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RESEARCH ARTICLE

Development and Optimization of Osmotically Controlled Oral Drug Delivery System of Aceclofenac

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ABSTRACT

The aim of the present study is to formulate and optimize porous osmotic pump tablets for controlled delivery of Aceclofenac for the treatment of Arthritis. Drugs can be delivered in a controlled pattern over a long period of time by osmotic technology. The formulation contains drug core and it is coated with semipermeable membrane. The formulation design was done by multilevel categoric factorial design using Design expert software. Solid dispersed form of Aceclofenac was used to improve the solubility of the drug. The dependent variables were considered are concentration of osmotic agent (Potassium chloride), solubility enhancer (Sodium lauryl sulphate) and percentage of weight gain after coating. The core tablets were coated with cellulose acetate (80%) and PEG 4000 (20%). All the formulations were studied for the physiochemical parameters and drug release studies. Numerical optimization techniques were applied to find the best formulation. The effect of pH, Osmotic pressure, agitation intensity on drug release, membrane morphology and stability studies were performed. The optimized formulation shows stable, physiological properties independent controlled drug delivery of Aceclofenac for the period of 24hours.

KEYWORDS

Aceclofenac, Osmotic pressure, Controlled porosity osmotic pump tablet, Osmogent, Semipermeable membrane

INTRODUCTION

Oral controlled drug delivery system provides the continuous delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit. Also included are systems that target the delivery of a drug to a specific region within the GI tract for either a local or a systemic action.[1]

In a typical therapeutic regimen, the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic effects. Survey indicated that dosing more than once or twice daily greatly reduces patient compliance. Oral controlled release system provide significant benefits over immediate release formulation, including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule.[2]

The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physico-chemical properties of the drug, presence of excipients, physiological factors such as

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presence or absence of food, pH of the gastro-intestinal tract (GI) and so on. However, 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.[3,4]

The oral osmotic pump tablet has many advantages, such as reducing risk of adverse reactions, improving patient compliance, zero–order delivery rate, a high degree of *in vitro–in vivo* correlation and they are simple in operation.[2,5]

The pump can be made with single or multi-compartment dosage form, in either form, the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure. The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall.[1,6]

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 water permeability of the semi permeable membrane and the osmotic pressure of the core formulation, thickness and total surface area of coating. All of these variable are under the control of the designer and do not vary under physiological condition.[7]

The drug of choice Aceclofenac recommended dose for adult is 100mg twice daily. So by making the controlled porosity osmotic pump tablet of this drug can improve the patient compliance by reducing the multiple dosing, improved therapeutic effect by maintaining the drug concentration in therapeutic level in the body, the physiological parameters in the body does not affects the drug release and also by reducing the side effects of the drugs by the minimal exposure of the dug in the GIT.[8,9]

MATERIALS AND METHOD

Materials

The pure drug Aceclofenac obtained as gift sample from Astrazeneca pharma India Ltd (Bangalore, India). Potassium chloride, Lactose, Cellulose acetate, Magnesium stearate and Mannitol were purchased from S. D. fine Chem. LTD (Mumbai, India). PEG 4000 and sodium lauryl sulphate was received as gift sample from Strides Arco labs LTD (Bangalore, India).

Method

Drug - Excipient Compatibility Studies

Fourier Transforms 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 compatibility studies were carried out using FT-IR spectroscopy. IR spectrum of pure drug and polymers was seen in between 600- 4000 cm^2.[10]

Experimental Design

Multilevel categoric factorial design was applied using the software Design-Expert software (Stat-Ease Inc, Minneapolis, USA). Factors considered as A, B & C. 'A' is the osmotic agent (Potassium chloride), 'B' is solubility enhancer (Sodium lauryl sulphate) and 'C' is % Weight gain after coating.[11]

Preparation of Solid Dispersion

Solid dispersion of Aceclofenac was prepared by using the carrier mannitol. The drug carrier ratio was taken as 1:1. The 5g drug was dissolved in 100 mL acetone and the 5g mannitol was dissolved in 100mL distilled H_2O.

Table 1: Master formula of controlled porosity osmotic pump tablet

Formula-tions	Aceclofenac solid dispersion (200mg drug + 200mg Mannitol) (mg)	Potassium chloride (mg)	Lactose (mg)	Sodium lauryl sulphate (mg)	Magnesium stearate (mg)	% Weight gain after coating
FA1	400	55	82	8	5	2.5
FA2	400	55	82	8	5	3
FA3	400	55	82	8	5	3.5
FA4	400	55	80	10	5	2.5
FA5	400	55	80	10	5	3
FA6	400	55	80	10	5	3.5
FA7	400	55	78	12	5	2.5
FA8	400	55	78	12	5	3
FA9	400	55	78	12	5	3.5
FA10	400	65	72	8	5	2.5
FA11	400	65	72	8	5	3
FA12	400	65	72	8	5	3.5
FA13	400	65	70	10	5	2.5
FA14	400	65	70	10	5	3
FA15	400	65	70	10	5	3.5
FA16	400	65	68	12	5	2.5
FA17	400	65	68	12	5	3
FA18	400	65	68	12	5	3.5
FA19	400	75	62	8	5	2.5
FA20	400	75	62	8	5	3
FA21	400	75	62	8	5	3.5
FA22	400	75	60	10	5	2.5
FA23	400	75	60	10	5	3
FA24	400	75	60	10	5	3.5
FA25	400	75	58	12	5	2.5
FA26	400	75	58	12	5	3
FA27	400	75	58	12	5	3.5

