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DEVELOPMENT AND EVALUATION OF OSMOTIC PUMP TABLETS OF ACECLOFENAC

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Abstract:
The aim of the work is to develop & evaluate bilayer-core osmotic pump tablet by wet granulation method, using Aceclofenac as model drug. The prepared bilayer- core osmotic pump tablet will be evaluated for influence of sodium chloride, PEO (WSR Coagulant) and PEG level on drug release profile, etc. The granules of drug layer and push layer were prepared separately by wet granulation method using isopropyl alcohol. The prepared osmotic tablet of Aceclofenac was coated using ethyl cellulose as semi permeable membrane and PEG 400 as pore forming agent, the prepared tablets were evaluated for bulk density, tapped density, compressibility index, angle of repose, weight variation test, hardness, friability, content uniformity and In vitro drug release studied using USP XXIX Paddle method; formulated tablets were also evaluated for effect of pH, effect of agitation, FTIR, the results of IR study showed that there is no interaction between osmo agent, and pure drug. Results showed that as the concentration of the sodium chloride and PEO (WSR Coagulant) increases it affects the in vitro drug release. Formulation F6 prepared with sodium chloride 65mg, PEO (WSR Coagulant) 37.5mg which exhibited excellent micro meritic properties, percentage yield, and percentage drug release 84.089 % for a period of 12 hrs.Osmotic tablets of Aceclofenac may be an effective alternative to conventional dosage form, which can be effectively used in the treatment of Rheumatoid arthritis.

Keywords: *Osmogent, Osmotic pump tablets, Aceclofenac, disintegration time.*

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INTRODUCTION:

Osmotic devices are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semi-permeable membrane coat.

Osmotically Controlled Drug Delivery System

Osmosis[1.2]

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device.

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).

Basic components of Osmotic systems[1,2]

1. Drug:

Which have short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic systems. Various drug candidates such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide, etc are formulated as osmotic delivery.

2. Osmotic agent:

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Different magnesium chloride or sulphate, lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate; water-soluble salts of organic acids like sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate; Carbohydrates like mannose, sucrose, etc.

3. Semi permeable membrane:

An important part of the osmotic drug delivery system is the SPM housing. Therefore, the polymeric membrane selection is key to osmotic delivery formulation. The membrane must possess certain performance criteria such as:

- Sufficient wet strength and water permeability
- Should be biocompatible
- Rigid and non-swelling
- Should be sufficient thick to withstand the pressure within the device.

Example: Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragits.

4. Plasticizers: [2]

Different types and number of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behaviour of polymers and these changes may affect the permeability of the polymeric films. Example: Polyethylene glycols, castor oil.

OBJECTIVES:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agent for their systemic effect. Such as patient acceptance, convenience in administration and cost-effective manufacturing process. Thus wide variety of approaches of drug delivery system have been investigated for oral application.[3]

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken or applied to reduced inflammation and as an analgesic reducing pain in certain conditions.[4]

Osmotic pump tablet systems offer potential clinical benefits. Such as being potentially able to mitigate the food effect increase patient compliance and treatment tolerance. Specially designed to deliver the poorly soluble drugs.[5]

Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drugs.[6]

Osmotic pump tablets reduce risk of adverse reactions, improving compliance of Patients. Its release rate will much more closer to zero – order.[7]

The aim of the work is to develop & evaluate bilayer-core osmotic pump tablet by wet granulation method, using Aceclofenac as model drug. The prepared bilayer- core osmotic pump table will be evaluated for influence of sodium chloride, PEO (WSR Coagulant) and PEO (N80) on drug release profile, influence of PEG 400 level on drug release profile, etc.

PLAN OF WORK

1. Formulation of the osmotic pump tablets of Aceclofenac using different concentration of sodium chloride and polyethylene oxide (WSR coagulant).
2. Coating of the osmotic pump tablets using ethyl cellulose as semi permeable

membrane and PEG 400 as pore forming agent in different concentration.

3. *In vitro* dissolution studies.
4. Effect of pH on drug release.
5. Effect of agitational intensity.
6. Stability studies.

MATERIALS AND METHODS:

Aceclofenac was bought from Hetro Laboratories Hyderabad, ethyl cellulose, sodium choride, Polyethylene oxide, poly vinyl pyrolidne, Sodium choride, isopropyl alcohol, lactose, magnesium stearate, was procured from S.D Fine chem.Pvt. Ltd in Mumbai.

EVALUATION OF ACECLOFENAC [8]

Standard calibration curve for Aceclofenac in pH 7.4 phosphate buffer:

Stock solution:

Accurately weighed quantity of 100 mg Aceclofenac was dissolved in few ml of ethanol in 100 ml volumetric flask and volume was made up to 100 ml with phosphate buffer pH 7.4 to produce 1 mg/ml of solution.

Sub-Stock Solution:

From the above stock solution a series of dilution viz., 2, 4, 6, 8,10,12,14 g/ml were prepared respectively. The absorbance was measured at 276 nm using PG instrument T_{80} model UV/VIS spectrophotometer against reagent blank and graph was plotted as shown in table 3.

FORMULATION OF ACECLOFENAC OSMOTIC PUMP TABLETS[9]

Core tablets of Aceclofenac were prepared by wet granulation method. The composition of the core tablets are given in Table 4,5. Aceclofenac was mixed with Nacl, lactose, PEO (N80) and passed through 30 mesh screen. The blend was mixed for 10 mins and the mixture was granulated with PVP k-30 in isopropyl alcohol. The resulting wet mass passed through 18 # sieve. The granules were dried at 50ºC in hot air oven for 30 mins after which they were passed through 22 # sieve. These sized granules were then blended with magnesium stearate.

Push layer The push layer comprise of PEO (WSR Coagulant), NaCl, Lactose and Magnesium stearate. All the ingredients were weighed accurately and blend mixed for 10 mins, the mixture was granulated with PVP k-30 in isopropyl alcohol. The resulting wet mass was passed through 18 # sieve. The granules were dried at 50ºC in hot air oven for 30 mins after which they were passed through 22 # sieve. These sized granules were then blended with magnesium stearate.

Finally osmotic tablet was compressed using 9mm concave punch (Karnavati press) firstly the push layer were laid into the die cavity and pre-compressed then the drug layer granules were loaded on it and the tablet was compressed.

An indentation at diameter and depth of 1.0mm was produced at the center of drug layer surface using mechanical drill.

Table 1: Formulation table of Aceclofenac Osmotic tablets F1 to F3

FORMULATION CODE	F-1	F-2	F-3
DRUG LAYER			
ACECLOFENAC (mg)	100	100	100
PEO(WSR N80) (mg)	15	15	15
SODIUM CHLORIDE (mg)	-	-	-
PVP K30 (mg)	4.5	4.5	4.5
LACTOSE (mg)	29	29	29
MAGNESIUM STEARATE (mg)	1.5	1.5	1.5
PUSH LAYER			
PEO (WSR COAGULANT) (mg)	22.5	30	37.5
SODIUM CHLORIDE (mg)	15	30	45
PVP K30 (mg)	4.5	4.5	4.5
LACTOSE (mg)	106.5	84	61.5
MAGNESIUM STEARATE (mg)	1.5	1.5	1.5
TOTAL WEIGHT(mg)	**300**	**300**	**300**
COATING			
ETHYL CELLULOSE (%W/V)	2	2	2
PEG 400 (%W/V)	20	25	30

Table 2: Formulation table of Aceclofenac osmotic tablets F4 to F 12

FORMULATION CODE	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
DRUG LAYER									
ACECLOFENAC (mg)	100	100	100	100	100	100	100	100	100
PEO(WSR N80) (mg)	15	15	15	15	15	15	15	15	15
SODIUM CHLORIDE (mg)	15	15	15	15	15	15	15	15	15
PVP K30 (mg)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
LACTOSE (mg)	14	14	14	14	14	14	14	14	14
MAGNESIUM STEARATE (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PUSH LAYER									
PEO (WSR COAGULANT) (mg)	22.5	30	37.5	22.5	30	37.5	22.5	30	37.5
SODIUM CHLORIDE (mg)	15	30	45	15	30	45	15	30	45
PVP K30 (mg)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
LACTOSE (mg)	106.5	84	61.5	106.5	84	61.5	106.5	84	61.5
MAGNESIUM STEARATE (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
TOTAL WEIGHT(mg)	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
COATING									
ETHYL CELLULOSE (%W/V)	2	2	2	2	2	2	2	2	2
PEG 400 (%W/V)	20	25	30	25	30	20	30	20	25

Coating of the osmotic pump tablets[10]

The core tablets of Aceclofenac were coated with ethyl cellulose in a coating pan (Swastic, Hyderabad, India). The compositions of the coating solution used for coating tablets are given in Table 1,2. The rotating speed of the pan was kept 20 rev/min. The coating was performed using sprayer and the spray rate of 3-5 ml/min. Coating was continued until desired weight gain (10%) was obtained on the active tablets. In all the cases, active tablets were dried at 50ºC for 10 h before further evaluation.

