International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE
V-1, I-2, 2012

Formulation and Evaluation of Oral Controlled Porosity Osmotic Pump Tablet of Zaltoprofen

Jadav MM*[1], Teraiya SR[1], Patel KN[1], Patel BA[1], Patel PA[1]

[1]*Department of Pharmaceutics, Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gujarat, India.*

Manuscript No: IJPRS/V1/I2/00085, Received On: 12/05/2012, Accepted On: 16/05/2012

ABSTRACT

Zaltoprofen is a non steroidal anti inflammatory class of drug which has excellent effect on post-surgery or post trauma chronic inflammation of the drug. So, Zaltoprofen may serve as a potent and superior analgesic for the treatment of pain. Zaltoprofen has the dose of 80 mg three times a day which reduce patient compliance. For that in this present study, an attempt has been made to prepare the controlled release CPOP tablet twice a day. An inclusion complex was prepared by kneading method using HP-β-CD in order to increase solubility of the poorly water soluble drug. Then, this complex is used for preparing the tablet with accessorial material. CPOP tablet containing Zaltoprofen were prepared by direct compression method by using various osmotic agent like sodium bicarbonate, sodium chloride, mannitol and potassium carbonate. Cellulose acetate, Sorbitol and Poly Ethylene Glycol 400 were selected for coating materials, and acetone: methanol (65:35) co-solvent was employed as the coating medium with 3% and 5% weight gain. Initially compatibility study was carried out using DSC and FT-IR Spectrometric method. The blend was examined for pre-compression parameters like angle of repose, density, compressibility index and Hausner's ratio. Formulated tablet also passes the various tablet parameters like hardness, friability, drug content, weight variation. From the result of *in-vitro* drug release study it was observed that as the amount of osmotic agent increased, amount of drug release increased. Also increased in % weight gain decreased the % drug release. Batch Z4 containing sodium bicarbonate as osmotic agent has shown 98.08% drug release compare to other batches so, accepted as optimized batch. The above optimized batch Z4 was also evaluated by different pharmacokinetic models like Zero order, First order, Higuchi, Korsmeyer Peppas, and Hixson Crowell model. The results of these models have shown that the batch Z4 controls the drug release for 12 hr and follows zero order release kinetics and which is independent of the pH and agitational intensity.

KEYWORDS

Controlled porosity osmotic pump, Osmotic agent, Zaltoprofen, Cellulose acetate.

INTRODUCTION

By using oral controlled drug delivery system can provide continuous delivery of drugs at predictable and reproducible kinetics throughout the GI transit. Also the systems that target the drug delivery to a specific region within the GI tract for either local or systemic action.

***Address for Correspondence:**
Jadav Mukesh M.
Department of Pharmaceutics,
Shree Swaminarayan Sanskar Pharmacy College,
Zundal, Gujarat, India.
Email Id: jadavmukesh25@gmail.com

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

Oral controlled release system that provides greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule. The drug release from oral controlled release dosage forms may be affected by pH, GI

motility and presence of food in the GI tract[1]. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis and also 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. The oral osmotic pump tablets have many advantages, such as reducing risk of adverse reactions, zero-order delivery rate, a high degree of *in-vivo in-vitro* correlation and improving patient compliance[2].

The controlled-porosity osmotic pump tablet concept was developed as an oral drug delivery system by Zentneret al (1985, 1991), Zentner and Rork (1990), Appel and Zentner (1991), and McCellandet al. (1991). The controlled-porosity osmotic pump tablet (CPOP) is a spray-coated or coated tablet with a semipermeable membrane (SPM) containing leachable pore forming agents. They do not have any aperture to release the drugs; drug release is achieved through the pores, which are formed in the semipermeable wall in situ during the operation. In this system, the drug, after dissolution inside the core, is released from the osmotic pump tablet by hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane. The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by a tablet component, after water is imbibed across the semipermeable membrane. This membrane after formation of pores becomes permeable for both water and solutes. A controlled-porosity osmotic wall can be described as having a sponge like appearance. The pores can be continuous that have micro porous lamina, interconnected through tortuous paths of regular and irregular shapes.

This system is generally applicable for only water-soluble drugs as poorly water soluble drugs cannot dissolve adequately in the volume of water drawn into the OPT. Recently this problem was overcome by adding agents like sulfobutyl ether-β-cyclodextrin (SBE)7m-β-CD or Hydroxypropyl-β-Cyclodextrin (HP-β-CD) as solubilizing and osmotic agents. Several approaches have been developed to prepare the porous membrane by spray coating using polymer solutions containing dissolved or suspended water-soluble materials.

Zaltoprofen is a non steroidal anti-inflammatory analgesic which has excellent effect on post-surgery or post trauma chronic inflammation of the drug, so Zaltoprofen may serve as a potent and superior analgesic for the treatment of pain. Zaltoprofen has biological half life of 2.8 hr and it absorbs throughout the intestinal tract. The drug shows linear pharmacokinetics, is suitable for oral controlled release tablets and it would be advantageous to slow down its release in GI tract not only to prolong its therapeutic action but also minimize possible side effects of Zaltoprofen[3].

In this present study Zaltoprofen inclusion complex with HP-β-CD is used to prepare the controlled porosity osmotic pump tablet. Further optimization is to be carried out by various evaluation parameters like powder flow properties, core tablets properties, in vitro drug release, and curve fitting analysis of the various prepared formulation. The effects of pH and agitation also evaluated for the optimized formulation. Then stability study is to be carried out in accelerated condition for 1 month.

MATERIALS AND METHODS

Zaltoprofen were obtained from Tonira Pharmaceutical Pvt. Ltd. (Baroda, India). Cellulose acetate was supplied from Alembic Pharma., Baroda. Gift sample of HP-β-CD was kindly provided by Gangwal Pharmaceuticals. (Mumbai, India). Spray dried lactose was obtained from Flumost Pharmaceuticals.(USA). Other ingredients used were of analytical grade.

Drug - Excipients Compatibility Study

Drug-Excipients Compatibility Study by FT-IR

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer. The Zaltoprofen and mixture of drug with other

excipients were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively[4]. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

Drug-Excipients Compatibility Study by DSC

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The samples (drug and excipients) were heated in sealed aluminum pans under nitrogen flow (30 ml/min) at a scanning rate of 5°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples[5].