Both the solutions were mixed and then evaporated to get the solid dispersion.[11]

Preparation of Porous Osmotic Pump Tablets

Preparation of Core Tablets

Core tablets were prepared by direct compression method. An accurately weighed quantity of ingredients as shown in the table 1 was passed through sieve number 60. All the ingredients except lubricant (Magnesium stearate) were blended homogenously by geometric dilution. The mix again blended with magnesium stearate for lubrication. The tablet mix were compressed in to round tablets with 9 mm standard punch using rotary tablet punching machine.[11]

Coating of Core Tablets

Coating was performed by spray coating method. The total solids in the coating solution were 4% w/v in acetone. Coating solution contains the components Cellulose acetate- 80% and P E G 4000 - 20%. The weight gain due to coating was adjusted in 2.5, 3 & 3.5% w/w.[11]

Evaluation of Porous Osmotic Pump Tablets

Physicochemical Parameters

The diameter, thickness, hardness, friability and weight uniformity of all the formulations were

determined as per the official standards. The tablets from all the formulations were randomly selected and the average results and standard deviations were calculated.[12]

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 274 nm. This procedure was repeated thrice. Amount of drug present was determined from the calibration curve of Aceclofenac in methanol.[12]

In Vitro Drug Release Studies Porous Osmotic Pump Tablets

The *in vitro* drug release studies were carried out using USP type II dissolution test apparatus for 24 hours. The dissolution medium was 900 ml phosphate buffer of pH 7.5 and the release was performed at 37 ± 0.5 °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 by UV spectrophotometer at 274 nm.[11]

Kinetics Modeling of Drug Dissolution Profiles

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 plot of % cumulative drug released versus time is the linear.[6,13]

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. A plot of log % drug release versus time is the linear.[6,13]

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, '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.[6,13]

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, $Mt/M\infty$ 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. 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.[6,13]

Optimization

By usning the Design expert software the numerical optimization techniques, the desirability approch was used to generate the optimum settings for the formulation. To find out the optimized formula the independent variables along with the drug release at 2 h, 8 h, 16 h, 24h, Zero order regression value, $T_{50\%}$ and release exponent(n) were considered as the dependent variables.[4,14]

Effect of pH on Drug Release

The optimized 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 50 rpm and 37 ± 0.5°C using USP type II dissolution test apparatus and compared.[13]

Effect of Agitation Intensity on Drug Release

The optimized formulation formulations 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 using USP type II dissolution test apparatus and compared.[13]

Effect of Osmotic Pressure

The *in vitro* drug 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±1 °C. Release studies were performed in 900 mL of media using USP type 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.[4,13]

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.[14,15]

RESULTS

Drug Polymer Compatibility Studies using FT-IR

FT-IR studies were carried out to analyze the chemical interaction between the drug and polymer. The FT-IR spectrum for pure drug and drug- polymers mixture shows 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.

Physicochemical Parameters

The hardness, friability, thickness, weight and drug content of all the formulations were determined and results were found to be within the limits (Table 2).

In Vitro Dissolution Study

In porous osmotic pump tablets the drug release rate depends on the concentration of the osmotic agent, surfactant used and also the % of weight gain after tablet coating. 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 surfactant concentration increases then the solubility of the active ingredients also increases, which causes easy leaching of drug from the formulation.

Table 2: Physicochemical parameters of the formulations

Formulation code	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Weight (mg)	Drug content (%)
FA1	5.2±0.15	0.043	4.74±0.017	563.24±1.23	99.41±0.253
FA2	5.3±0.11	0.065	4.80±0.015	566.33±1.24	99.55±0.624
FA3	5.3±0.17	0.026	4.85±0.014	569.49±1.025	99.53±0.342
FA4	5.1±0.16	0.045	4.76±0.017	563.54±1.33	99.76±0.672
FA5	5.2±0.15	0.048	4.88±0.016	566.71±1.57	99.46±0.731
FA6	5.2±0.13	0.039	4.90±0.014	569.49±1.29	99.95±0.237
FA7	5.2±0.12	0.092	4.73±0.016	563.51±0.98	99.56±0.535
FA8	5.3±0.15	0.078	4.82±0.013	566.39±1.62	99.67±0.211
FA9	5.2±0.11	0.082	4.88±0.015	569.22±1.02	99.46±0.261
FA10	5.4±0.12	0.048	4.70±0.012	563.14±1.12	99.60±0.408
FA11	5.2±0.14	0.033	4.79±0.019	566.24±1.023	99.45±0.242
FA12	5.3±0.13	0.065	4.86±0.017	569.33±1.24	99.78±0.662
FA13	5.2±0.16	0.086	4.73±0.006	563.49±1.25	99.45±0.332
FA14	5.1±0.14	0.035	4.80±0.019	566.54±1.33	99.84±0.631
FA15	5.3±0.13	0.078	4.84±0.017	569.71±1.57	99.65±0.532
FA16	5.2±0.11	0.029	4.72±0.012	563.49±1.29	99.73±0.243
FA17	5.1±0.12	0.092	4.78±0.014	566.51±0.98	99.56±0.321
FA18	5.3±0.14	0.078	4.83±0.011	569.39±1.62	99.37±0.521
FA19	5.3±0.15	0.062	4.74±0.017	563.22±1.02	99.69±0.334
FA20	5.2±0.12	0.048	4.79±0.016	566.14±1.12	99.24±0.424
FA21	5.2±0.14	0.053	4.83±0.012	569.24±1.23	99.39±0.422
FA22	5.3±0.13	0.045	4.72±0.017	563.33±1.24	99.68±0.424
FA23	5.3±0.11	0.056	4.79±0.003	566.49±1.25	99.43±0.332
FA24	5.2±0.15	0.045	4.85±0.016	569.54±1.33	99.83±0.324
FA25	5.2±0.14	0.048	4.74±0.012	563.71±1.57	99.57±0.32
FA26	5.2±0.12	0.049	4.81±0.014	566.49±1.29	99.92±0.132
FA27	5.2±0.16	0.062	4.86±0.013	569.51±0.98	99.06±0.135

