linear model was found to be significant for the time for 50% of drug release. The Model F-value of 34.79 and value of p is less than 0.0023 indicate the model is significant. The equation indicates that $T_{50\%}$ increase as factors decreases (negative effect).

Effect of formulation variable on release exponent

The linear model was found to be not significant for release exponent with the model F-value 0.52 and p value 0.7267 (Table 6). In this response, factor A and B was found to be not significant. So, the model equation is as follows:

$$R6= + 0.64 - 0.026 * A - 0.023 * B$$

The n value of optimized formula found to be 0.695 which indicates the mechanism of release is non Fickian.

Table 6: Result of release parameter obtained for formulations by D-Optimal design

Run	Sodium chloride	PEG 400	Drug release after				n value	$T_{50\%}$
			2 h	4 h	8 h	12 h		
OP1	60	20	18.68	26.71	46.07	61.04	0.606	8.6
OP2	80	30	21.39	31.32	56.08	72.06	0.678	7.1
OP3	100	40	23.54	35.66	63.48	83.51	0.689	5.8
OP4	60	20	21.09	31.62	54.93	76.73	0.690	7.1
OP5	80	30	25.08	38.44	65.46	87.76	0.665	5.5
OP6	100	40	30.87	48.32	69.53	96.58	0.612	4.3
OP7	60	20	26.31	42.74	67.32	91.66	0.695	5.3
OP8	80	30	36.37	51.79	77.44	99.25	0.568	3.8
OP9	100	40	39.42	53.68	80.69	99.87	0.552	3.7

Curve fitting analysis

The *in vitro* release data was fitted to various kinetic models like Higuchi, First order, Zero order and Peppas. In porous osmotic pump tablets OP1, OP2 follows first order kinetics, OP3 to OP7 follows zero order kinetics, OP8 and OP9 follows Higuchi release model. Results are given in the table 7. When the data were plotted according to the first-order equation, the formulations showed a comparatively poor linearity, with regression value of 0.945; whereas the regression value for zero-order equation was 0.982, which indicated that drug release from optimized formulation (OP7) was independent of drug concentration. In matrix tablets and porous osmotic pump tablets the n value for Peppas model was found to be in between 0.45 and 0.89, indicates that the drug released from the formulation by anomalous (non-Fickians) mechanism.

Table 7: Summary of drug release kinetics of formulations

Kinetic profile of formulation	Korsmeyer Peppas			Zero order		First order		Higuchi	
	n	K_{KP}	R^2	K_0	R^2	K	R^2	K_H	R^2
Porous osmotic pump tablets									
OP1	0.606	13.00	0.965	4.796	0.978	-0.076	0.989	18.43	0.967
OP2	0.678	13.21	0.989	5.807	0.983	-0.106	0.989	22.24	0.967
OP3	0.689	15.10	0.990	6.760	0.982	-0.147	0.979	25.95	0.969
OP4	0.690	13.30	0.990	6.045	0.987	-0.115	0.981	23.09	0.965
OP5	0.665	16.63	0.984	7.056	0.982	-0.173	0.961	27.07	0.968
OP6	0.612	20.37	0.994	7.317	0.972	-0.237	0.875	28.40	0.981
OP7	0.695	16.33	0.997	7.334	0.982	-0.196	0.945	28.19	0.972
OP8	0.568	23.88	0.995	7.477	0.959	-0.322	0.812	29.35	0.990
OP9	0.552	25.59	0.999	7.584	0.948	-0.348	0.865	29.99	0.993

Drug release exponents(n), Korsmeyer Peppas release constant(K_{KP}), Correlation coefficient(R^2) of different models, Zero order release rate constants(K_0), First order release rate constant(K),

Table 8: Summary of ANOVA table for porous osmotic pump tablets from D-Optimal design

Source	d.f	Sum square	Mean square	F value	p value
OP release at 2 h					
A	2	254.43	127.21	21.06	0.0075
B	2	130.19	65.10	10.78	0.0245
Model	4	384.62	96.16	15.92	0.0101*
OP release at 4 h					
A	2	630.70	315.35	18.04	0.0100
B	2	240.37	120.18	6.88	0.0508
Model	4	871.07	217.77	12.46	0.0157*
OP release at 8 h					
A	2	603.42	301.71	196.89	0.0001
B	2	357.34	178.67	116.60	0.0003
Model	4	960.76	240.19	156.75	0.0001*
OP relase at 12 h					
A	2	928.95	464.48	29.82	0.0040
B	2	429.80	214.90	29.82	0.0160
Model	4	1358.75	339.69	21.81	0.0056*
$T_{50\%}$					
A	2	12.63	6.31	40.88	0.0022
B	2	8.86	4.43	28.69	0.0042
Model	4	21.49	5.37	34.79	0.0023*
n value					
A	2	5.345E-003	2.672E-003	0.66	0.5674
B	2	3.201E-003	1.600E-003	0.39	0.6989
Model	4	8.546E-003	2.136E-003	0.52	0.7267ns

Note: (*) significant ($p<0.05$), ns: not significant

ANOVA

In porous osmotic pump tablets the result of ANOVA demostrate all the independent variables (Factors) were found to be significant for response R1, R2, R3, R4, R5 but not significant for response R6 (Table 8). The linear model were found to be significant for all responses except R6. So, above result indicate that both the factors play an important role in the formulation of porous osmotic pump tablet containing Diclofenac sodium.