Preparation of Inclusion Complex

Inclusion complexes were prepared using 1:0.25M ratio of Zaltoprofen and HP-β-CD on the basis of molecular weight. Inclusion complex was prepared by the kneading method[6]. Zaltoprofen and molar quantities of HP-β-CD were wetted in a mortar with (1:2) water: methanol until a paste was obtained and mixed for 1 hr. Then, these pastes were left to air dry for one night and finally mildly ground and stored under vacuum in a dessicator for 1 days, after that product was sieved through a 60 # mesh size[7].

Characterization of Inclusion Complex

Prepared inclusion complex was evaluated by two methods like the FT-IR and DSC method.

Characterization of Inclusion Complex by FT-IR method[8]

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan).The inclusion complex was mixed with KBr. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press, which were analyzed. All the spectra acquired scans between 400 to 4000 cm^{-1}.

Characterization Inclusion Complex by DSC method

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. Inclusion complex was heated in sealed aluminum pans under nitrogen flow (30 ml/min) at a scanning rate of 5°C/min from 25 to 250°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the sample. If the endothermic peak of Zaltoprofen changed than it indicates drug is complexed with the HP-β-CD[9].

Preparation of Core Tablets

Controlled porosity osmotic pump tablet was prepared by direct compression method. The drug, osmogent, excipients were weighed accurately and then pass though 40# mesh sieve[10]. All the mixture is blended properly. Compression was done on a Rotary tablet compression machine (Karnavati Engineering) using 9.5 mm standard concave punches. CPOP concave tablets having 9.5 mm size and 5-6 kg/cm^2 hardness were prepared. Prepared tablets were evaluated for various other parameters[11].

Coating of Tablets

CPOP core tablets are coated by cellulose acetate (3% w/v) by preparing coating solution. Coating solution was prepared in solvent mixture of acetone: methanol (65:35) containing PEG 400 and Sorbitol in concentration of 40% and 30% respectively. The coating conditions were as follows: pan, 9 inch circular; baffles, 4; nozzle diameter, 1mm; and drying temperature, 55–60 ˚C. The surface morphology of the coated tablet had a smooth and uniform appearance. After coating, the tablets were dried overnight at 60˚C to remove residual solvent[12].

Table: 1 Composition of Batch Z1 to Z8

Ingredients	Z1*	Z2*	Z3*	Z4*	Z5*	Z6*	Z7*	Z8*
Zaltoprofen + HP-β-CD complex (1:0.25M)	275	275	275	275	275	275	275	275
Sodium chloride	50	-	75	-	50	-	75	-
$NaHCO_3$	-	50	-	75	-	50	-	75
Spray dried lactose	65	65	40	40	65	65	40	40
Sodium lauryl sulphate	10	10	10	10	10	10	10	10
Poly ethylene oxide	25	25	25	25	25	25	25	25
Sodium starch glycolate	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10
Weight Gain	3%	3%	3%	3%	5%	5%	5%	5%

**All values are expressed in mg/tablet*

Evaluation of powder blend

Angle of Repose

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

$$\tan \theta = h/r$$

Where, h, r and θ are the height, radius and angle of repose of the powder pile[13].

Bulk Density and Tapped Density

Accurately weighed of the sample was transferred to the measuring cylinder of bulk density apparatus and noted the volume as bulk volume. The apparatus was adjusted for 100 tapping and noted the final volume as tapped volume[14].

Bulk density = mass of powder (w) / bulk volume (Vb)

Tapped density = mass of powder (w) / tapped volume (V_t)

Compressibility Index

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

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

Where, TBD is the total bulk density and LBD is the loose bulk density.[15]

Hausner's Ratio

The Hausner's ratio and Carr's index are measures of the flow properties of powders. A Hausner's ratio of <1.25 indicates a powder that is free flowing whereas >1.25 indicates poor flow ability[16].

Hausner's ratio = tapped density / Bulk density

Total Porosity

Porosity of the powder was determined by using formula:

Porosity = [(Vb – Vp)/ Vb] ×100

Where Vb is the bulk volume and Vp is the true volume

EVALUATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLET

Weight Variation Test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated[17].

Content Uniformity

Tablets were crushed in mortal and sufficient amount of ethanol was added to dissolve properly. Then appropriate dilution was done and analyzed by the use of UV Spectrometer at 340 nm[18].

Hardness and Friability

The hardness of the core tablets and coated tables were measured using the Pfizer hardness tester. Six tablets from each formulation were randomly selected and used. The average hardness and the standard deviation were calculated. It is expressed in Kg/cm^2.[19]

***In-Vitro* Drug Release Study**

Perform the dissolution test with 6 tablets of Zaltoprofen at 100 revolutions per minute according to the Paddle method, using 900 ml of 6.8 pH phosphate buffer as dissolution medium at 37 ºC. Withdraw not less than 5 ml of the dissolution solution at 1 hr time interval, and filter through a membrane filter. The samples were analyzed after appropriate dilution by UV spectrophotometer at λmax 340 nm[20].

Effect of pH

The optimized formulation of porous osmotic pump tablets is tested for the effect of pH on drug release. The best formulations are undergone dissolution studies in 0.1N HCl, 4.5 pH phosphate buffer and 6.8 pH phosphate buffer in rotation speed of 100 rpm and 37 ± 0.5°C using USP dissolution test apparatus (type II) and compared. The samples (5 ml) were withdrawn at predetermined intervals and analyzed after filtration through 0.45-mm nylon membrane filters[21].

Effect of Agitational Intensity

The optimized formulation of matrix and porous osmotic pump tablet is tested for the effect of agitation intensity on drug release. The best formulations are undergone dissolution studies by maintaining different rotation speed of 50, 75, 100 rpm and at 37 ± 0.5 °C in 6.8 pH phosphate buffer for 12 hr using USP dissolution test apparatus (type II) and compared. Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45-mm nylon membrane filters[22].

Curve Fitting Analysis

To analyze the release pattern of the drug from dosage form, the data obtained were graphed as:

- Cumulative percentage drug released Vs Time (*In-Vitro* drug release plots, Zero order plots)
- Log cumulative percentage drug remaining Vs Time (First order plots)
- Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
- Log percentage drug released Vs Log time (Peppas plots)
- Cube root of percentage drug remain Vs Time (Hixson-Crowell plots)

Zero Order Release Rate Kinetics

The equation for zero order treatment is represented as;

$$\mathbf{Q_t = K_0 t}$$

Where Q_t=amount of drug released in time (t)

K_0 = zero order release constant

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0[23].

First Order Kinetics

The equation for first order treatment is represented as

$$\mathrm{Log\,Q} = \mathrm{LogQo} - \frac{K_1 t}{2.303}$$

Where,

Q = amount of drug remaining unreleased at time t

Q_0= initial amount of drug in solution

K_1= first order rate constant

When, the data is plotted as cumulative percent drug remaining versus time yields a straight line, indicating that the release follows First-order kinetics. The constant 'K_1' can be obtained by multiplying 2.303 with slope values.

