Design and Optimization of Solid Dispersed Osmotic Pump Tablets of Aceclofenac, A Better Approach to Treat Arthritis

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ABSTRACT – The aim of this work was to prepare porous osmotic pump tablets for controlled delivery of Aceclofenac. Aceclofenac solid dispersion was prepared to improve the solubility by using the drug - carrier (Mannitol) ratio of 1:1. The osmotic pump tablets were prepared using the solid dispersed product of Aceclofenac. The formulation contains potassium chloride as osmotic agent, cellulose acetate as semipermeable membrane, poly ethylene glycol (PEG 4000) as pore former and sodium lauryl sulphate (SLS) as solubility enhancer. The formulations were designed by the general factors such as osmotic agent and pore former. All formulations were evaluated for various physical parameters and, the *in vitro* release studies were conducted as per USP. The drug release kinetic studies such as zero order, first order, and Higuchi and Korsmeyer peppas were determined and compared. All the formulations gave more controlled release compared to the marketed tablet studied. Numerical optimization techniques were applied to found out the best formulation by considering the parameter of *in vitro* drug release kinetics and dissolution profile standards. It was concluded that the porous osmotic pump tablets (F7) composed of Aceclofenac solid dispersion/Potassium chloride/Lactose/Sodium lauryl sulphate/Magnesium Stearate (400/40/95/10/5, mg/tab) and coating composition with Cellulose acetate/ PEG 4000 (60/40 %w/w) is the most satisfactory formulation. The porous osmotic pump tablets provide prolonged, controlled, and gastrointestinal environment-independent drug release.

Keywords – Porous osmotic pump tablet; Aceclofenac; Controlled release; Pore former; Osmotic agent.

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages (Chien, 2005). Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects and increase the safety margin for high-potency drugs (Banker, 2007).

Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogent. Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. Hence the release rate of drugs from osmotic dispensing devices is dependent on the solubility and molecular weight and activity coefficient of the

solute (Osmogent) (Robinson and Vincent, 2005; Donald, 2000).

Porous osmotic pump tablets when exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents. Rate of drug delivery depends upon the factors are water permeability of the semi permeable membrane and the osmotic pressure of the core formulation, thickness and total surface area of coating (Sharma, 2008; Gohel et al., 2009).

Aceclofenac is an Non-steroidal anti-inflammatory drug (NSAID) used for relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis (Indian Pharmacopoeia, 2007).

The mode of action of Aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins (Charles and Robert, 2005).

Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose. The drug is highly protein bound

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(7.99%). The presence of food does alter the extent of absorption of aceclofenac but the absorption rate is reduced. The plasma concentration of aceclofenac was approximately twice that in synovial fluid after multiple doses of the drug in-patient with knee pain and synovial fluid effusion (Thripathi, 1999). The drug having the biological half life around 4 h (Indian Pharmacopoeia, 2007).

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 Aceclofenac.

Materials and Methods

Materials

Aceclofenac was obtained as gift sample from Astrazeneca pharma India Ltd (Bangalore, India). Cellulose acetate, mannitol was purchased by S.D Fine Chem. Ltd (Mumbai, India). PEG 4000, sodium lauryl sulphate was received as gift sample from Strides Arco labs LTD (Bangalore, India). Potassium chloride, lactose and magnesium stearate and talc was purchased from S. D. fine Chem. LTD (Mumbai, India).

Methods

Experimental design

General factorial design was applied using the software Design-Expert software (Stat-Ease Inc, Minneapolis, USA). Factors taken as A & B. 'A' is the osmotic agent (Potassium chloride), 'B' is the pore former (PEG 4000) (James, 2007).

Drug - excipient compatibility studies

Fourier transform infrared (FT-IR) spectroscopy

Compatibility studies were carried out to know the possible interactions between Aceclofenac and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compat-

ibility studies were carried out using FT-IR spectroscopy (Chauhan and Choudhury, 2006).

Formulation development

Preparation of solid dispersion

Solid dispersion of aceclofenac was prepared by using the carrier mannitol. The drug carrier ratio taken as 1:1. The 5 g drug was dissolved in 100 mL acetone and the 5 g mannitol was dissolved in 100 mL distilled water. Both the solutions was mixed and then evaporated to get the solid dispersion.

Preparation of porous osmotic pump tablets of Aceclofenac

Preparation of core tablets

Core tablets were prepared by direct compression method. An accurately weighed quantity of ingredients as shown in the Table I was passed through #60 sieve. All the ingredients except lubricant (MS) were manually blended homogenously in a mortar with a pestle through geometric dilution. The tablet mix were compressed in to round tablets with 9 mm standard concave punch using rotary tablet punching machine (Rani et al., 2003).