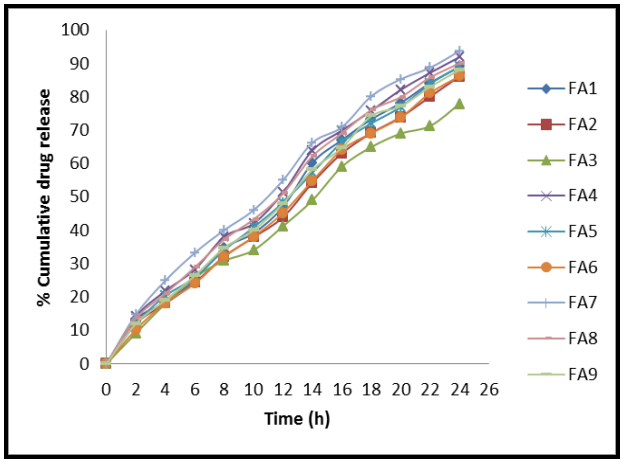

Figure 1: Dissolution profile of formulation FA1 to FA9

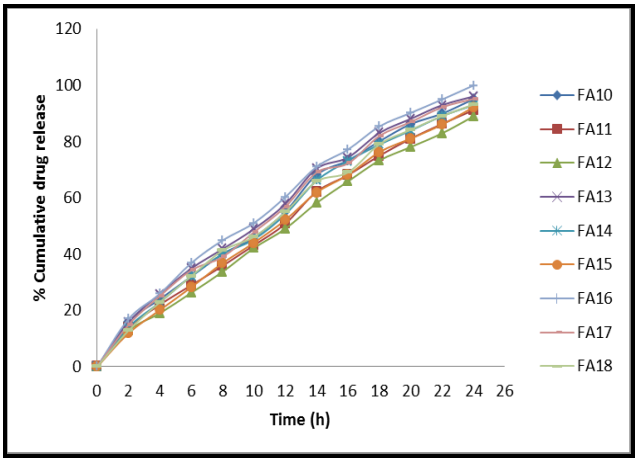

Figure 2: Dissolution profile of formulation FA10 to FA18

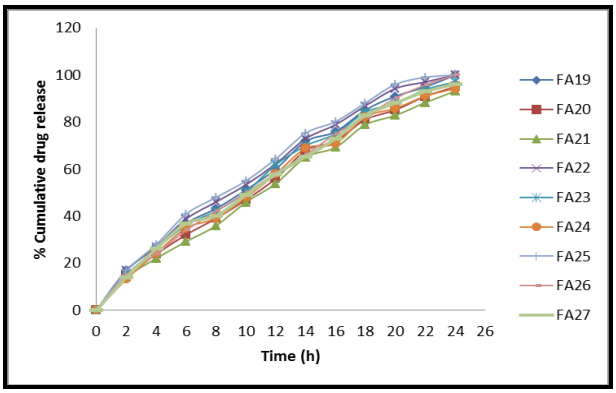

Figure 3: Dissolution profile of formulation FA19 to FA27

If the increase in % of weight gain after coating leads to increase in the thickness of the coat which causes decrease in the rate of drug release. This is due to the increase in the path length to be traversed by the drug molecule. Results are shown in the figure 1, 2, 3.

In Vitro Drug Release Study after 2 Hour (h)

Total amount of Aceclofenac released from all formulations ranges from 9.13% to 16.92% in 2 h (Table 3). Increased rate of drug release was observed after 2 h with increase of the concentration of osmogent and surfactant. The rate of drug decreases with increase in the % of weight gain by the coating. The effect of osmogent, surfactant and % of weight gain can be explained by mathematical equation in terms of actual factors:

R1 = 14.00 - 1.76*A(1) + 0.31*A(2) - 0.49*B(1) - 0.33*B(2) + 1.67*C(1) - 0.20*C(2)

The linear model is selected for this response with Model F-value 30.39 and p value is < 0.0001. p value less than 0.0500 indicate model terms are significant. The factor A, potassium chloride and B, SLS increases the 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 4). Higher release of Aceclofenac was found after 2 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. The factor C, weight gain decreases the drug release from the formulation (negative effect). The factor A(1), B(1), C(1) represents lower value and A(2), B(2) and C(2) represents upper value.