Higuchi Release Model

The simplified Higuchi equation is represented as

$$Q_t = K_H\, t^{1/2}$$

Where; Q_t= amount of drug released in time t

K_H = Higuchi's constant

A linear relationship between amount of drug released (Q) versus square root of time ($t_{1/2}$) is observed if the drug release from the matrix is diffusion controlled[24].

Hixson-Crowell Model

The simplified equations is represented as

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}.t$$

Where Q_t= amount of drug released in time (t)

Q_0= initial amount of drug in solution

K_{HC} = cube–root constant

A graphic representation of cubic root of unreleased fraction of drug versus time will be linear if geometric shape of the formulation diminishes proportionally over time.

Korsmeyer and Peppas Release Model

The Korsmeyer-Peppas model relates drug release exponentially to time. It is described by the following equation;

$$\frac{M_t}{M_\infty} = K_{KP} \cdot t^n$$

Where, M_t/ M_∞= fractional release of drug

K_{KP} = constant depending on structural and geometric characteristics of the drug dosage form

n = release exponent

The value of n indicates the drug release mechanism. For a slab the value n=0.5 indicates Fickian diffusion and values of n between 0.5 and 1.0 or n=1.0 indicate non-Fickian mechanism. In case of a cylinder n=0.45 instead of 0.5, and 0.89 instead of 1.0.

This model is used to analyze the release of drug from polymeric dosage forms, when the release mechanism is not understood or when there is a possibility of more than one type of release mechanisms are involved[25].

Table: 2 Interpretation of Diffusional Release Mechanism from Polymeric Membrane

Release Exponent (n)	Drug Transport Mechanism
0.5	Fickian diffusion
0.5 < n < 1.0	Anomalous transport
1.0	Case-II
> 1.0	Super case-II transport

Stability Study

Optimized formulations of Zaltoprofen were packed in strips of 0.04 mm thick aluminium foil laminated with PVC. The packed formulations were stored in ICH certified stability chambers (KBF 720, Binder, Germany) maintained at 40°C and 75% RH for 1 months. The samples were withdrawn periodically and evaluated for drug content, hardness, and release studies[25,26].

RESULT AND DISCUSSION

Interpretation of FTIR spectra

Compatibility studies were performed using FTIR spectrophotometer. The characteristic absorption peaks of Zaltoprofen pure drug and mixture with other excipients were obtained at different wave numbers.

The peaks obtained in the spectra of pure drug correlates with the peaks of drug with other excipients. It does not show any major changes in peaks which indicate no well-defined interaction of Zaltoprofen with other excipients. This indicates that the drug is compatible with the formulation components. The spectrum for pure drug and excipients are shown in figure 1 to 8 and interpretations of spectrum are reported in Table: 3.