Coating of core tablets

Coating was performed by dip coating method. The total solids in the coating solution were 4% w/v in acetone. Coating formula given in Table I. The weight gain due to coating was maintained at 3%w/w (Rani et al., 2003).

Evaluation of porous osmotic pump tablets

Physicochemical parameters

Diameter

The diameter of the matrix tablets and coated tablets of porous osmotic pump were determined by using screw gauge. Ten tablets from each formulation were randomly selected and used. Then the average diameter and standard deviation were calculated (Rani et al., 2003).

Thickness

The thickness of the matrix tablets, core and coated tablets

Table I. Master formula for porous osmotic pump tablet

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Core tablets										
Aceclofenac solid dispersion	400	400	400	400	400	400	400	400	400	400
Potassium chloride	40	60	80	40	60	80	40	60	80	-
Lactose	95	75	55	95	75	55	95	75	55	135
Sodium lauryl sulphate	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Coating- Components in % w/w										
Cellulose acetate	80%	80%	80%	70%	70%	70%	60%	60%	60%	70%
P E G 4000	20%	20%	20%	30%	30%	30%	40%	40%	40%	30%

of porous osmotic pump were determined by using screw gauge. Ten tablets from each formulation were randomly selected and used. Then the average diameter and standard deviation were calculated (Rani et al., 2003).

Hardness

The hardness of the matrix tablets, core and coated tablets of porous osmotic pump were determined using the Pfizer hardness tester. Six tablets from each formulation were randomly selected and used. The average hardness and the standard deviation were calculated (Rani et al., 2003).

Friability

Friability of the matrix tablets and core tablets of porous osmotic pump tablets were determined. Six 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 (Rani et al., 2003),

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

Weight uniformity

Ten Tablets were randomly selected from each batch and

individually weighed. The average weight and standard deviation of 10 tablets were calculated (Rani et al., 2003).

Determination of drug content

Five tablets were accurately weighed and powdered. A quantity of the powder equivalent to 100 mg of Aceclofenac 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 273 nm. This procedure was repeated thrice. Amount of drug present was determined from the calibration curve of Aceclofenac in methanol (Rani et al., 2003).

In vitro drug release studies porous osmotic pump tablets

Drug release studies were carried out using USP dissolution test apparatus (Apparatus II paddle type). The dissolution medium was 900 ml of phosphate buffer pH 7.5. The release was performed at $37 \pm 0.5^\circ\text{C}$, with a rotation speed of 50 rpm. 1 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were diluted to 10 mL with fresh buffer. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution

Table II. Physicochemical parameters of developed porous osmotic pump tablets

Formulation code	Hardness (kg/cm ²)	Friability (%)	Thickness (mm)	Weight (mg)	Drug content (%)
F1	5.2±0.12	0.013	4.84±0.013	566.24±1.023	100.1±0.253
F2	5.4±0.16	0.035	4.80±0.011	565.33±1.24	99.58±0.627
F3	5.2±0.10	0.046	4.75±0.007	566.49±1.025	99.03±0.372
F4	5.4±0.11	0.055	4.82±0.014	565.54±1.33	99.86±0.672
F5	5.0±0.14	0.028	4.77±0.012	566.71±1.57	99.55±0.711
F6	5.2±0.09	0.019	4.75±0.012	565.49±1.29	100.12±0.127
F7	5.2±0.13	0.102	4.78±0.015	565.51±0.98	99.06±0.185
F8	5.2±0.12	0.058	4.74±0.010	566.39±1.62	99.27±0.331
F9	5.0±0.11	0.082	4.71±0.016	566.22±1.02	99.49±0.281
F10	5.4±0.10	0.078	4.70±0.014	565.14±1.12	99.20±0.418

Table III. Summary of in vitro drug release kinetics of formulations

Formulation	Korsmeyer Peppas		Zero order		First order	Higuchi
	n	R ²	K ₀	R ²	R ²	R ²
F1	0.716	0.996	2.857	0.980	0.987	0.967
F2	0.781	0.994	4.3	0.989	0.993	0.951
F3	0.797	0.990	6.722	0.977	0.997	0.971
F4	0.680	0.998	5.313	0.965	0.989	0.984
F5	0.570	0.970	5.782	0.955	0.985	0.985
F6	0.774	0.996	7.315	0.983	0.997	0.966
F7	0.782	0.995	8.663	0.992	0.970	0.945
F8	0.798	0.998	9.89	0.990	0.972	0.963
F9	0.796	0.993	11.34	0.986	0.907	0.959
F10	0.809	0.989	3.52	0.995	0.995	0.934
Hifenac SR	0.498	0.964	12.69	0.935	0.733	0.981