EVALUATION FOR PRE-COMPRESSIVE PARAMETER

Micromeritic properties[11,12]

Prior to the compression, the Aceclofenac powder blends were evaluated for micromeritic properties such as bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose.

Bulk Density:

Loose bulk Density: An accurately weighed (2.5G) quantity of powder was transferred to a 10ml measuring cylinder and the volume occupied by the powder in terms of ml was recorded.

$$\text{Loose bulk Density (L.B.D)} = \frac{\text{Weight of powder in gm.}}{\text{Volume of packing in ml}}$$

Tapped bulk Density: The loosely packed powder in the measuring cylinder was to tapping 100 times on a plane hard wooden surface and volume occupied in ml was noted.

$$\text{Tapped bulk Density (T.B.D)} = \frac{\text{Weight of powder in gm}}{\text{Tapped volume in ml}}$$

% Compressibility index

Compressibility index was determined by using the following formula:

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's factor:

Hausner's found that the ratio D_F / D_O was related to interparticle friction and, as such, could be used to predict powder flow properties.

Hausner's factor = Tapped bulk density / Poured bulk density

Carr's Compressibility Index:

$$\textbf{Percent Carr's Index} = \frac{TBD - LBD}{TBD} \times 100$$

Angle of repose

Angle of repose (θ) of the powder blend, which measures the resistance to particle flow, was determined by a fixed funnel method. The height of the funnel was adjusted in such a way that the tip of

the funnel just touches the heap of the blends. Accurately weighed powder blend were allowed to pass through the funnel freely on to the surface.

The height and radius of the powder cone was measured and angle of repose was calculated using the following equation.

$\theta = \tan^{-1} h / r$

Where,

θ - Angle of repose

h - Height of granules above the flat surface

r - Radius of the circle formed by the granule heap.

EVALUATION FOR POST COMPRESSIVE PARAMETERS[13,14,15]

Uniformity of thickness

Thickness and diameter of both core tablets and coated tablets were measured using a Vernier calliper. Three tablets of each formulation were picked randomly and a dimension is determined. It is expressed in mm and standard deviation was also calculated.

Weight variation test:

The average weight of core tablets and coated tablets were determined using a digital weighing balance. Ten tablets were selected randomly from each batch and weighed individually, calculating the average weight and comparing the individual tablet weight to the average. From this, percentage weight difference was calculated and then checked for USP specifications.

Hardness test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of both core and coated tablets were determined using a Monsanto hardness tester. It is expressed in kg/cm^2. Ten tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated.

Friability test:

The friability of core tablets was determined using Roche Friabilator. It is expressed in percentage (%). Twenty core tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were weighed again (W_{final}). The % friability was then calculated.

Content uniformity test:

The Aceclofenac core tablets were tested for their drug content. Five tablets were finely powdered; quantities of the powder equivalent to 100 mg of Aceclofenac were accurately weighed and transferred to a 100-ml of volumetric flask containing 20ml of ethanol, the solution was made up to volume using phosphate buffer pH 7.4 and filtered The solutions was filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were determined at 276 nm by UV spectrophotometer.

***IN-VITRO* DISSOLUTION STUDY:[16]**

In vitro dissolution of Aceclofenac osmotic tablets was determined in a USP dissolution apparatus by using paddle method, under stirring at 100 rpm. The dissolution media consisted of 900 ml of phosphate buffer (pH 7.4) at 37±0.5 ◦C. Dissolution study was carried out for 12 hrs. Samples were withdrawn every 1 hrs and analyzed at 276 nm for Aceclofenac by using a PG instrument T-80 UV-spectrophotometer. An equivalent volume of phosphate buffer was replaced with fresh buffer into the dissolution bath following the removal of each sample.

Dissolution test were performed in triplicate.

Kinetic values obtained from Aceclofenac from *in vitro* release profile

1) Zero order, 2) First order & 3) Higuchi model

EFFECT OF CONCENTRATION OF PORE FORMER ON DRUG RELEASE[17]

In order to assess the effect of concentration of pore former on *In Vitro* drug release, formulations were coated with a ethyl cellulose as semi permeable membrane with varying amount of pore former (PEG 400) i.e. 20%, 25% and 30% as per the procedure described earlier. The effect of increasing concentration of pore former on in vitro drug release was studied.

EFFECT OF PH ON DRUG RELEASE[17]

To study the effect of pH on *In Vitro* drug release and to assure a reliable performance of the developed formulations independent of pH release studies of the optimized formulations were conducted according to pH change method. The release media was simulated gastric fluid (SGF, pH 1.2) phosphate buffer pH 4.5 acetate buffer and pH 7.4 phosphate buffer. The samples were withdrawn at predetermined intervals and analyzed spectrophotometrically.

EFFECT OF AGITATIONAL INTENSITY[17]

In order to study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution was carried at 50, 75 and 100 rpm in 900 ml of phosphate buffer pH 7.4 maintained at 37 ± 0.5°C in the dissolution medium.

STABILITY STUDIES[18]

The optimized formulation of Aceclofenac osmotic tablets (F6) was packed in strips of thick aluminium foil and these packed formulations were used to carry out stability studies as per ICH guidelines using certified stability chambers (Thermal instrument and equipment, Hyderabad) at room temp 20ºC and 40ºC and 60% and 75% RH for 3 months The samples were withdrawn periodically and evaluated for their hardness, content uniformity and for *in vitro* drug release.

FOURIER-TRANSFORMER INFRARED (FTIR) SPECTROSCOPY

Infrared spectra of pure drug and excipient are carried out by using KBr pellet technique and were recorded on a Shimadzu FTIR spectrophotometer.

RESULTS:

Table 3: Standard Calibration Data of Aceclofenac phosphate buffer pH 7.4 (λmax=276nm)

Sl. No.	Concentration	Absorbance
1	0	0
2	2	0.121
3	4	0.224
4	6	0.292
5	8	0.378
6	10	0.447
7	12	0.596
8	14	0.712

Figure 1: Standard Calibration Curve of Aceclofenac in phosphate buffer pH7.4 (λmax=276nm)