In Vitro Drug Release Study after 8 Hour

Total amount of Aceclofenac released from all formulations ranges from 30.79% to 47.94% in 8 h (Table 3). Increased rate of drug release was observed after 8 h with increase of the concentration of osmogent and solubility enhancer. The effect of osmogent, surfactant and % of weight gain can be explained by mathematical equation in terms of actual factors:

R2 = 38.72 – 3.89*A(1) + 0.53*A(2) -2.59*B(1) + 0.16*B(2) + 3.12*C(1) - 0.78*C(2)

The Equation shows both factors A and B have significant positive effect on the response and the factor C have significant negative effect. The effect of A and B can be further elucidated with the help of 3D surface plot (Figure.5).

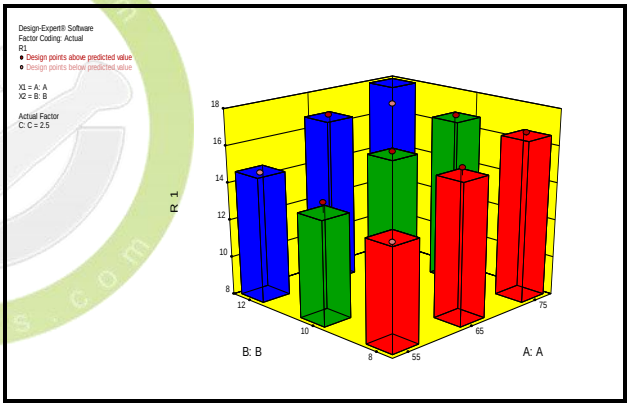

Figure 4: 3D surface plot showing effect of factor A &B on drug release after 2h

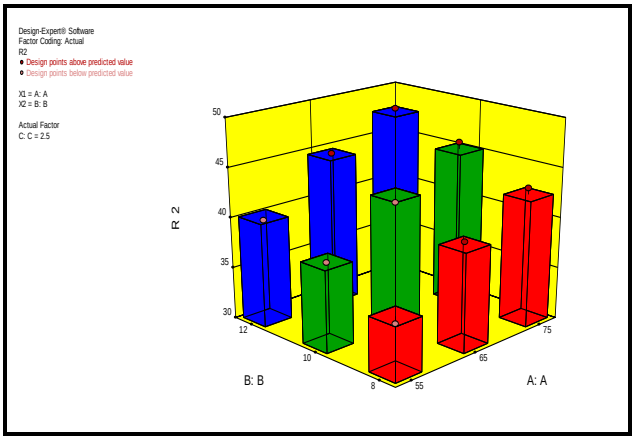

Figure 5: 3D surface plot showing effect of factor A &B on drug release after 8h

In Vitro Drug Release Study after 16 Hour

Total amount of Aceclofenac released from all formulations ranges from 59.03% to 80.19% in 16 h (Table 3). Increased rate of drug release was observed after 16 h with increase of the concentration of osmogent and solubility enhancer (positive effect) and factor C have negative effect. The effect of osmogent, surfactant and % of weight gain can be explained by mathematical equation in terms of actual factors:

R3 = 70.66 - 4.66*A(1) + 0.56*A(2) - 2.52*B(1) + 0.52*B(2) + 3.50*C(1) - 0.26*C(2)

The effect of A and B can be further elucidated with the help of 3D surface plot (Figure 6).

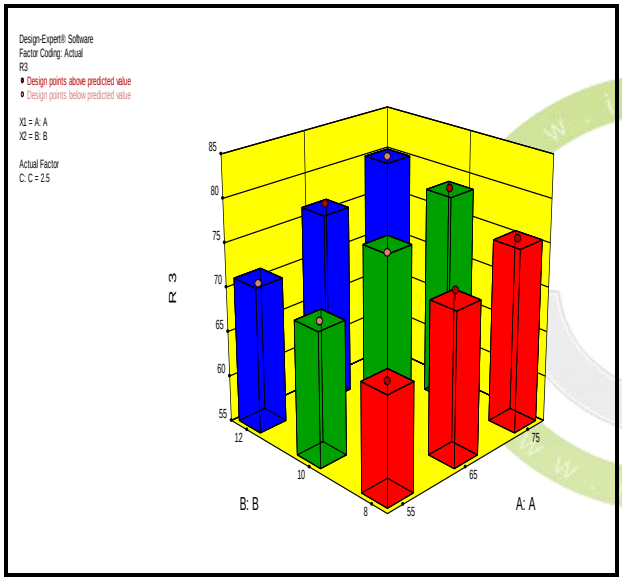

Figure 6: 3D surface plot showing effect of factor A &B on drug release after 16h

In Vitro Drug Release Study after 24 Hour

Total amount of Aceclofenac released from all formulations ranges from 77.85% to 99.97% in 24 h (Table 3). Increased rate of drug release was observed after 24 h with increase of the concentration of osmogent, solubility enhancer (positive effect) and the factor % of weight gain have negative effect. The effect of factors osmogent, surfactant and % of weight gain can be explained by mathematical equation in terms of actual factors:

R4 = 93.14 - 5.17*A(1) + 0.65*A(2) -2.48*B(1) + 0.11*B(2) + 3.01*C(1) - 0.25*C(2)

The effect of A and B can be further elucidated with the help of 3D surface plot (Figure 7).