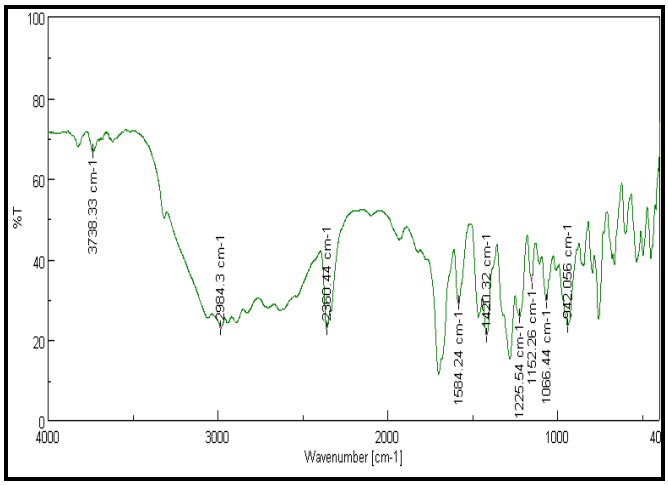

Figure: 1 FT-IR Spectrum of Zaltoprofen

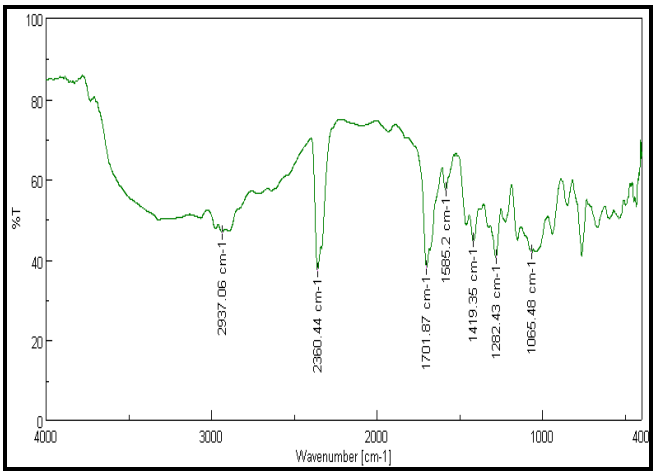

Figure: 4 FT-IR Spectra of Zaltoprofen with HP-β-CD Physical Mixture

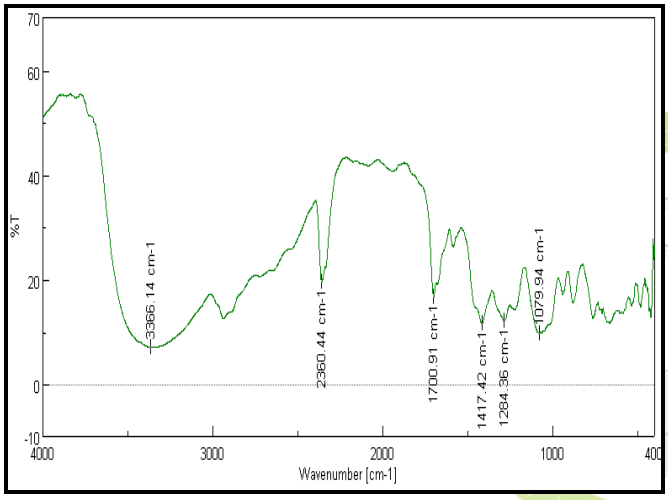

Figure: 2 FT-IR Spectra of Zaltoprofen with Sodium bicarbonate Mixture

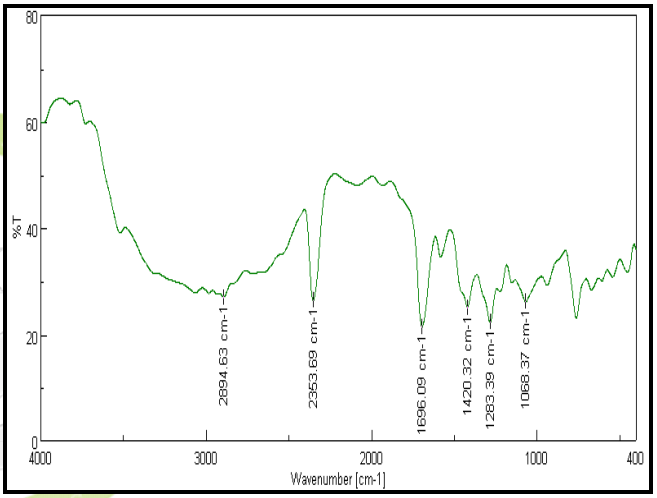

Figure: 5 FT-IR of Spectra Zaltoprofen with Spray Dried Lactose Mixture

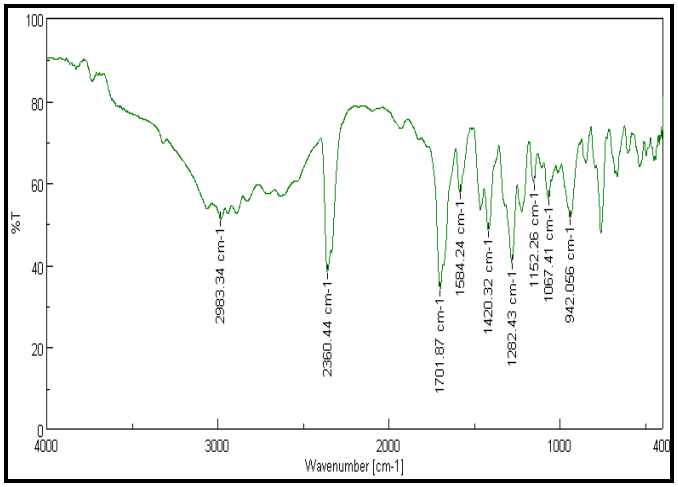

Figure: 3 FT-IR Spectra of Zaltoprofen with Sodium Chloride Mixture

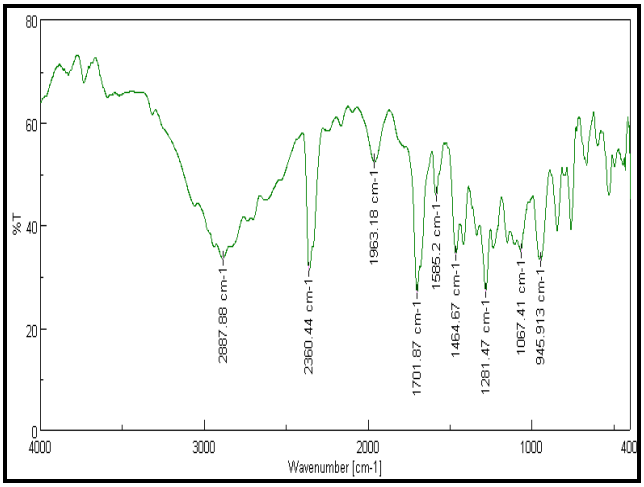

Figure: 6 FT-IR Spectra of Zaltoprofen with Poly Ethylene Oxide Mixture

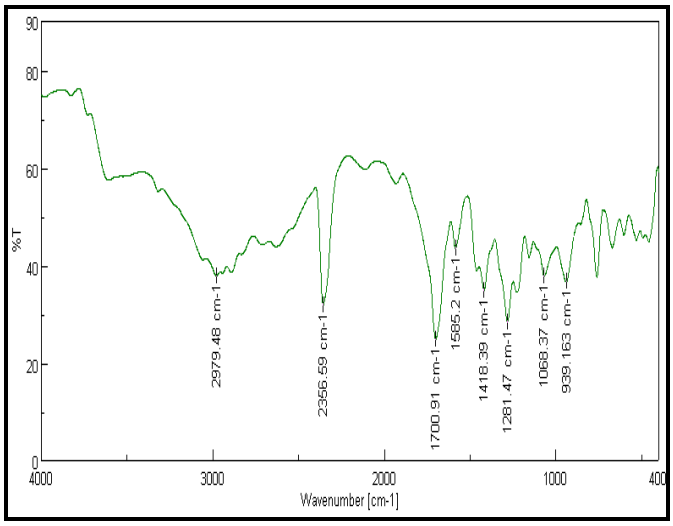

Figure: 7 FT-IR Spectra of Zaltoprofen with Cellulose Acetate Mixture

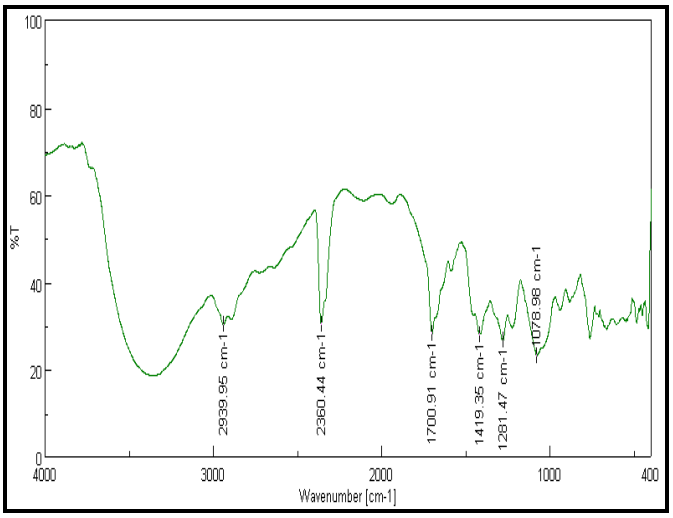

Figure: 8 FT-IR Spectra of Zaltoprofen with all Formulation Excipients

Table: 3 Interpretations of FT-IR Spectra

Functional Group	Drug + $NaHCO_3$	Drug + NaCl	Drug + HP-β-CD	Drug + Spray Dried Lactose	Drug + Poly ethylene oxide	Drug + Cellulose acetate	Physical mixture
Aromatic-C-H Stretching	3366.14	2983.34	2937.06	2894.63	2887.88	2979.48	2939.95
Arile-C-H Stretching	2360.44	2360.44	2360.44	2353.69	2360.44	2356.59	2360.44
O=C Stretching	1700.91	1701.87	1701.87	1696.09	1701.87	1700.91	1700.91
C-O Stretching	1284.36	1282.43	1282.43	1283.89	1281.47	1281.47	1281.47
O-H Stretching	1079.94	1067.41	1065.48	1068.37	1067.41	1068.37	1078.98
C-S-C Stretching	1417.42	942.05	1419.35	1420.32	1464.67	1418.39	1419.35

Drug-Excipients Compatibility Study by DSC

The DSC thermograms of pure Zaltoprofen and with other excipients are depicted in Figure 9. Here, pure drug has the melting point at 138.60 ºC and mixture has the melting point at 135.64 ºC. No change in the endotherm peak of the drug was observed in the mixture of drug with other excipients. From this, it was inferred that there was no interaction between the drug and excipients.