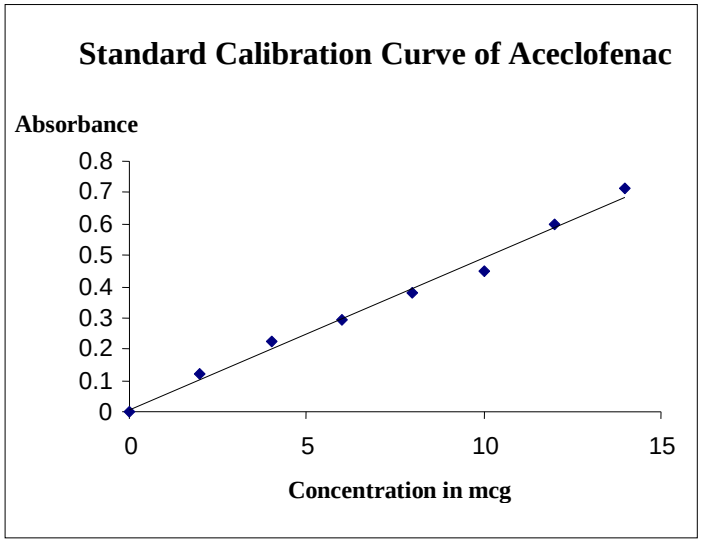

Table 4: Micromeritic properties of Aceclofenac osmotic tablets

Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's Ratio	Carr's Index	Angle of Repose
F 1	0.704±0.04	0.770±0.02	1.10±0.07	12.17±1.3	17.18±1.13
F 2	0.714±0.02	0.782±0.03	1.13±0.09	13.33±1.4	23.14±2.42
F 3	0.704±0.04	0.801±0.02	1.15±0.07	13.99±2.2	22.53±1.95
F 4	0.766±0.05	0.822±0.04	1.14±0.02	15.11±09	16.88±1.57
F 5	0.755±0.03	0.811±0.02	1.17±0.09	11.58±1.2	19.24±2.32
F 6	0.741±0.06	0.789±0.08	1.15±0.05	14.11±1.4	21.35±1.49
F 7	0.801±0.03	0.867±0.03	1.17±0.04	14.78±2.2	19.35±2.42
F 8	0.804±0.02	0.871±0.02	1.19±0.08	16.14±1.5	20.38±1.85
F 9	0.815±0.03	0.881±0.03	1.14±0.06	15.77±1.2	18.28±2.4
F 10	0.799±0.03	0.848±0.02	1.17±0.03	16.45±1.9	16.96±1.48
F 11	0.784±0.04	0.851±0.03	1.16±0.06	14.24±1.8	15.1.2±1.56
F 12	0.802±0.02	0.874±0.04	1.13±0.09	13.33±1.7	17.44±1.87

All values are represented as mean □ □standard deviation (n=3)

Table 5: Evaluation of thickness, weight, hardness, friability and contain uniformity of Aceclofenac osmotic tablets

Formulation Code	Thickness Nm (N=3)		Average Weight Mg (N=10)		Hardness (N=10)		Friability (N=10)	Content Uniformity (N=10)
	Before Coating	After Coating	Before Coating	After Coating	Before Coating	After Coating		
F 1	4.13	4.48	302.2	342.2	6.6	8	0.052	102
F 2	4.16	4.43	303.3	344.6	6.4	7.7	0.056	103
F 3	4.12	4.45	301.3	339.3	6.8	7.8	0.065	101
F 4	4.09	4.39	300.2	335.2	6.4	7.6	0.067	102
F 5	4.13	4.48	298.9	339.8	6.7	8	0.054	99
F 6	4.16	4.51	300.4	339.9	6.9	8.4	0.059	101
F 7	4.11	4.42	303.3	339.4	6.6	8	0.059	98
F 8	4.12	4.43	297.9	336.9	6.5	8.2	0.065	103
F 9	4.15	4.44	298.8	340.9	6.8	8.4	0.062	101
F 10	4.13	4.45	301.2	342.3	6.4	7.5	0.059	98
F 11	4.14	4.47	299.5	345.6	6.6	8.3	0.066	97
F 12	4.10	4.46	304.2	345.3	6.3	7.9	0.064	101

Table 6: *In-vitro* Drug Release from formulation F 1 to F6

Time (hr)	F 1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	4.00 ± 0.12	4.00 ± 0.21	4.14 ± 0.36	4.07±0.33	4.07±0.41	4.38 ± 0.30
2	7.60 ± 0.32	7.79 ± 0.33	8.07 ± 0.41	8.17±0.42	7.67±0.55	8.38 ± 0.56
3	14.30 ± 0.36	15.08 ± 0.39	15.41 ± 0.45	14.78±0.51	13.40±0.69	15.65 ± 0.41
4	20.65 ± 0.56	21.10 ± 0.41	21.29 ± 0.66	21.03±0.66	20.77±0.91	23.54 ± 0.66
5	27.47 ± 0.91	27.07 ± 0.42	29.36 ± 0.61	28.65±0.91	27.94±0.93	33.39 ± 0.75
6	35.76 ± 0.84	36.47 ± 0.45	36.07 ± 0.81	38.13±1.02	35.76±1.32	39.07 ± 0.65
7	39.78 ± 1.04	41.44 ± 0.49	43.57 ± 0.89	45.47±0.88	41.02±1.01	50.68 ± 0.81
8	47.60 ± 1.64	52.10 ± 0.53	49.97 ± 0.91	54.23±0.67	50.92±1.41	58.02 ± 0.91
9	56.84 ± 1.66	58.97 ± 0.75	57.78 ± 0.97	60.68±0.84	65.52±0.87	64.89 ± 0.67
10	58.05 ± 1.84	62.07 ± 0.86	60.84 ± 1.10	67.60±0.81	69.81±0.99	72.23 ± 0.99
11	60.05 ± 1.91	64.76 ± 0.91	64.42 ± 1.31	69.76±0.99	70.73±1.32	77.68 ± 1.23
12	62.00 ± 1.97	67.02 ± 1.23	65.81 ± 1.56	71.68±1.36	72.78±1.33	84.78 ± 1.41

All values are represented as mean □ □standard deviation (n=3)

Table 7: *In-vitro* Drug Release from formulation F 7 to F12

Time (hr)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	4.19 ± 0.41	4.90 ± 0.64	4.31 ± 0.55	4.35 ± 0.32	4.239 ± 0.66	4.42 ± 0.32
2	8.14 ± 0.44	9.09 ± 0.66	8.00 ± 0.31	9.09 ± 0.91	8.052 ± 0.81	8.17 ± 0.51
3	15.25 ± 0.35	16.00 ± 0.84	15.51 ± 0.81	16.29 ± 0.82	15.51 ± 0.89	15.72 ± 0.66
4	21.48 ± 0.86	23.30 ± 0.89	21.57 ± 1.21	23.06 ± 0.77	21.45 ± 0.99	23.23 ± 0.81
5	28.65 ± 0.91	32.68 ± 0.91	28.65 ± 0.94	31.73 ± 1.31	29.84 ± 1.61	31.00 ± 0.92
6	37.42 ± 1.32	40.26 ± 0.99	35.76 ± 0.81	39.78 ± 1.10	38.84 ± 1.66	40.00 ± 1.32
7	45.94 ± 1.52	48.55 ± 1.21	44.52 ± 1.33	46.18 ± 1.35	44.28 ± 1.87	47.13 ± 1.36
8	54.23 ± 1.21	56.84 ± 1.32	52.34 ± 1.46	51.63 ± 0.81	52.34 ± 0.94	55.42 ± 1.21
9	61.34 ± 1.38	62.28 ± 1.41	61.81 ± 1.81	60.86 ± 0.66	59.92 ± 1.65	63.07 ± 1.66
10	67.26 ± 1.67	69.39 ± 1.63	69.15 ± 1.66	67.97 ± 0.91	68.02 ± 1.22	68.92 ± 1.87
11	72.23 ± 1.95	75.03 ± 1.21	78.15 ± 1.98	75.78 ± 1.32	73.65 ± 1.34	77.68 ± 1.99
12	76.73 ± 1.61	80.28 ± 1.44	82.02 ± 1.06	82.55 ± 1.84	79.10 ± 1.71	83.36 ± 1.32

All values are represented as mean □ □standard deviation (n=3)

Fig. 2: Cumulative percentage drug release of Aceclofenac from formulation F1 to F3