Effect of Formulation Variable on Release Exponent

The linear model was found to be significant for release exponent with the model F-value 20.53 and p value < 0.0001. In this response, factor A, B and C was found to be significant (Figure 8). So, the model equation is as follows:

R5 = 0.79 + 0.032*A(1) - 5.667E -003*A(2) + 9.222E-033*B(1) + 7.111E-003*B(2) - 0.030*C(1) + 1.556E-003*C(2)

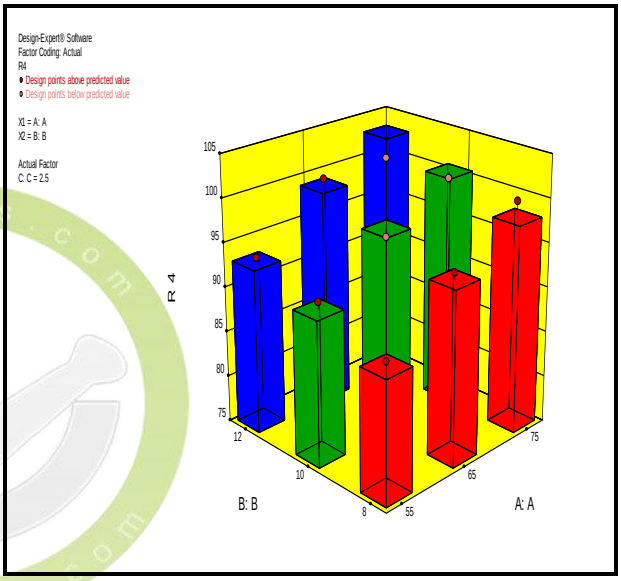

Figure 7: 3D surface plot showing effect of factor A &B on drug release after 24h

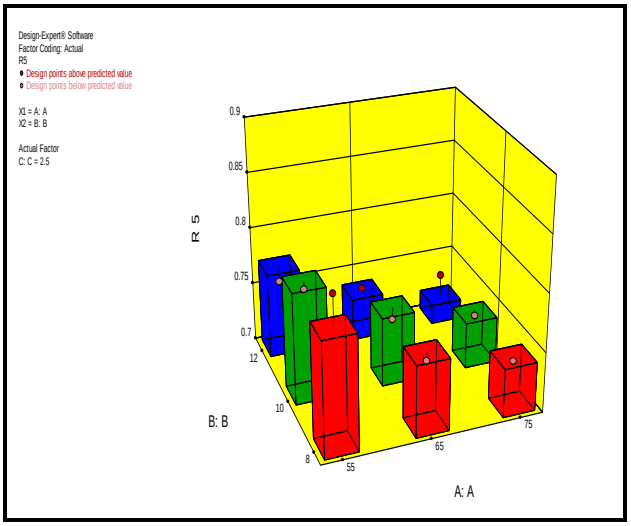

Figure 8: 3D surface plot showing effect of factor A &B on release exponent

Effect of Formulation Variable on Zero Order Regression Value

The linear model was found to be significant for zero order regression value with the model F-value 9.17 and p value < 0.0001. In this response, factor A, B and C was found to be significant (Figure 9). So, the model equation is as follows:

R6 = 0.99 + 3.815E-003*A(1) + 5.926E-004*A(2) + 2.37E-003*B(1) - 6.296E-4B(2) - 4.852E-3*C(1) + 2.593E-3*C(2)

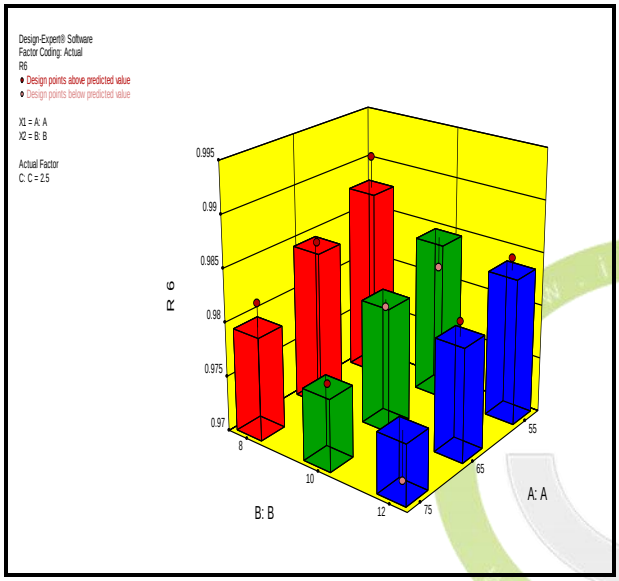

Figure 9: 3D surface plot showing effect of factor A &B on zero order regression value

Effect of Formulation Variables on $T_{50\%}$

The value of $T_{50\%}$ ranges from the 4.4 to 7.2 h (Table 3). The increased $T_{50\%}$ was observed at low concentrations of osmogent and solubility enhancer (negative effect). But the increase in % of weight gain increases $T_{50\%}$ (positive effect). The effect of factors osmogent, surfactant and % of weight gain can be explained by mathematical equation in terms of actual factors:

R7 = 11.21 + 1.36*A(1) - 0.15*A(2) + 0.70*B(1) - 0.081*B(2) - 0.77*C(1) + 0.19*C(2)

The linear model was found to be significant for the time for 50% of drug release. The Model F-value of 205.47 and value of p is less than < 0.0001indicate the model is significant (Figure 10).