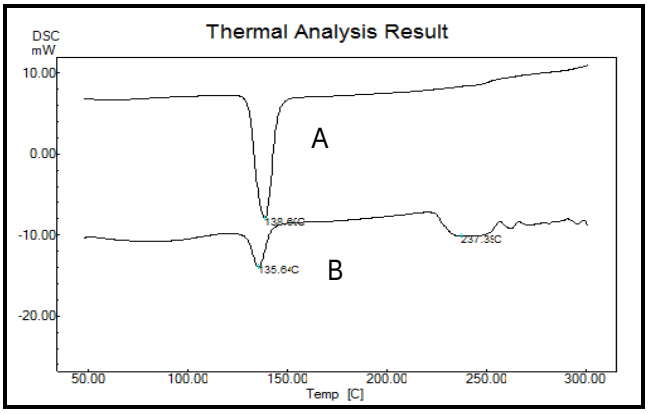

Figure: 9 DSC Thermogram of (A) Zaltoprofen (B) Mixture of Zaltoprofen with other Excipients

Characterization of Zaltoprofen and HP-β-CD Inclusion Complex

Inclusion complex of Zaltoprofen and HP-β-CD was evaluated by two methods like FT-IR and DSC study.

Characterization of Zaltoprofen and HP-β-CD Inclusion Complex by FT-IR method

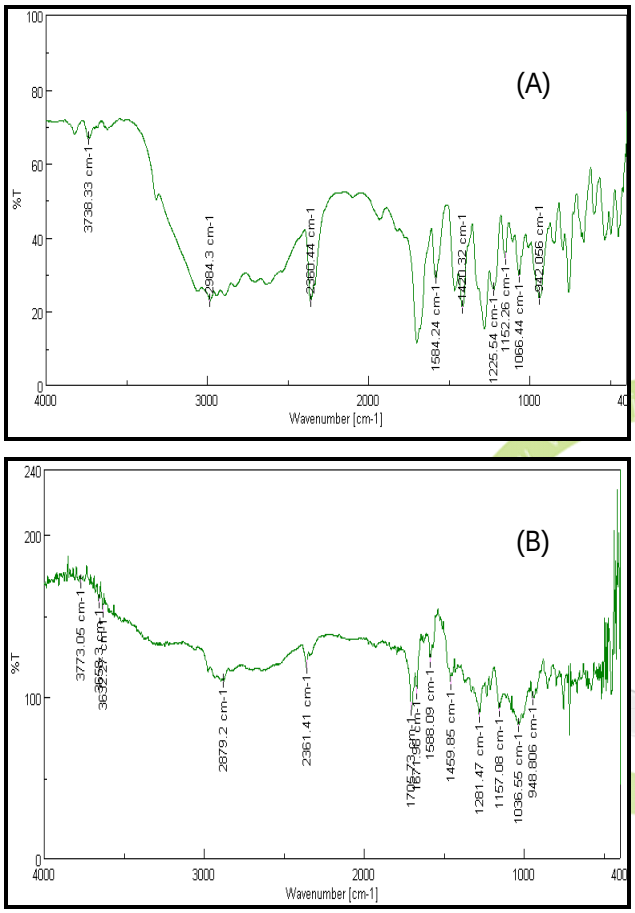

Figure: 10 FT-IR Spectra Comparison of (A) Zaltoprofen and (B) Zaltoprofen with HP-β-CD Inclusion complex

The FTIR spectra of Zaltoprofen and Inclusion complex of Zaltoprofen with HP-β-CD are shown in figure 10. The characteristic peak of Zaltoprofen was disappeared in FTIR spectra of Zaltoprofen and HP- β-CD mixture. This may be indicative of the drug monomeric dispersion as a consequence of the interaction with HP-β-CD, which could result in its inclusion into the hydrophobic cavity of the carrier.

Characterization Zaltoprofen and HP-β-CD Inclusion complex by DSC:

In below thermogram, endothermic peak of the complex is changed from 138.6 ºC to 100.84 ºC. From this DSC thermogram, it was concluded that the drug was complexed with HP-β-CD.

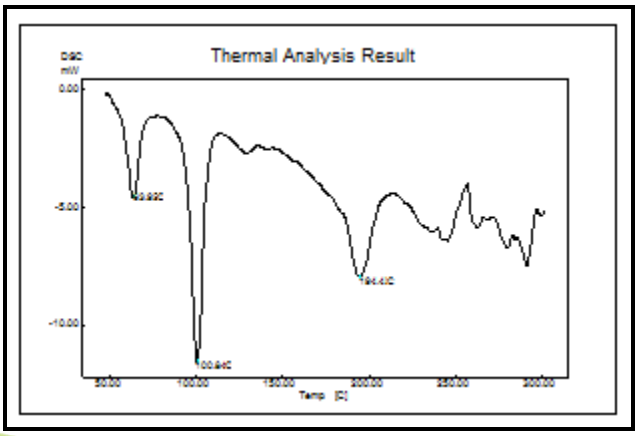

Figure: 11 DSC Thermogram of Zaltoprofen and HP-β-CD Inclusion Complex

Evaluation of Powder blend

Angle of Repose

The values obtain for the angle of repose for Zaltoprofen and batch Z1 to Z8 are given in table 4. The value was found to be in the range which indicates good flow property of powder blends.

Bulk Density

Bulk density of Zaltoprofen was found to be 1.013gm/ml. Bulk density of batch Z1 to Z8 ranges between 1.257 - 1.358gm/ml. The values obtained for bulk density of Zaltoprofen and batch Z1 to Z8 are given in table 4.

Tapped Density

The values obtained for tapped density of Zaltoprofen and batch Z1 to Z8 are listed in table 4. Tapped density value of Zaltoprofen was found to be 1.319 gm/ml. Tapped Density value of batch Z1 to Z8 ranges between 1.523 - 1.587gm/ml.