Correlation coefficient (R²) of different models, drug release exponents (n), zero order release rate constants (K₀)

by UV spectrophotometer at 273 nm. The *in vitro* drug release profile of all the matrix and CPOP formulations were compared with the marketed product Hifenac SR (Company: Intas Pharmaceuticals, Batch number: DL 2392) (Kanagale et al., 2004).

Kinetics modeling of drug dissolution profiles

Zero order release kinetic

In many of the modified release dosage forms, particularly sustained or controlled release dosage forms (those dosage forms that release the drug in planned, predictable and slower than the normal manner) is zero order 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, 'K₀' is the zero order release rate constant and 't' is the release time. The plot of % cumulative drug released versus time is the linear (Donald, 2000).

First order release kinetic

Most conventional dosage forms exhibits this dissolution mechanism. Some modified release preparation, particularly prolonged release formulations, adheres to this type of dissolution pattern. It assumes that the drug molecules, diffuses out through a gel like layer formed around the drug during the dissolution process. 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, 'K₁' is the first order release rate constant and 't' is the release time. A plot of log % drug release versus time is the linear (Donald, 2000).

Higuchi release model

A large number of modified release dosage form contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the drug is

dictated by water penetration rate (diffusion controlled). To study the Higuchi release model the release rate data are fitted into the following equation:

$$Q = K_H t^{1/2}$$

Where, 'Q' is the fraction of drug release, 'K_H' is the release rate constant and 't' is the release time. In Higuchi model, a plot of % cumulative drug released versus square root of time is linear (Donald, 2000).

Koresmeyer and Peppas kinetics

To study the Koresmeyer and Peppas release kinetics the release rate data was fitted in to following equation:

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

Where, Mt/M 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. In Peppas model the 'n' value is used for analysis of the drug release mechanism from tablets were determined from log (drug fraction released at time t) Vs log (time) plots, and the value indicates the release pattern of the drug from tablets (Donald, 2000).

Optimization

In the numerical optimization techniques, the desirability approach was used to generate the optimum settings for the formulation. For the optimized formulation, the drug release at 1 h, 4 h, 8 h, T_{50%} and release exponent(n) were considered as the dependent variables (Table IV).

Effect of pH on drug release

The optimized formulation of porous osmotic pump tablets were tested for the effect of pH on drug release. The formulation was 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

Table IV. Result of release parameter obtained for formulations by general factorial design

Run	Potassium chloride (mg)	PEG 4000 (%)	% Cumulative drug release after			n value	T _{50%} (h)
			1 h	4 h	8 h		
F1	40	20	5.42	14.54	24.54	0.716	16
F2	60	30	6.96	19.56	35.82	0.781	11
F3	80	40	10.09	34.93	54.96	0.797	7
F4	40	20	10.85	29.13	44.83	0.680	9
F5	60	30	12.63	33.01	49.83	0.570	8
F6	80	40	15.10	36.02	60.29	0.774	6.2
F7	40	20	14.14	39.94	72.22	0.782	5.5
F8	60	30	15.55	48.12	81.09	0.798	4.2
F9	80	40	17.06	54.06	93.76	0.796	3.5

dissolution test apparatus (type II) and compared (Kanagale et al., 2007).

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 $37 \pm 0.5^\circ\text{C}$ in 7.5 pH phosphate buffer for 8 h using USP dissolution test apparatus (type II) and compared (Kanagale et al., 2007).

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 $37^\circ\text{C} \pm 1^\circ\text{C}$). Release studies were performed in 900 mL of media using USP-II dissolution apparatus (50 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 (Kanagale et al., 2007).

$$\pi V = nRT$$

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 (Prakash et al., 2009).

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 aluminium foil and stored at $30 \pm 2^\circ\text{C}$, $65 \pm 5\%$ RH and at $40 \pm 2^\circ\text{C}$, $75 \pm 5\%$ RH for 6 months. Tablets were periodically removed and evaluated for physical characteristics, in-vitro drug release (Thripathi KD, 1999).