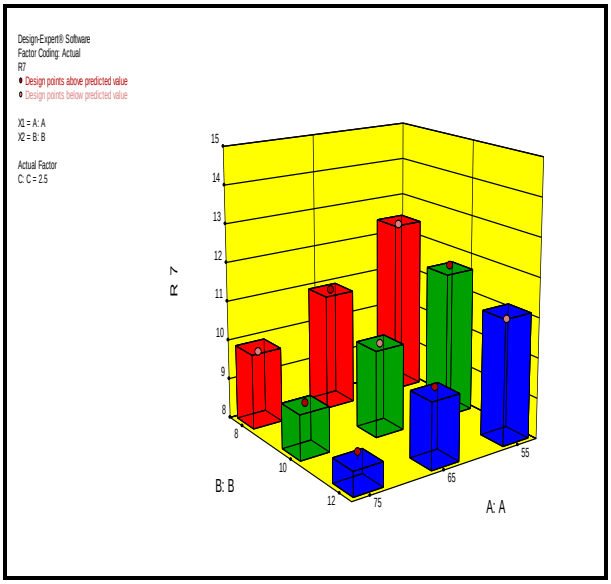

Figure 10: 3D surface plot showing effect of factor A &B on $T_{50\%}$

***In Vitro* Drug Release Kinetics**

The *in vitro* release data was fitted to various kinetic models like Higuchi, First order, Zero order and Peppas. All the formulations follow zero order kinetics. Results are given in the table 4. When the data were plotted according to the first-order equation, the formulations showed a comparatively poor linearity whereas the regression value for zero-order equations shows more linearity. 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.

Correlation coefficient (R^2) of different models, drug release exponents (n), zero order release rate constants (K_0).

ANOVA

In porous osmotic pump tablets the result of ANOVA demostrate all the independent variables were found to be significant for response R1, R2, R3, R4, R5, R6 & R7 (Table 5). The results indicates that the factors A, B and C plays an important role in the formulation of porous osmotic pump tablet containing Aceclofenac.

Table 3: Release parameter obtained for formulations by general factorial design

Run	% cumulative drug release after				n value (R5)	Zero order (R^2) (R6)	$T_{50\%}$ (in hour) (R7)
	2 h (R1)	8 h (R2)	16 h (R3)	24h (R4)			
FA1	13.21	34.62	67.01	88.98	0.828	0.991	12.4
FA2	11.19	32.12	63.02	86.12	0.832	0.995	13.4
FA3	9.13	30.79	59.08	77.85	0.852	0.989	14.4
FA4	14.11	38.02	69.88	91.89	0.792	0.982	11.8
FA5	12.02	34.01	66.31	89.02	0.829	0.995	12.6
FA6	10.21	32.02	64.06	86.13	0.872	0.995	13.2
FA7	14.68	40.02	70.87	93.69	0.760	0.985	11
FA8	13.59	37.22	69.06	89.99	0.797	0.989	12
FA9	12.01	34.66	64.69	88.02	0.836	0.993	12.4
FA10	15.87	40.02	73.22	95.02	0.756	0.985	11
FA11	13.78	35.79	68.04	91.11	0.789	0.991	12
FA12	12.77	33.71	65.79	88.88	0.824	0.993	12.2
FA13	15.79	41.79	74.31	95.98	0.750	0.981	10.2
FA14	13.99	40.02	73.09	92.89	0.787	0.991	11.2
FA15	11.89	36.79	68.11	92.13	0.846	0.992	11.6
FA16	16.92	44.88	77.13	99.89	0.739	0.982	9.8
FA17	14.88	39.01	72.21	95.10	0.767	0.984	10.6
FA18	12.88	41.25	69.01	93.11	0.804	0.986	11
FA19	16.78	43.21	75.89	99.91	0.737	0.982	9.8
FA20	14.92	39.01	71.99	94.89	0.774	0.986	10.8
FA21	13.88	35.91	69.22	93.11	0.802	0.989	11.2
FA22	16.89	46.01	78.89	99.98	0.738	0.977	9.2
FA23	14.89	42.15	75.01	97.01	0.765	0.980	10
FA24	13.21	39.10	70.89	94.21	0.798	0.981	10.4
FA25	16.78	47.94	80.19	99.97	0.737	0.971	8.8
FA26	14.87	42.12	74.88	99.89	0.787	0.992	10
FA27	14.03	40.11	72.98	96.04	0.771	0.984	10.2