Hausner's Ratio

Hausner's ratio of Zaltoprofen was found to be 1.302 which indicates poor flow property. Hausner's ratio of batch Z1 to Z8 ranges

between 1.147 - 1.214 indicating that the powder blends have the good flow property for flow through hopper during tablet punching. The values obtained for Hausner's ratio for Zaltoprofen and batch Z1 to Z8 are tabulated in table 4.

Carr's Compressibility Index

Compressibility index value of Zaltoprofen was found to be 23.20% which indicates passable compressibility. Compressibility index value of batch Z1 to Z8 formulations ranges between 12.78% - 17.63% indicating that the powder blends have the required compressibility for tablet punching. The values obtained for compressibility index for Zaltoprofen and batch Z1 to Z8 are tabulated in table 4.

Core tablet are evaluated for the Pharmacopeial evaluation like weight variation, content uniformity, hardness and friability of the tablet.

***In-vitro* dissolution study**

From the data of % cumulative drug release, it was concluded that batches Z1-Z4 which were formulated by the 3% weight gain has shown higher % drug release than the batches Z5-Z8 which were formulated by the 5% weight gain of the coating solution. So, it was revealed that as the % weight again increased, amount of drug release decreased. Batches Z1, Z2, Z3 and Z4 have shown 79.83%, 87.19%, 85.85% and 98.08% respectively.

Table: 4 Evaluation of the Powder Mixture

Formulations	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's Ratio	Carr's Index (%)
Pure Drug	34.763±0.732	1.071±0.039	1.493±0.183	1.360±0.024	15.233±0.762
Z1	25.637±1.957	1.389±0.125	1.839±0.158	1.250±0.026	13.806±0.949
Z2	26.123±0.715	1.462±0.120	1.665±0.282	1.276±0.011	14.280±0.456
Z3	26.777±0.631	1.384±0.048	1.830±0.129	1.259±0.025	13.796±0.249
Z4	25.093±0.638	1.337±0.100	1.736±0.156	1.284±0.006	13.409±0.470
Z5	28.007±0.350.	1.338±0.008	1.680±0.230	1.273±0.014	14.217±1.430
Z6	26.920±0.165	1.269±0.145	1.590±0.219	1.277±0.001	13.810±1.011
Z7	26.640±0.498	1.239±0.198	1.542±0.376	1.251±0.039	13.540±1.055
Z8	26.893±0.0323	1.328±0.397	1.456±0.973	1.324±0.038	13.876±1.092

All values are expressed as mean ± standard deviation, n=3

Table: 5 Evaluation of the Core Tablet

Formulation	Weight variation #	Content uniformity*	Hardness*	Friability*
Z1	450.300±1.929	97.10±0.830	5.133±0.414	0.443±0.064
Z2	450.433±1.550	97.93±0.757	5.233±0.412	0.483±0.063
Z3	448.900±3.555	97.94±0.808	4.900±0.398	0.447±0.058
Z4	451.900±1.400	97.27±0.688	4.933±0.419	0.483±0.062
Z5	450.900±2.227	97.57±0.656	5.400±0.412	0.497±0.067
Z6	450.767±1.914	98.14±0.717	5.333±0.410	0.423±0.062
Z7	451.100±0.656	98.18±1.078	5.267±0.404	0.520±0.044
Z8	450.667±1.134	98.14±1.273	5.788±0.398	0.523±0.058

*All values are expressed as mean ± standard deviation, # =20 and * =5 tablets*

Comparison of *in vitro* drug release data of batch Z1 to Z4 indicated that as the amount of osmotic agent i.e. sodium chloride and sodium bicarbonate increased, % drug release increased. From these *in vitro* drug release data, batch Z4 has shown 98.08% drug release within 12 hr in a controlled and zero order pattern. % Cumulative Drug release Vs Time graph of Zaltoprofen tablet with 3% and 5% coating weight gain is given in figure 12 and 13 respectively.

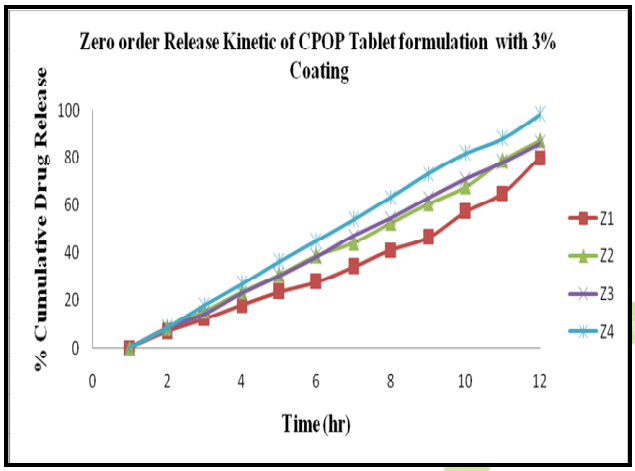

Figure: 12 Zero order Release Kinetic of CPOP Tablet formulation with 3% Coating

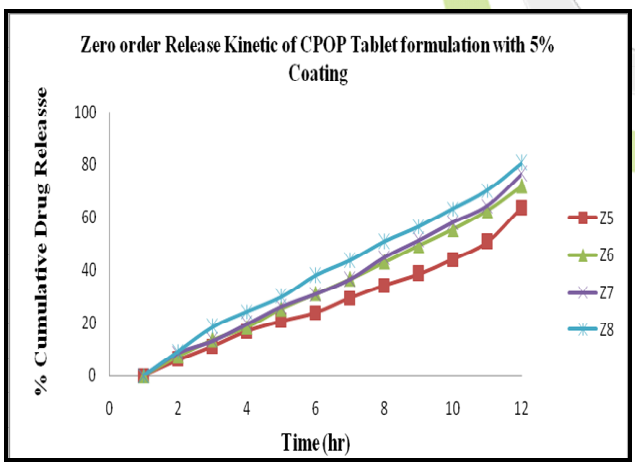

Figure: 13 Zero order Release Kinetic of CPOP Tablet formulation with 5% Coating

Effect of pH

Release studies of the optimized formulation were conducted according to pH change method to study the effect of pH on drug release. The release media were HCl buffer (pH 1.2), Phosphate buffer (pH 4.5) and Phosphate buffer (pH 6.8). Figure 14 shows release of Zaltoprofen from optimized formulation and it is clearly evident that the release profile is similar in all the media, demonstrating that the developed formulation shows pH independent release.