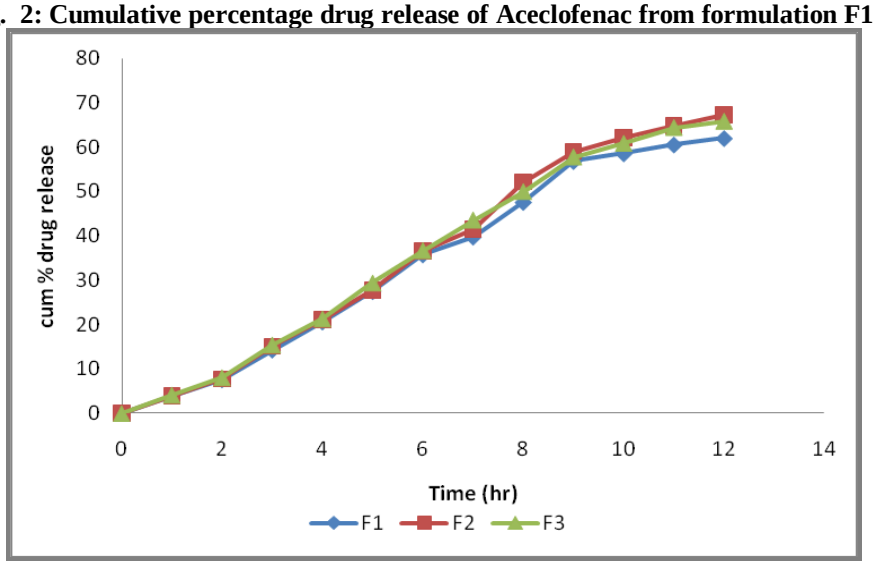

Fig. 3: First order plots of Aceclofenac formulation F 1 to F 3

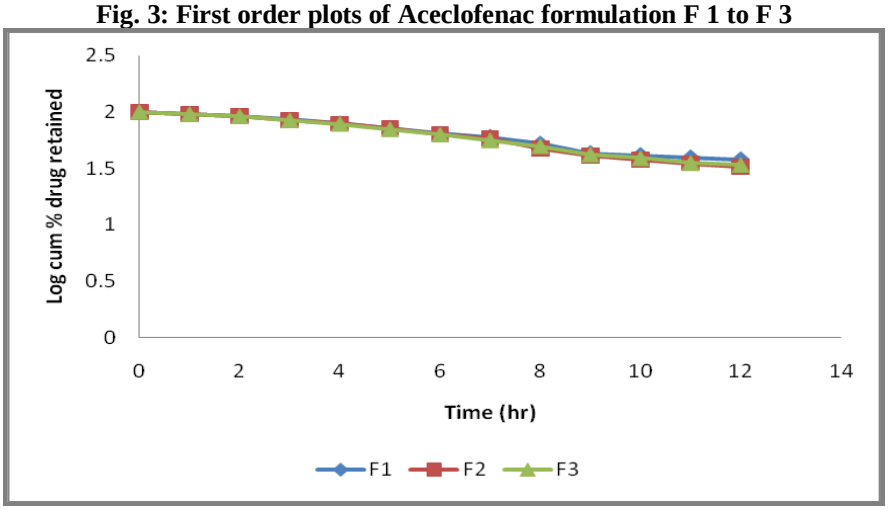

Fig. 4: Higuchi order plots of Aceclofenac formulation F 1 to F 3

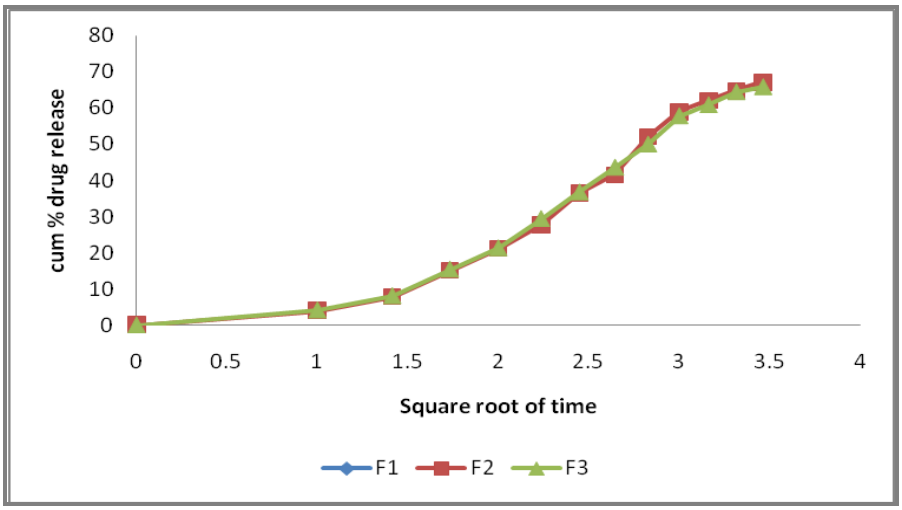

Fig. 5: Cumulative percentage drug release of Aceclofenac from formulation F4 to F 6