Table 4: Summary of *in vitro* drug release kinetics

Formulation	Korsmeyer Peppas		Zero order		First order	Higuchi
	n	R^2	K_0	R^2	R^2	R^2
FA1	0.828	0.984	3.729	0.991	0.951	0.939
FA2	0.832	0.990	3.551	0.995	0.951	0.937
FA3	0.852	0.993	3.213	0.989	0.970	0.944
FA4	0.792	0.991	4.055	0.982	0.961	0.951
FA5	0.829	0.995	3.679	0.995	0.970	0.945
FA6	0.872	0.996	3.597	0.995	0.954	0.938
FA7	0.760	0.996	3.835	0.985	0.942	0.963
FA8	0.797	0.995	3.737	0.989	0.959	0.955
FA9	0.836	0.995	3.673	0.993	0.956	0.945
FA10	0.756	0.992	3.905	0.985	0.929	0.959
FA11	0.789	0.994	3.753	0.991	0.946	0.953
FA12	0.824	0.992	3.684	0.993	0.954	0.947
FA13	0.750	0.996	3.958	0.981	0.928	0.966
FA14	0.783	0.996	3.856	0.991	0.971	0.947
FA15	0.846	0.998	3.822	0.992	0.941	0.953
FA16	0.739	0.997	4.055	0.982	0.671	0.970
FA17	0.767	0.995	3.941	0.984	0.931	0.962
FA18	0.804	0.998	3.845	0.986	0.944	0.963
FA19	0.737	0.997	4.057	0.982	0.661	0.969
FA20	0.774	0.995	3.922	0.986	0.931	0.960
FA21	0.802	0.994	3.868	0.989	0.940	0.953
FA22	0.738	0.997	4.118	0.977	0.634	0.972
FA23	0.765	0.997	3.992	0.980	0.912	0.970
FA24	0.798	0.995	3.920	0.981	0.944	0.963
FA25	0.737	0.996	4.146	0.971	0.706	0.975
FA26	0.787	0.998	4.106	0.992	0.664	0.961
FA27	0.771	0.995	3.950	0.984	0.916	0.965

Table 5: Summary of ANOVA table for formulations from general factorial design

Source	d.f	Sum square	Mean square	F value	p value
Drug release at 2 h (R1)					
A-A	2	47.54	23.77	42.57	< 0.0001
B-B	2	9.29	4.64	8.32	0.0024
C-C	2	44.97	22.48	40.27	< 0.0001
Model	6	101.80	16.97	30.39	< 0.0001*
Drug release at 8 h (R2)					
A-A	2	239.85	119.93	117.10	< 0.0001
B-B	2	113.50	56.75	55.41	< 0.0001
C-C	2	141.98	70.99	69.31	< 0.0001
Model	6	495.33	82.55	80.61	< 0.0001*
Drug release at 16 h (R3)					
A-A	2	349.74	174.87	171.43	< 0.0001
B-B	2	95.47	47.74	46.80	< 0.0001
C-C	2	205.24	102.62	100.60	< 0.0001
Model	6	650.46	108.41	106.27	< 0.0001*
Drug release at 24 h (R4)					
A-A	2	428.11	214.05	80	< 0.0001
B-B	2	106.27	53.13	19.86	< 0.0001
C-C	2	150.80	75.40	28.18	< 0.0001
Model	6	685.18	114.20	42.68	< 0.0001*
Release exponent (R5)					
A-A	2	0.015	7.699E-003	27.18	< 0.0001
B-B	2	3.622E-003	1.811E-003	6.39	<0.0001
C-C	2	0.016	7.937E-003	28.02	0.0071
Model	6	0.035	5.816E-003	20.53	< 0.0001*
Zero order regression value (R6)					
A-A	2	3.090E-004	1.545E-004	11.99	0.0004
B-B	2	8.141E-004	4.070E-004	3.16	0.0642
C-C	2	3.183E-004	1.591E-004	12.35	0.0003
Model	6	7.087E-004	1.181E-004	9.17	< 0.0001*
$T_{50\%}$ (R7)					
A-A	2	30.20	15.10	398.13	< 0.0001
B-B	2	7.83	3.91	103.16	< 0.0001
C-C	2	8.73	4.37	115.12	< 0.0001
Model	6	46.76	7.79	205.47	< 0.0001*

Note: (*) significant ($p<0.05$)

Optimization

Optimization criteria's were made to find out the best optimized formula. All the independent variables and the responses R1, R2, R3, R4 and R7 were considered in the range. The responses R5 and R6 were considered in the maximum value. Details are given in table 6. According to desirability approach after the optimization, around 18 solutions were obtained. In that the most desired and preferred one is selected as optimized formula. The best 5 results were given in table 7. By the optimization technique the optimized formula was considered is FA15. The desirability to become the best formulation was demonstrated by bar diagram of formulation FA15 in figure 11.