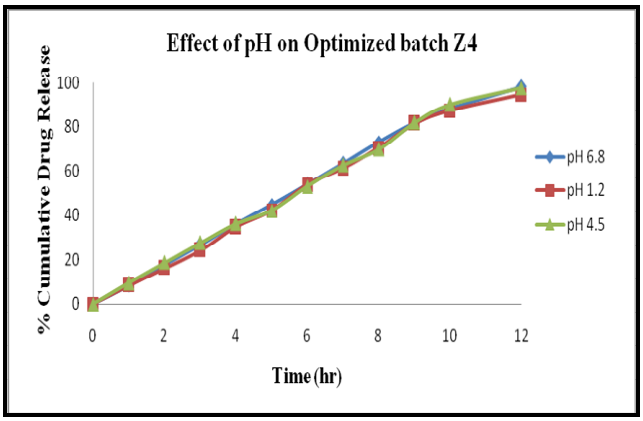

Figure: 14 Effect of pH on Optimized Batch Z4

Effect of Agitational Intensity:

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 apparatus used was USP-II (rotating Paddle) at 50, 75, and 100 rev./min. Figure 15 shows that the release profile of Zaltoprofen from the developed formulation is fairly independent of the agitational intensity of the release media and hence, it can be expected that the release from the developed formulation will be independent of the hydrodynamic conditions of the body.

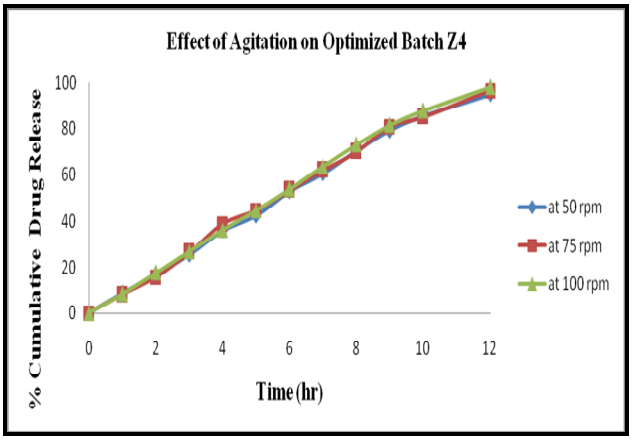

Figure: 15 Effect of Agitation on Optimized Batch Z4

Curve Fitting Analysis:

The in vitro release data was fitted to various kinetic models like, Zero order, First order, Higuchi, Hixson-Crowell model, and Korsmeyer-Peppas. Release kinetics of Osmotic pump tablets formulation is given in Table 14. When the data were plotted according to the first order equation, the formulations showed a comparatively poor linearity, with regression value of 0.93; whereas the regression value for zero order equation was 0.998, which indicated that drug release from optimized formulation Z4 was independent of drug concentration. The Results were shown in table 5.

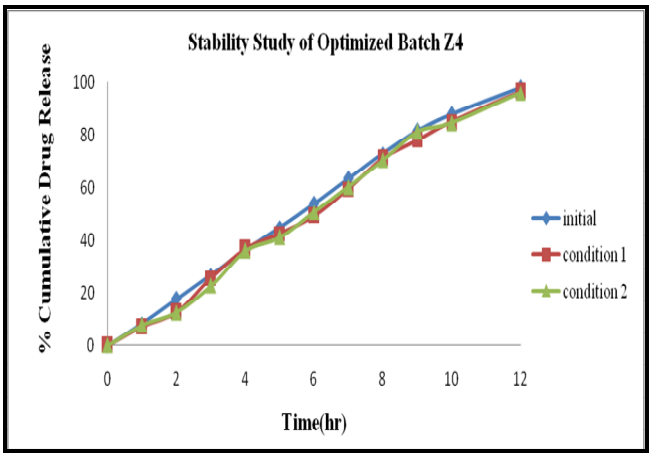

Figure: 16 Stability Testing Data of Optimized Batch Z4

Table 5: Different Kinetic Models Applied on CPOP Tablets

Batch Code	Zero Order Model			First Order Model			Higuchi Square Root Model			Korsmeyer-Peppas Model				Hixson-Crowell Model			Best Fit Model
	K_0	SSQ	R^2	K_1	SSQ	R^2	K_H	SSQ	R^2	N	K_{KP}	SSQ	R^2	K_{HC}	SSQ	R^2	
Z1	6.238	82.09	0.9875	0.086	500.73	0.92	17.00	1285.39	0.80	1.15	4.517	32.83	0.9950	0.026	345.51	0.9476	Zero
Z2	7.534	26.64	0.9969	0.115	446.42	0.94	20.76	1181.55	0.86	0.97	8.003	23.62	0.9973	0.034	236.99	0.9725	Zero
Z3	7.617	46.95	0.9947	0.118	425.33	0.95	20.99	1201.76	0.86	0.95	8.32	39.95	0.9955	0.034	212.90	0.9760	Zero
Z4	8.764	75.43	0.9934	0.148	748.65	0.93	24.20	1457.73	0.87	0.93	10.12	50.60	0.9956	0.042	379.89	0.9670	Zero
Z5	5.057	22.26	0.9943	0.066	129.68	0.96	13.90	592.06	0.84	1.01	4.87	21.80	0.9944	0.020	83.06	0.9788	Zero
Z6	6.149	9.23	0.9984	0.086	148.74	0.97	16.94	729.46	0.87	0.985	6.73	4.68	0.999	0.026	69.10	0.9877	Zero
Z7	6.392	10.11	0.9984	0.090	238.00	0.96	17.59	872.28	0.85	0.99	6.52	9.87	0.9984	0.027	128.20	0.9793	Zero
Z8	7.066	66.31	0.9903	0.107	154.13	0.97	19.62	668.20	0.90	0.86	9.36	5.34	0.9992	0.031	58.44	0.9915	Zero

*R^2-Correlation coefficients, SSQ-Sum of Square, K_0, K_1, K_H, K_{KP} K_{HC}, Release rate constant for zero order, First order, Higuchi, Korsmeyer-Peppas release equation and Hixson Crowell, respectively, n - diffusional exponent, indicative of release mechanism in Korsmeyer equation. All formulations Z9 to Z16 followed Zero drug release.

Stability testing of optimized batch Z4

The selected formulation Z4 were evaluated for stability studies and it was stored at 25ºC ± 2ºC/60%RH ± 5%RH and 40ºC ± 2ºC/75%RH ± 5%RH and tested after 1 month. At the end of 1 month, formulation was analyzed for their drug content and dissolution study. The residual drug contents of formulations were found to be within the permissible limits and the results of 1 month duration are shown in the table 6.