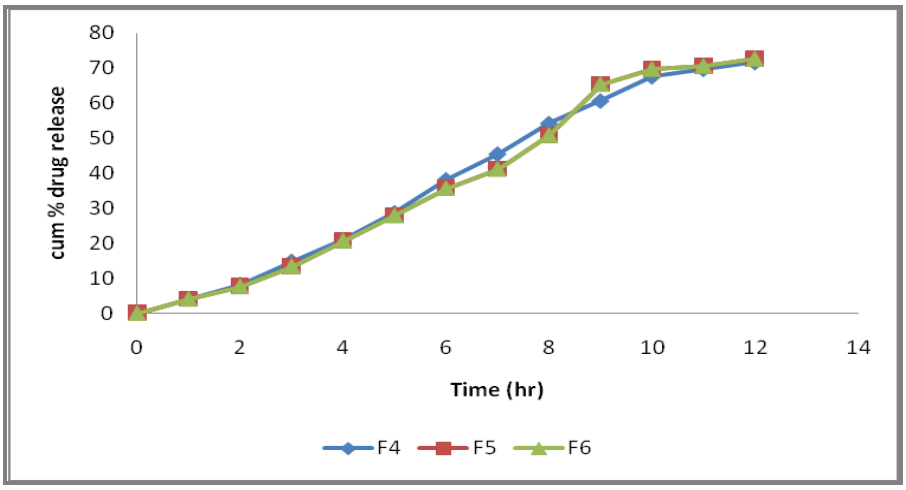

Fig. 6: First order plots of Aceclofenac formulation F 4 to F 6

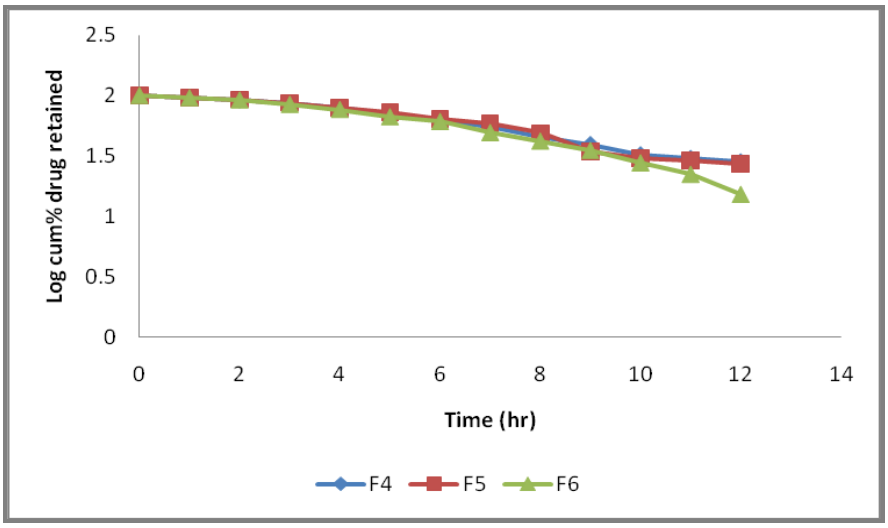

Fig. 7: Higuchi order plots of Aceclofenac formulation F 4 to F 6

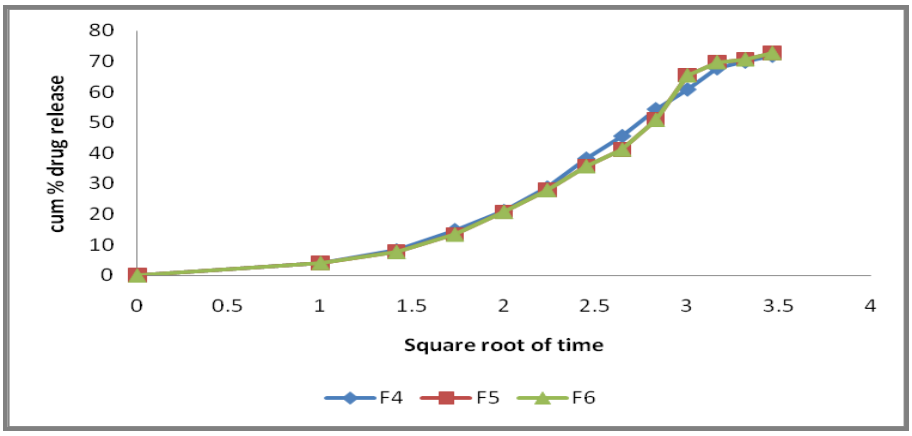

Fig. 8: Cumulative percentage drug release of Aceclofenac from Formulation F 7 to F 9

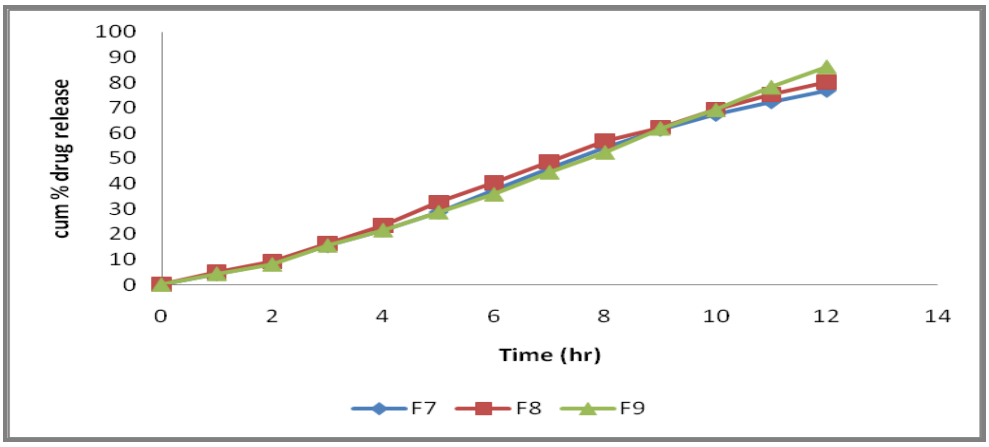

Fig. 9: First order plots of Aceclofenac formulation F 7 to F 9

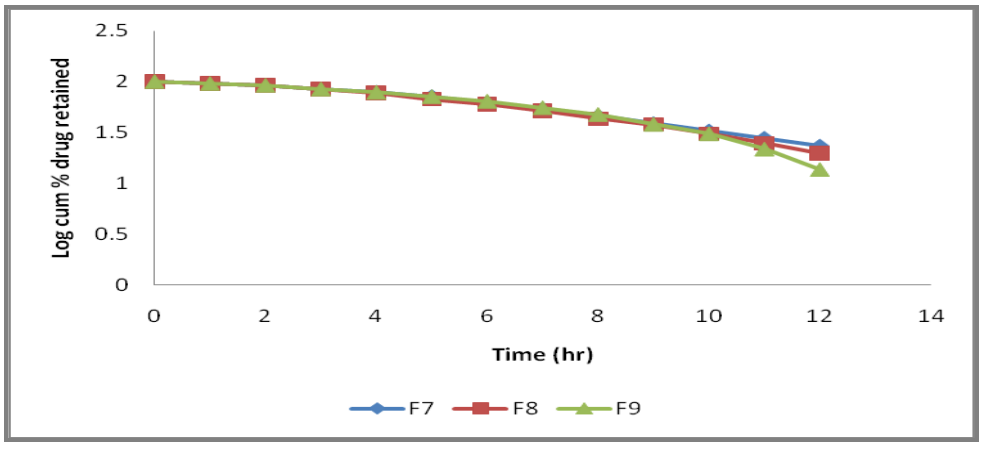

Fig. 10: Higuchi order plots of Aceclofenac formulation F 7 to F 9

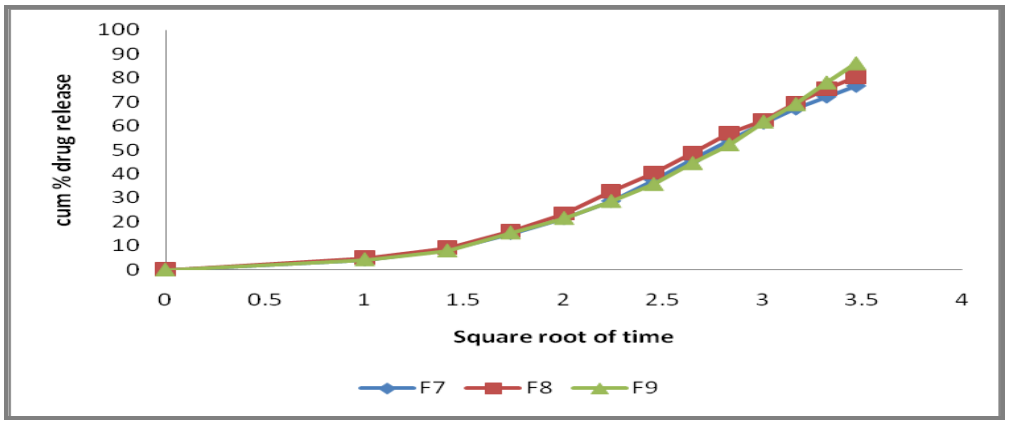

Fig. 11: Cumulative percentage drug release of Aceclofenac From Formulation F 10 to F 12