Table 6: Optimization criteria's

Variables	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:A	in range	55	75	1	1	3
B:B	in range	8	12	1	1	3
C:C	in range	2.5	3.5	1	1	3
R1	in range	10	20	1	1	3
R2	in range	35	50	1	1	3
R3	in range	65	85	1	1	3
R4	in range	90	100	1	1	3
R5	maximize	0.735	0.872	1	1	3
R6	maximize	0.971	0.995	1	1	3
R7	is in range	9	14	1	1	3

Table 7: Results of optimization

Number	Factors			Desirability	Selection
	A	B	C		
1	65	10	3.5	0.691	Selected
2	55	12	3	0.663	
3	65	8	3	0.618	
4	75	8	3.5	0.566	
5	65	10	3	0.562	

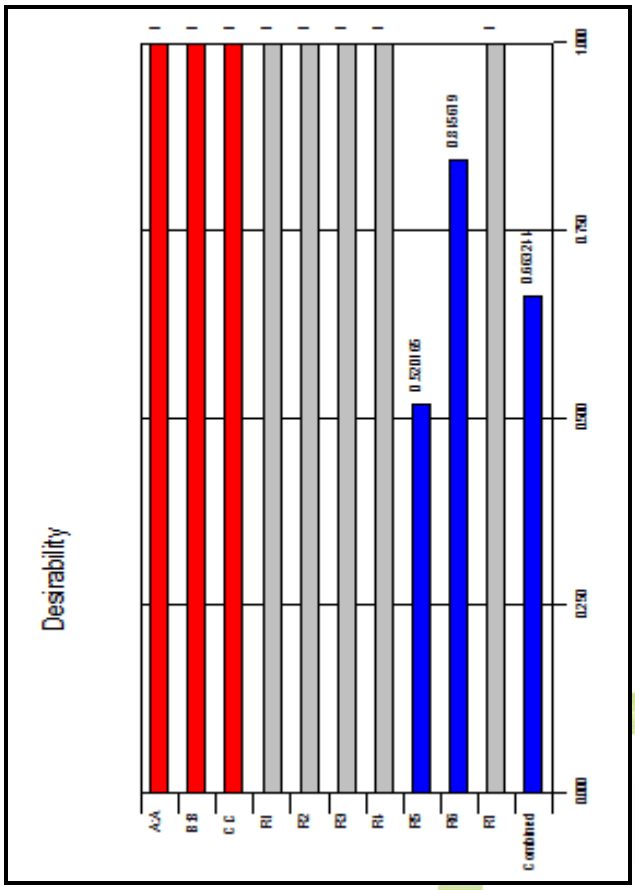

Figure 11: Desirability of Optimized formula

A good relationship between the experimental and predicted values (Table 8), which confirms the practicability and validity of the model.

Table 8: Comparison of experimented and predicted values of optimized formulation FA15

Dependable variables	Predicted	Experimental
% Cumulative drug release at 2 h	12.509	11.89
% Cumulative drug release at 8 h	37.075	36.79
% Cumulative drug release at 16 h	68.486	68.11
% Cumulative drug release at 24 h	91.139	92.13
Release exponent (n value)	0.821	0.846
Zero order regression value	0.989	0.992
$T_{50\%}$ (h)	11.57	11.6

Membrane Morphology of Porous Osmotic Pump Tablets

The scanning electron microscopy of membrane clearly showed pores formed in range of 1 to 30 µm (Figure 12). The leaching of PEG 4000 from the membrane leads to formation of pores, and thus the release of drug takes place.

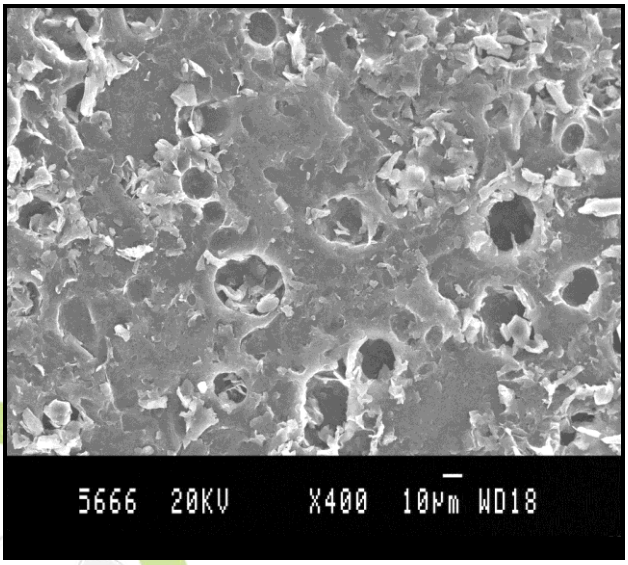

Figure 12: Membrane of formulation after dissolution

Effect of Physiological Parameters on Drug Release

The FA15 was subjected to *in vitro* release studies in buffers with different pH and distilled water, no significant difference in the release profiles were seen. Thus the fluid in different parts of the GI tract will scarcely affect drug release. The release profile obtained from dissolution studies in different rpm concluded that it was independent of the agitational intensity of the release media. The drug release studies in different osmotic pressure media shows drug release rate decreased with increase in osmotic pressure of the media; however, the lag time was prolonged. This finding confirms that the mechanism of drug release is by the osmotic pressure.

CONCLUSION

The results obtained from all the studies concluded that the optimized formulation of Aceclofenac (FA15) shows controlled delivery of drug for the period of 24h. The formulation

prepared by using the solid dispersion of Aceclofenac to improve the solubility of the drug. The formulation shows the drug release independent of the physiological parameters like pH of the gastric fluid and agitation intensity. The drug release from the formulation is controlled by the concentration of osmotic agent, solubility enhancer and percentage of weight gain after coating. Due to the controlled release of the drug it can improve the patient compliance by reducing the frequency of dosing, side effect caused by over exposure of the drug to body and also it can be very effective for the acute and chronic arthritis pain management.

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