Optimization

It was concluded that the formulation OP7 is the most satisfactory formulaion for the physiologically independent controlled delivery of Diclofenac sodium.

A good releationship between the experimental and predicted values (Table 11), which confirms the practicability and validity of the model.

Membrane morphology of porous osmotic pump tablets

Membranes obtained before dissolution clearly showed non porous region (Fig. 4A). After 12 h dissolution, clearly showed pores formed in range of 1 to 25 µm owing to dissolution of PEG 400 (Fig. 4B). The leaching of PEG 400 from the membrane leads to formation of pores, and thus the release of drug takes place. In formulation OP7 contains 20% PEG which produces less pores compare to OP8 (30% PEG 400) and OP9 (40% PEG 400).

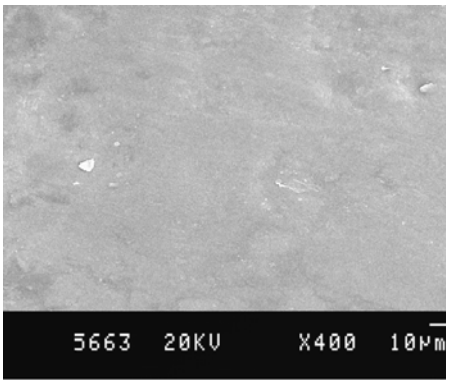

Fig. 4A: Before dissolution

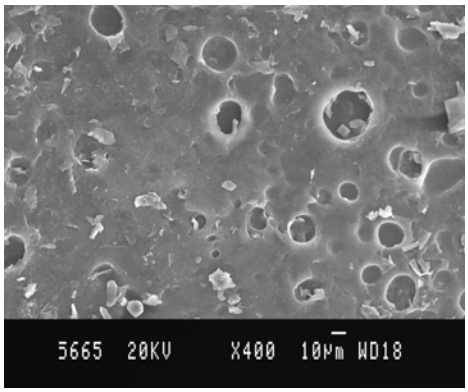

Fig. 4B: After dissolution

Fig. 4: Membrane morphology of formulation OP7 by scanning electron microscopy

Effect of pH on drug release

When formulation OP7 was subjected to *in vitro* release studies in buffers with different pH and distilled water, no significant difference in the release profiles were seen compared to that in phosphate buffer pH 7.5. Thus the fluid in different parts of the GI tract will scarcely affect drug release from the osmotic system.

Effect of agitation intensity on drug release

The release profile of Diclofenac sodium from the optimized formulation OP7 was independent of the agitational intensity of the release media.

Effect of Osmotic Pressure

The drug release rate decreased with increase in osmotic pressure in the media; however, the lag time was prolonged. The drug release profiles with varying osmotic pressure are shown in table 9. This finding confirms that the mechanism of drug release is by the osmotic pressure.

Table 9: Dissolution parameters of optimized formulation with varying osmotic pressure

Osmotic Pressure (atm)	Lag time (h)	Dissolution rate (%/h)
7.753	1.45	7.68
31.009	1.95	6.71

Stability studies

After the 6 months storage of formulation OP7, values of all parameters like hardness, diameter, thickness, % drug content, friability were checked periodically and found to be almost similar to the initial values. The drug dissolution and diffusion profile were similar to the initial profile. There was not any significant change in any value and also no changes in the physical appearance. So it can be said that formulation is stable.

Table 10: Comparison of release profile of USP Diclofenac sodium extended release tablets with optimized CPOP formulation

Time (h)	Release profile of Diclofenac sodium extended release tablets labelled for 12 h dosing(USP tolerance limit) (%)	Release profile of optimized formulation OP7 (%)
2	Between 22% and 42%	26.31
4	Between 34% and 61%	42.74
8	Between 52% and 82%	67.32
16	Not less than 73%	91.66 in 12 h

Table 11: Comparison of experimented and predicted values of optimized formulation

Optimized formula OP7	Dependable variables					
	Drug release at 2 h	Drug release at 4 h	Drug release at 8 h	Drug release at 12 h	$T_{50\%}$	Release exponent
Predicted	29.0878	44.5333	66.7011	88.0189	5.57778	0.629222
Experimental	26.31	42.74	67.32	91.66	5.3	0.695

CONCLUSION

The observed independent variables were found to be very close to predicted values of optimized formulation which demostrates the feasibility of the optimization procedure in successful development of porous osmotic pump tablets containing Diclofenac sodium (100 mg) by using sodium chloride (100mg) as osmotic agent and 20% w/w (with 80% w/w cellulose acetate) of PEG 400 as pore former. Stability studies revealed that optimized formulation is stable.

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