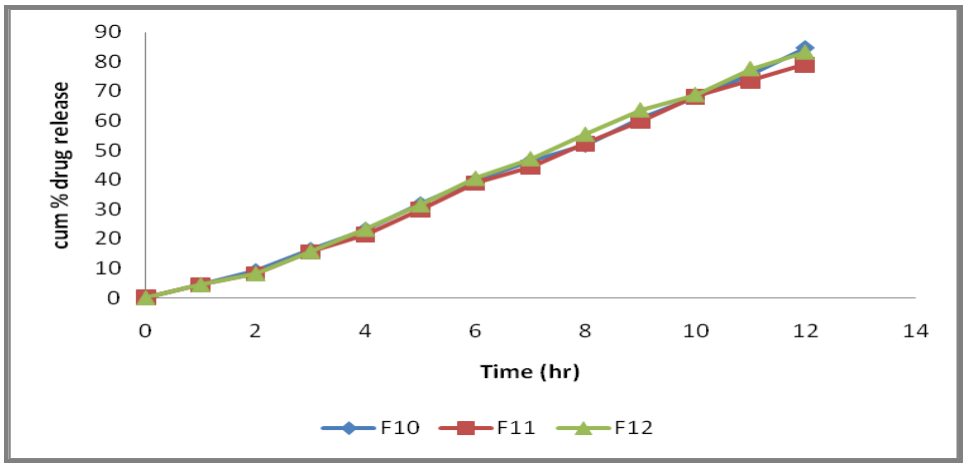

Fig. 12: First order plots of Aceclofenac formulation F 10 to F 12

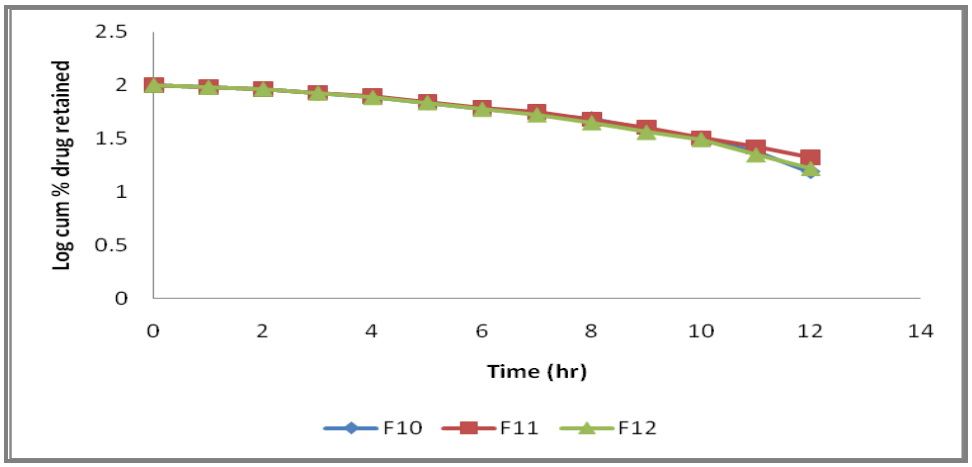

Fig. 13: Higuchi order plots of Aceclofenac formulation F 10 to F 12

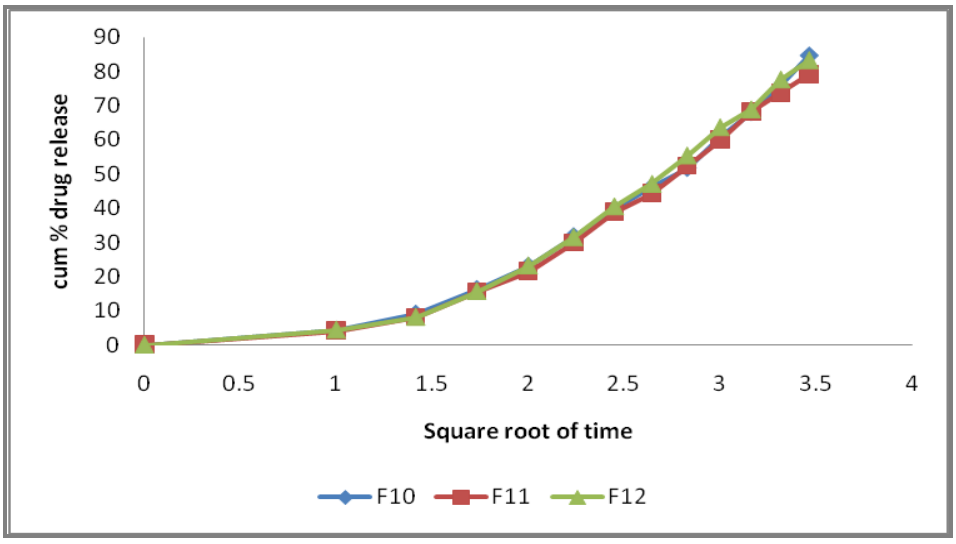

Table 8: Kinetic values obtained from in-vitro release profile of osmotic tablets of Aceclofenac

Formulation Code	Zero order kinetic data	First order kinetic data	Higuchi Matrix kinetic data
	Regression coefficient (r)	Regression coefficient (r)	Regression coefficient (r)
F 1	0.9994	-0.1922	0.9672
F 2	0.9989	-0.1133	0.9729
F 3	0.9984	-0.1526	0.9591
F 4	0.9965	-0.1144	0.9749
F 5	0.9975	-0.1658	0.9781
F 6	0.9985	-0.2462	0.9274
F 7	0.9993	-0.1196	0.9693
F 8	0.9976	-0.1588	0.9719
F 9	0.9994	-0.2163	0.9731
F 10	0.9999	-0.1571	0.9685
F 11	0.9993	-0.2624	0.9615
F 12	0.9997	-0.2184	0.9704

Table 9: Effect of pore former on *In Vitro* drug release study

Formulation	PEG 400% wt/ v		
	20%	25%	30%
1	4.073	4.073	4.381
2	8.171	7.673	8.384
3	15.788	14.405	16.655
4	22.031	21.771	24.542
5	28.657	27.763	33.394
6	38.131	41.021	39.078
7	46.473	51.921	52.684
8	54.236	65.526	58.026
9	60.688	69.815	64.894
10	67.605	70.736	72.236
11	69.765	76.621	77.604
12	75.684	81.709	86.589

Fig. 14: Effect of pore former on *in vitro* drug release study

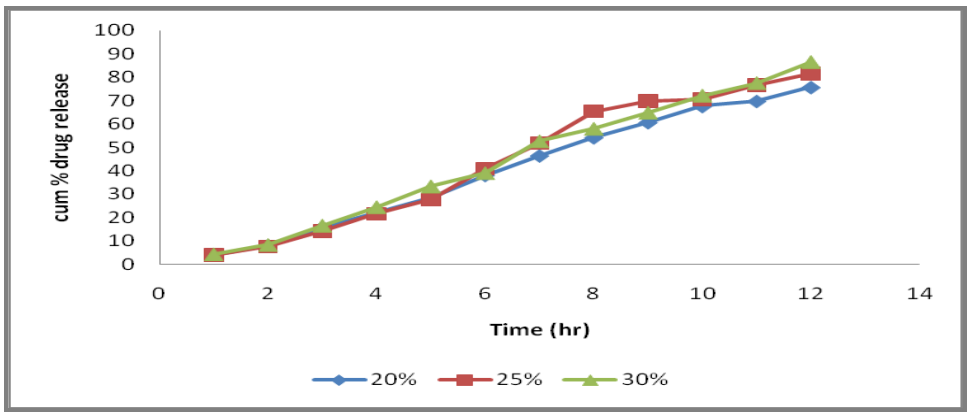

Table 10: Effect of pH on *In vitro* drug release from optimized formulation F6

Time (hrs)	Cumulative % drug released		
	pH 1.2	pH 4.5	pH 7.4
1	1.99±0.38	2.01±1.32	2.14±1.23
2	4.23±2.13	2.45±0.84	3.8±3.08
3	9.28±3.10	6.74±2.02	8.89±2.33
4	18.13±3.59	17.92±1.48	20.64±2.63
5	25.22±2.46	26.44±2.50	27.29±2.79
6	38.5±4.05	40.16±2.30	42.24±4.23
7	50.78±1.53	51.76±1.22	53.52±5.62
8	65.5±1.89	63.52±2.19	62.72±2.48
9	72.16±2.04	71.60±3.05	70.06±1.74
10	79.18±2.46	80.20±2.17	81.29±1.04
11	80.28±3.02	81.47±1.89	82.94±3.18
12	81.27±2.6	82.03±2.90	83.5±2.46

Fig. 15: Effect of pH on *in vitro* drug release from optimized formulation F6

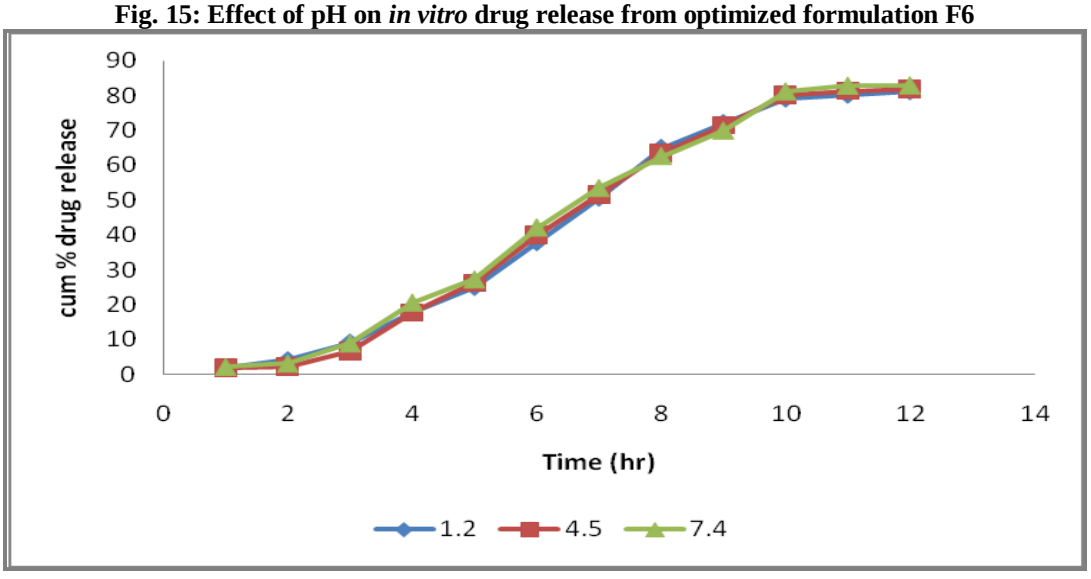

Table 11: Effect of Agitational on *In vitro* drug release from optimized formulation F6