Results 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 3350 cm^{-1} (NH stretch), 1646 cm^{-1} (C=O), 3080 cm^{-1} (Aromatic CH), 743 cm^{-1} (-Cl stretch), 1434 cm^{-1} (CH bend), 1547 cm^{-1} (NH bend). The FTIR characteristic of Aceclofenac with polymers resembles almost with the spectra of authentic sample of Aceclofenac. The studies suggest that there is no incompatibility between drug and polymer. Spectra are shown in the Figure 1.

Evaluation of matrix and porous osmotic pump tablets

Physicochemical parameters

The mean values of hardness, friability, thickness, weight and drug content of prepared porous osmotic pump tablets is recorded in the Table II. The results were found to be within

Figure 1. FT-IR spectra.

A-Pure drug Aceclofenac, B-Solid dispersion of drug and mannitol, C-Physical mixture of osmotic pump tablet of Aceclofenac

the limits. The weight and percentage friability of all formulations of the batches was found to be within the pharmacopoeial limit.

In vitro dissolution study

In porous osmotic pump tablets the drug release rate 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. If the pore former concentration increases then the number of pore formed or the pore size also increases, which causes easy leaching of drug from the formulation. If the concentration of the pore former or the osmotic agent increased beyond a limit will cause the release of the drug in diffusion manner (Makhija and Vavia, 2003). The results were compared with the marketed SR tablet Hifenac SR. Within 7 h the total drug in the marketed product was released. Results are shown in the Figure 2 & 3.

Figure 2. Dissolution profile of porous osmotic pump tablets F1-F6.

Figure 3. Dissolution profile of porous osmotic pump tablets F7-F10.

In vitro drug release kinetics

The *in vitro* release data was fitted to various kinetic models like Higuchi, First order, Zero order and Peppas. In porous osmotic pump tablets F1 to F6 follows first order kinetics, F7 to F10 follows zero order kinetics. Results are given in the Table III. When the data were plotted according to the first-order equation, the formulations showed a comparatively poor linearity, with regression value of 0.970; whereas the regression value for zero-order equation was 0.992, which indicated that drug release from optimized formulation (F7) was independent of drug concentration (Kanagale et al., 2007). In all the formulations 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.

In the case of marketed product the regression value of zero order (0.935) and *n* value of peppas (0.498) were less than the optimized formulation (F7) which shows the optimized formulation is much better than the marketed product.

Optimization

In vitro drug release study after 1 hour (h)

Total amount of Aceclofenac released from all formulations ranges from 5.42% to 17.06% in 1 h (Table IV). Increased rate of drug release was observed after 2 h with increase of the concentration of osmogen and pore former. When the tablets contact with dissolution media the pore formation on membrane will take place. The porous membrane and concentration of osmogen in the core tablet acts as rate controlling for the release of drug. In this case, effect of both osmogen and pore former can be explained by mathematical equation in terms of actual factors:

$$R1 = + 12.09 + 2.14 * A + 4.05 * B$$

The linear model is selected for this response with Model F-value 75.97 and *p* value is 0.0005. *p* value less than 0.0500 indicate model terms are significant. Both the factor A, potassium chloride and B, PEG 4000 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 (Figure 4A). Higher release of Aceclofenac was found after 1 h in higher concentrations of both factors. At high level of A and B the percentage release has high value which indicates factor A and B helps more release of drug (Sudeesh et al., 2011).

In vitro drug release study after 4 hour

Total amount of Aceclofenac released from all formulations ranges from 14.54% to 54.06% in 4 h (Table IV). 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:

$$R2 = +34.37 + 6.90 * A + 12.18 * B$$

The linear model is selected for this response with Model F-value 19.32 and p value is 0.0070 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 (Figure 4B).

In vitro drug release study after 8 hour

Total amount of Aceclofenac released from all formulations ranges from 24.54% to 93.76% in 8 h (Table IV). 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:

$$R3 = +57.48 + 11.24 * A + 21.96 * B$$

The linear model is selected for this response with Model F-value 65.87 and p value is 0.0007 indicate the model is significant. The effect of A and B can be further elucidated with the help of 3D surface plot (Figure 4C).

Effect of formulation variables on T50%

The value of $T_{50\%}$ ranges from the 3.5 to 16 h (Table IV). 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:

$$R5 = +7.82 - 2.30 * A - 3.47 * B$$

The linear model was found to be significant for the time for 50% of drug release. The Model F-value of 6.94 and value of p is less than 0.0436 indicate the model is significant. The equation indicates that $T_{50\%}$ increase as factors decreases (negative effect) (Figure 4D).