Table: 6 Similarity and Difference Factor for Stability Testing

Condition	Drug Content	Physical Appearance*	% CDR after 12 hr
Initial stage	98.27%	+++	98.08%
After 1 month at 25ºC±2ºC/ 60%RH±5%RH	96.43%	+++	97.27%
After 1 month at 40ºC±2ºC/ 75%RH±5%RH	95.89%	+++	96.19%

*+++ = Same as on zero day, ++ = Slight change in color

CONCLUSION

Aim of present study was to prepare controlled porosity osmotic pump of Zaltoprofen that can deliver Zaltoprofen for 12 hr. Zaltoprofen is a poorly water soluble drug so improvement of solubility was performed. Result says that complexation with HP-β-CD increases the % drug release of Zaltoprofen. Osmotic agents like Sodium chloride and Sodium Bicarbonate were used for the preparation of controlled porosity osmotic pump tablet. The result says that as the amount of osmotic agent increased the drug release increased.

From present study conclude that; by the use of both the controlled porosity osmotic pump and the use of complexation technique; Zaltoprofen can be delivered in a controlled manner for 12 hr in a dose of 120 mg two times a day. From the FT-IR and DSC study it was also concluded that excipients which used for preparation of formulation were compatible with drug. The batch Z4 which was prepared by the use of $NaHCO_3$ in 75 mg and 3% coating weight gain has the maximum % drug release of 98.08% in dissolution study. From that it was concluded that the batch Z4 is an optimized batch. Batch Z4 also delivers Zaltoprofen in zero-order release manner from devices which is independent of both agitation and pH. The stability study of optimized batch Z4 shows no remarkable change in Drug Content, Physical Appearance, and % Drug Release.

REFERENCES

1. Lee TW, and Robinson. In Remington: The Science and Practice of Pharmacy, 2nd Edn, Lippincott Williams and Wilkins, Baltimore, 2000, 903-929.
2. Das N, and Das S, In Controlled Release of Oral Dosage Form Formulation, Fill and Inish, 2003, 10-15.
3. Ansel HC, Allen LV, and Popovich NC, In Pharmaceutical Dosage Form and Drug Delivery System, 7th Edn, Lippincott Williams and Wilkins, Baltimore, 2000, 231.
4. Vyas SP, and Khar RK, In Controlled Drug Delivery Concept and Advances, Osmotically Regulated Systems, Vallabh Prakashan, Delhi 1995, 477-501.
5. Verma S and Garg S, "Formulation Aspects in Development of Osmotically Controlled Oral Drug Delivery System", Journal of Controlled Release, 2002, 79, 7-27.
6. Welling PG and Dobrinnska MR, "Dosing Consideration and Bioavailability Assessment of Controlled Drug Delivery System", Controlled drug delivery, 1978, 29, 254-373.
7. Jain NK, Advance In Novel Controlled Delivery, 2th Edn, CBS Publisher, 18-39.
8. Edavalath S, Shivanand K and Prakasam K, "Formulation Development and Optimization of Controlled Porosity Osmotic Pump Tablets of Diclofenac Sodium", International Journal of Pharmaceutical Science, 2011, 3, 438-446.
9. Rastogi K, Vaya N and Mishra B, "Osmotic Pump: A Novel Concept in Rate Controlled Oral Drug Delivery", Eastern Pharmacist, 1995, 38, 79-82.
10. Martin Alfred, In A Physical Pharmacy, 4th Edn, Lippincott W, and Wilkins, 1994, 116-117.
11. Pandey S and Devmurari V, "Osmotic Pump Drug Delivery Devices: From Implant to Sandwiched Oral Therapeutic System", International Journal of Technology and Research, 2010, 2, 693-699.
12. Robert C and Gupta SK, "Clinical Spectrum of the Osmotic-Controlled Release Oral Delivery System (Oros), An Advanced Oral Delivery Form", Current Technology of Medical Research and Opinion, 2006, 22(10), 1879–1892.
13. Mahalaxm R and Pritam K, "Enhancement of Dissolution of Glipizide from Controlled Porosity Osmotic Pump using a Wicking Agent and a Solubilizing Agent",

International Journal of Pharmaceutical Technology, 2009, 1, 705-711.

14. Gaylen NZ and Gerald SR, "The Controlled Porosity Osmotic Pump", Journal of Controlled Release, 1985, 1, 269-282.
15. Padmaja SA and Omar LS, "A Controlled Porosity Drug Delivery System", International Journal of Pharmaceutics, 1998, 167, 83–96.
16. Makhija SN and Vavia PR, "Controlled Porosity Osmotic Pump-Based Controlled Release Systems of Pseudoephedrine", Journal of Controlled Release, 2003, 89, 5–18.
17. Wen JX and Ning L, "Preparation of Controlled Porosity Osmotic Pump Tablets for Salvianolic Acid and Optimization of the Formulation Using an Artificial Neural Network Method", Acta Pharmaceutica Sinica, 2011, 1(1), 64–70.
18. Longxiao L Jeong K, "Nifedipine Controlled Delivery by Sandwiched Osmotic Tablet System", Journal of Controlled Release, 2000, 68,145–156.
19. Li PR and Guang MF, "Improving the Solubility of Ampelopsin by Solid Dispersions and Inclusion Complexes", International Journal of Pharmaceutical Science, 2005, 38, 457-464.
20. Young G and Weisan P, "Cyclodextrin Complex Osmotic Tablet for Glipizide Delivery", Drug Development of Indian Pharmaceutics, 2002, 1015-1021.
21. The Japanese Pharmacopoeia, The Ministry of Health, Labour and Welfare Ministerial, Japan, 15th Edn, 2006, 1259-1264.
22. Raymond CR, Paul J, Sheskey S, Handbook of Pharmaceutical Excipients, 6th Edn, Pharmaceutical Press, London, 364-368.
23. The Indian Pharmacopoeia, Ministry of Health and Family Welfare, Government of India, Controller of Publications, New Delhi, 4th Edition, 1996, 593-603.
24. Subramanyam CVS, Text book of Physical Pharmaceutics, thoroughly revised and enlarge, 3rd Edn, Vallabh prakashan, New Delhi, 223.
25. Patrick JS, Martin's Physical Pharmacy and Pharmaceutical science, 4th Edn, Lippincott Williams & Wilkins, A Wolters Kluwer Business, Baltimore, 2006, 333.
26. International Conference on Harmonization (ICH), Harmonized Tripartite guideline for Stability Testing of New Drugs Substances and Products Q1A(R2) Feb 6, 2003.