Time (hrs)	Cumulative % drug released		
	50 rmp	75 rmp	100 rpm
1	1.85 ±5.25	2.14±1.28	2.93±0.29
2	6.05 ±1.55	8.64±2.07	10.4±1.25
3	14.34±3.88	24.29±3.28	26.37±2.59
4	33.15±2.85	35.16±3.46	39.85±2.29
5	42.27±4.36	44.06±4.25	53.43±2.36
6	54.23±3.59	56.24±1.48	66.77±4.59
7	66.22±3.48	67.52±2.78	70.43±2.48
8	73.95±1.38	72.72±4.49	75.74±1.27
9	76.29±3.19	73.06±2.68	76.87±3.46
10	77.8±2.08	77.29±3.63	79.64±1.34
11	82.73±3.68	80.94±3.44	82.48±2.94
12	83.39±2.55	84.50±1.39	86.23±1.2

Fig.16: Effect of agitational on in vitro drug release from optimized formulation F6

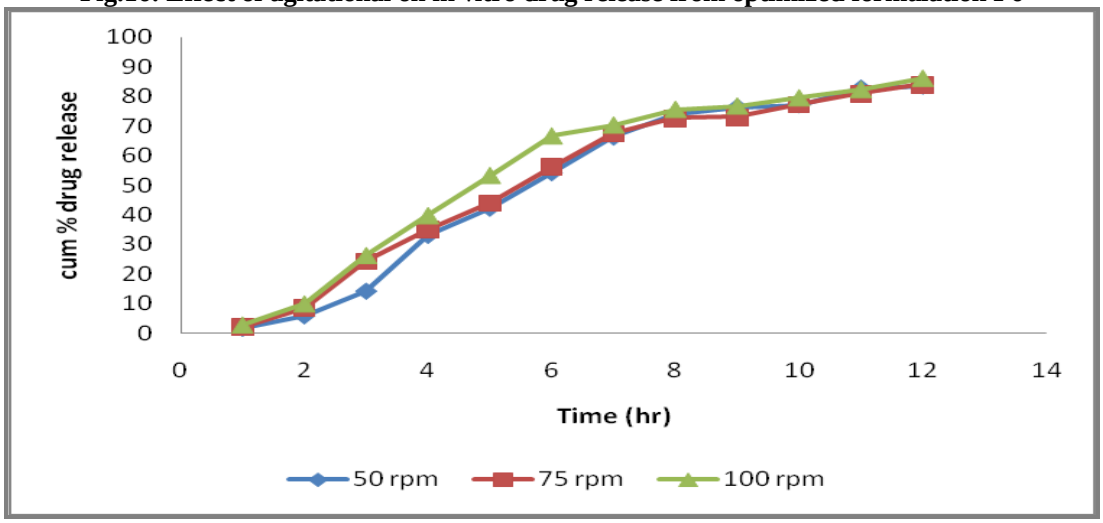

Table 12: Stability studies of formulation F6 at temp. 25°C, RH 60 %, & 40°C, RH 75 %

Formulation F 6	**% Drug content At room temp. 25° C & Relative humidity 60 %**				**% Drug content At temp. 40° C & Relative humidity 75 %**		
	1 st day	After 30 Days	After 60 Days	After 90 Days	After 30 Days	After 60 Days	After 90 Days
	92.46	92.46	92.4	92.31	92.43	92.4	92.3

***In Vitro* Release Profile of Best Formulation F 6**							
Formulation F 6	**Time (hr)**	**% Drug release**				**% Drug release**		
	1	3.772	3.772	3.767	3.765	3.771	3.761	3.759
	12	94.07	94.079	94.076	94.069	94.076	94.06	94.056

DISCUSSION:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agent for their systemic effect. Such as patient acceptance, convenience in administration and cost effective manufacturing process. Thus wide varieties of approaches of drug delivery system have been investigated for oral application.

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken or applied to reduced inflammation and as an analgesic reducing pain in certain conditions.

Osmotic pump tablet systems offer potential clinical benefits. Such as being potentially able to mitigate the food effect increase patient compliance and treatment tolerance. Specially designed to deliver the poorly soluble drugs.

Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drugs. Osmotic pump tablets reduce risk of adverse reactions, improving compliance of Patients. Its release rate will much more closer to zero – order.

The aim of the work is to develop & evaluate bilayer-core osmotic pump tablet by wet granulation method, using Aceclofenac as model drug, sodium chloride, PEO (WSR Coagulant) & (N80), the prepared tablets will be coated with ethyl cellulose using PEG 400 as pore former agent.

PREFORMULATION METHOD

Calibration curve

In pre formulation studies it was found that, the estimation of Aceclofenac by spectrophotometric method at 276 nm had good reproducibility (as shown in figure 1).

Micromeritic properties

Bulk Density

The bulk density of the Formulation F 1 to F 3 ranges from 0.704±0.04gm/cm^3 to 0.714±0.02gm/cm^3, formulation F 4 to F 6 ranges from 0.741±0.06 gm/cm^3 to 0.766±0.05 gm/cm^3, formulation F 7 to F 9 ranges from 0.801±0.03 gm/cm^3 to 0.815±0.03 gm/cm^3, formulation F 10 To F 12 ranges from 0.799±0.03 gm/cm^3 to 0.802±0.02 gm/cm^3 respectively (as shown in table no. 4).

Tapped Density

The tapped density of the formulation F 1 to F 3 varied from 0.770±0.02 to 0.801±0.02, formulation F 4 to F 6 varied from 0.789±0.08 to 0.822±0.04, formulation F 7 to F 9 varied from 0.867±0.3 to 0.881±0.03, formulation F 10 to F 12 varied from 0.848±0.02 to 0.874±0.04 respectively (as shown in table no. 4).

Hausner's Ratio

The hausner's ratio of the entire formulation F 1 to F-12 were in the range of 1.10±0.07 to 1.19±0.08 (as shown in Table no. 4)

Carr's Index

The carr's index of entire formulation F 1 to F 12 were in range of 11.58±1.2 to 16.45±1.9 (as shown in table no. 7) The Carr's compressibility index values showed up to 15% result in good to excellent flow properties.

Angle of repose (θ):

The data obtained from angle of repose for formulations F 1 to F 3were found to be in the range of 17.18±1.13° θ to 23.14±2.42 ° θ. The angle of repose less than 30°, which reveals good flow property (as shown in table no. 4).

POST FORMULATION METHOD

Thickness: The thickness of entire formulation F_1 to F_{12} were in range of before coating 4.09 to 4.16 and after coating 4.39 to 4.51 (as shown in table no. 5).

Average Weight: The average weight of entire formulation F_1 to F_{12} were in range of before coating 297.9 to 304.2 after coating 335.2 to 345.6 (as shown in table no. 5).

Hardness: The hardness of entire formulation F_1 to F_{12} were in range of before coating 6.3 to 6.9 and after coating 7.5 to 8.4 (as shown in table no. 5).