Effect of formulation variable on release exponent

The linear model was found to be not significant for release exponent with the model F-value 2.08 and p value 0.2473 (Table IV). In this response, factor A and B was found to be not significant (Figure 4E). So, the model equation is as follows:

$$R6 = +0.74 + 0.032 * A + 0.014 * B$$

The n value of optimized formula found to be 0.782 which indicates the mechanism of release is non Fickian.

Figure 4. A-3D surface plot showing the effect of factor A and factor B on drug release after 1 h, B-3D surface plot showing the effect of factor A and factor B on drug release after 4 h, C-3D surface plot showing the effect of factor A and factor B on drug release after 8 h, D-3D surface plot showing the effect of factor A and factor B on $T_{50\%}$, E-3D surface plot showing the effect of factor A and factor B on drug release exponent.

ANOVA

In porous osmotic pump tablets the result of ANOVA demonstrate all the independent variables (Factors) were found to be significant for response R1, R2, R3, R4 but not significant for response R5 (Table V). So, above result indicate that both the factors play an important role in the formulation of porous osmotic pump tablet containing Aceclofenac.

It was concluded that the formulation F7 is the most satisfactory formulaion for the physiologically independent controlled delivery of Aceclofenac. A good reletionship between the experimental and predicted values (Table VI), which confirms the practicability and validity of the model (Sudeesh et al., 2011).

Membrane morphology of porous osmotic pump tablets

After 12 h dissolution, clearly showed pores formed in range

Table V. Summary of ANOVA table for porous osmotic pump tablets from general factorial design

Source	d.f	Sum square	Mean square	F value	p value
Drug release at 1 h					
A	2	28.11	14.06	75.97	0.0034
B	2	103.74	51.87	119.54	0.0003
Model	4	131.85	32.96	75.97	0.0005*
Drug release at 4 h					
A	2	288.72	144.36	9.37	0.0309
B	2	902.35	451.17	29.28	0.0041
Model	4	1191.07	297.77	19.32	0.0070*
Drug release at 8 h					
A	2	773.86	386.93	26.69	0.0049
B	2	3046.08	1523.06	105.05	0.0003
Model	4	3819.91	954.98	65.97	0.0007*
T _{50%}					
A	2	31.78	15.89	4.24	0.1026
B	2	72.14	36.07	9.63	0.0296
Model	4	103.92	25.98	6.94	0.0436*
n value					
A	2	9.343E-003	4.671E-003	1.22	0.3862
B	2	0.023	0.011	2.95	0.1634
Model	4	0.032	7.989E-003	2.08	0.2473 ^{ns}

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

Figure 5. Membrane morphology of formulation F7 by scanning electron microscopy.

of 1 to 30 µm owing to dissolution of PEG 4000 (Figure 5). The leaching of PEG 4000 from the membrane leads to formation of pores, and thus the release of drug takes place (Kanagale et al., 2007; Prakash et al., 2009). In formulation F7 contains 40% PEG which produces more pores compare to F1 (20% PEG 4000) and F4 (30% PEG 4000).

Effect of Physiological parameters on drug release

When formulation F7 was subjected to *in vitro* release studies in buffers with different pH and distilled water, no significant difference in the release proles were seen compared to that in phosphate buffer pH 7.5. Thus the uid in different parts of the GI tract will scarcely affect drug release from the osmotic system.

The release profile from the optimized formulation was concluded that it was independent of the agitational intensity of the release media.

The osmotic pressure of the media at 7.753/31.009 atm showed the lag time 1.4/1.9 h and dissolution rate 7.65/6.66%/h respectively. The drug release rate decreased with increase in osmotic pressure in the media; however, the lag time was prolonged. This finding confirms that the mechanism of drug release is by the osmotic pressure (Kanagale et al., 2007; Prakash et al., 2009)).

Table VI. Comparison of experimented and predicted values of optimized formulation

Optimized formula F7	Dependable variables				
	% Cumulative drug release at 1 h	% Cumulative drug release at 4 h	% Cumulative drug release at 8 h	T _{50%} (h)	Release exponent (n value)
Predicted	13.6311	40.8744	72.0711	6.74444	0.774222
Experimental	14.14	39.94	72.22	5.5	0.782

Stability studies

After the 6 months storage of formulation F7, 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.

Conclusion

By considering the factors such as *in vitro* drug release and n value, it was concluded that F7 is the best formulation. The results were compared with the marketed SR tablet and concluded that the optimized formulation of prepared porous osmotic pump tablets was more effective for controlled delivery of Aceclofenac.

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