Friability: The friability of entire formulation F_1 to F_{12} were in range of 0.052 to 0.067 (as shown in table no. 5).

Content uniformity: The content uniformity of entire formulation F_1 to F_{12} were in range of 97 to 103 (as shown in table no. 5).

***IN VITRO* DRUG RELEASE**

In vitro drug release studies of Aceclofenac from osmotic tablets were performed in pH 7.4 for 12hrs. Using USP Type I dissolution test apparatus. It was found that *in vitro* drug release of formulation F1 to F 3 were in the range of 62.002±1.97 to 67.021±1.23.

Formulation F 4 to F 6 were in the range of 71.684±1.36 to 84.789±1.41. Formulation F 7 to F 9 were in the range of 76.736±1.61 to 82.021±1.06 and formulation F 10 to F 12 were in the range of 82.552±1.84 to 83.368±1.32. Among all formulations F6 was found to be the best formulation as it release Aceclofenac 84.789±1.41 % in a sustained manner with constant fashion over extended period of time (for 12hr).

It was observed that the concentration of sodium chloride and PEO (WSR Coagulant) increased, percent of drug release of Aceclofenac increases.

Higher the concentration of sodium chloride and PEO (WSR Coagulant) drug release was in a sustain manner.

The release rates obtained were subjected for Kinetic treatment to know the order of release. The 'r' values for zero order kinetics of formulation F 1 to F 12 are 0.9994, 0.9989, 0.9984, 0.9965, 0.9975, 0.9985, 0.9993, 0.9976, 0.9994, 0.9999, 0.9993 and 0.9997 respectively (as shown in table no. 8). The 'r' values indicate that drug release of all formulation F 1 to F 12 follows zero order kinetics.

To ascertain the drug release mechanism, the in-vitro data were also subjected to Higuchi diffusion. The 'r' values of Higuchi diffusion was in the range of 0.9274 to 0.9781 of all formulation F 1 to F 12. It suggests that the Higuchi diffusion plots of all the formulations were fairly linear because 'r' values near about 1 in all the cases. So it confirms the drug release by Higuchi diffusion mechanism (as shown in table no.8).

Effect of pore former on *In Vitro* drug release study:

The amount of PEG 400 (pore former) in the coating was verified and its effect on the drug release on formulations was evaluated. PEG 400 was used in three different concentrations 20, 25, and 30% w/w and ethyl cellulose 2% as semi permeable membrane. The *in vitro* release profile containing varying amount of PEG 400 in the coating are shown as in Table No.9 and in fig no. 14. Coating solution containing 20, 25 & 30% PEG 400 released 75.684, 81.709, 86.589% of drug after 12hrs. While highest release was obtained with 30%w/w of PEG 400 in the coating membrane with a cumulative release of 86.589% after 12hrs.

Increase of PEG 400 level led to an increase of drug release rate. As PEG is a pore forming agent, it could be leached easily and left behind porous structure, which enhanced the membrane permeability and drug release rate.

Effect of pH on *In Vitro* drug release:

In general, drug release from osmotic pumps, is pH independent. The effect of pH of dissolution media on drug release was evaluated by pH change method. Release studies of formulation F6 were conducted in phosphate buffer solution pH 1.2 and pH 4.5 acetate buffer and pH 7.4, drug release data of optimized formulation F6 are given as in table no.10 and fig. no. 15 there is no significant change in release.

Therefore, it was evident that pH of the dissolution media has no significant effect on the release of drug. So it can be expected that variations in pH of gastrointestinal tract may not affect the drug release from the core formulation.

Effect of agitational intensity on *In Vitro* drug release:

Drug release test under different agitation rates were also conducted at three different rpm (50, 75, and 100) in order to investigate the influence of agitation rate on drug release profiles. Formulation F6 was considered for this study. Dissolution studies were carried out using USP- Type I dissolution apparatus and results are given in the table no. 11 and fig. no. 16. The cumulative percentage of drug released after 12 hrs, were 83.39±2.55, 84.50±1.39 and 86.23±1.2% respectively for 50, 75, and 100 rpm. The results indicate that drug release from controlled porosity osmotic pump is independent of agitation intensity.

Stability Study:

The promising formulations were subjected to short term stability study by storing the formulations at 25°C with relative humidity 60% and 40°C with relative humidity 75% showed the maximum stability. The values of drug content and in vitro drug release were close to initial data with only slight variations. Accelerated stability studies for 3 month revealed that the formulations were stable up to 40°C and 75% RH. It should be stored in a cool, dry place. Stability studies are shown in table 12.

Infrared spectroscopy (FTIR)

The prepared osmotic tablets were characterized by FTIR spectroscopy to find out any chemical interaction between Aceclofenac and polymers used.

A characteristic IR spectra of Aceclofenac showed at 1573 cm^{-1} for C=C, 1089 cm^{-1} for C-N str, 3867 cm^{-1} for N-H str, 1279 cm^{-1} for C-C str, 952 cm^{-1} for C-O, 2879 cm^{-1} for O-H.

All these prominent peaks of drug is observed in formulation F6. Thus, indicating the compatibility of drug with polymers and excipient used. Here, the FT-IR Spectrum of Aceclofenac and "F 6" are matching with each other. So there is no interaction take place in optimized formulation as shown in table 13.

CONCLUSION:

The data obtained from the study of "Development and evaluation of osmotic pump tablets of Aceclofenac" reveals following conclusion.

The present study has been satisfactory attempt to formulate osmotic tablets of an NSAID drug Aceclofenac with a view of improving its bioavailability and giving controlled release of drug. From the experimental results it can be concluded that:

Biocompatible polymers like PEO (WSR Coagulant), PEO WSR (N80), ethyl cellulose, PEG

400 and osmotic agent sodium chloride can be used to formulate osmotic tablets.

The flow properties of all the prepared powder blends were good as indicated by low angle of repose (□□< 40º) and low compressibility index (I < 25). The good flow properties suggested that the powder blends produced were non aggregated.
In vitro release of Aceclofenac was found to be in following order. F 6 > F 12 > F 10 > F 9 > F 8 > F 11 > F 7 > F 5 > F 4 > F 2 > F 3 > F 1. Among all formulations, F 6 prepared using 37% of PEO (WSR Coagulant), 45% sodium chloride and coated with 30% PEG 400 (pore former) was found to be the best formulation as it release Aceclofenac 84.789% in a sustained manner with constant fashion over extended period of time (after 12hr).

In vitro release data fitted into various kinetic models suggest that the release obeyed zero order kinetic, higuchi diffusion mechanism.

Hence, finally it was concluded that the prepared osmotic tablets of Aceclofenac may prove to be potential candidate for safe and effective sustained drug delivery over an extended period of time which can reduce dosing frequency.

SUMMARY:

Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drug. Drug release from there systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.

In the present study, osmotic tablets of Aceclofenac were prepared using different polymers like ethyl cellulose, PEO (WSR Coagulant), PEO (WSR N80) PVP K-30, PEG-400 as (pore forming agent), Nacl, Lactose and magnesium strearate by wet granulation method.

The objective of the study is presented in chapter-2. Initially, an extensive literature survey was done for the collection of theoretical and technical data. The review of literature, drug profile and excipient profiles, are presented in chapter-3. This was followed by procurement and characterization of raw materials used in the study.

The prepared osmotic tablets also characterized by FTIR spectroscopy to find out any chemical interaction between Aceclofenac and polymers used. The prepared osmotic tablets were evaluated for micromeritic properties (like bulk density, tapped density, hausner's ratio, angle of repose, compressibility index) in vitro drug release study.
Osmotic tablets improved the in vitro drug release using Nacl, PEO (WSR coagulant) and pore former PEG 400 in varying drug to excipient ratio, which suggest that in future they could be easily and successfully developed into drug delivery system.
Thus the prepared osmotic tablets proved to be a potential candidate as a sustained release drug delivery device.

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