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Research Article

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Design, development and evaluation of zaltoprofen sustained release tablet

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ABSTRACT

Zaltoprofen is BCS Class-II drug which rapidly and completely absorbed but plasma level achieved is highly variable after oral administration. Besides it also has relatively short elimination half-life (4.83 ± 2.01 hours). A drug with a short half-life requires frequent dosing and this makes Zaltoprofen an ideal candidate for a sustained-release formulation. Hydrophilic and swellable polymer matrix such as Polyox WSR 303, Carbopol 934 and HPMC K15M are widely used in sustained-release delivery because of their flexibility to obtain a desirable drug release profile. To provide a sustained-release composition which releases Zaltoprofen over a time period of at least about 24 hours when exposed to gastrointestinal milieu thus facilitating a reduction in frequency of drug administration through sustain-drug delivery system. To develop a sustained-release dosage form that has desirable in vitro dissolution profile as compared to Theoretical release profile.

Key words: Zaltoprofen, Polyox WSR 303, Theoretical drug release, 6.8 Phosphate Buffer.

INTRODUCTION

The scenario of pharmaceutical drug delivery is rapidly changing conventional pharmaceutical dosage forms are being replaced by new drug delivery systems. These new drug delivery systems are having edge over conventional ones in terms of many biopharmaceutical parameters. One such drug delivery system is sustained-release drug delivery system [1]. The primary objective of sustained release drug delivery system is to ensure safety, improve the efficacy, reduce the dose frequency and ultimately result in improved patient compliance. The aim of present work is to formulate sustained drug delivery system of Zaltoprofen suitable for once-a-day dosing [2]. In general, sustained-release drug delivery is attempted to maintain constant, effective drug level in the body with concomitant minimization of undesired side-effects. Zaltoprofen is a Non-steroidal anti-inflammatory drug [3]. Mainly used for the treatment of rheumatoid arthritis. It has maximum absorption in small intestine. The bioavailability of drug is (70-85%) as lesser portion of drug misses the absorption window when given orally owing to an important first pass metabolism [4]. The recommended adult dosage of Zaltoprofen is 80 mg thrice a day or 240 mg once daily. The short biological half life of drug also favours development of a sustained release formulation [5].

EXPERIMENTAL SECTION

Zaltoprofen was obtain as a gift sample from Astron Research Ltd. Ahmadabad, HPMC K4M from S.D Fine chem., Polyox WSR from Roquette Pharma, HPMC K100LV from S.D Fine chem, Povidone K 30 from BASF Ltd, Magnesium stearate from Signet chemicals, Avicel pH101 from S.D Fine chem, IPA from Triveni Chemicals.

Particle size analysis

The particle size or the globule size of selected formulations was analysed using Malvern analyzer. A graph was plotted for size in nm against % of intensity. The size where there was maximum intensity was observed is the mean particle size of the drug. Particle size analysis was performed to confirm that the drug were of nano-size range [6].

Differential Scanning Calorimetry
Thermogram of drug and excipient in various ratio were employed for the determination of glass transition temperature [7].

Compatibility studies:
Compatibility of the drug with excipients was confirmed by FTIR studies. The blend was to be filled in transparent glass vials and were closed with gray coloured rubber stoppers and further sealed with aluminium seal and charged into stress condition at 25ºCº±2°C / 60%RH± 5 % RH and 40ºC±2°C / 75%RH± 5 % RH. Similarly API was also kept at same condition as for the samples. Samples were withdrawn for analysis within two days of sampling date as per the compatibility study plan. Physical observation should be done at every week up to 1 month and DSC studies were carried out to determine the compatibility of excipients with the drug. These were examined using shimadzu spectrometer model. The spectra of drug and other ingredients in the formulation were compared with that of the original spectra [8].

Dose Calculation [9]
The total dose of Zaltoprofen for a once-daily sustained release formulation was calculated by the following available pharmacokinetic data.

Volume of distribution (V_d) = 3.3 Liter,

Maximum plasma concentration (C_{max}) = 16.41µg/ml

Therefore, loading dose (D_L) can be calculated by,

$D_L = C_{max} X V_d$

D_L = 16.41 µg/ml X 3300 ml = 54.153 mg

Calculation of maintenance dose:

$D_T = D_L (1+0.693X t / t_{1/2})$

Where,
D_T = Total dose, D_L = Loading dose, $t_{1/2}$ = half life of drug, t = time during which sustained release is desired

D_T = 54.153 (1+ (0.693 X 24/4.83) = 239.89 ≈ 240 mg is total dose

D_L = 54.153 (Loading dose), $D_{M=}$ 185.847 mg (Maintenance dose)

Hence, the formulation should release 54.153 mg in 1 hour like conventional tablets and 185.847 mg up to 24 hours thereafter.

Method of Preparation of Sustained Release Matrix Tablets
Zaltoprofen matrix tablets were prepared by using wet granulation technique. In this research work there are twelve different formulations are prepared. Here three different hydrophilic polymers were used in different concentration to retard the drug release. Other excipients like binder, lubricant and anti-adherent were used.

Procedure for tablet preparation
Weighing and Shifting: All the ingredients were weighed accurately, according to their respective weight. Zaltoprofen and remaining excipient passed through sieve no # 40.

Granulation: Povidone was dissolved in 150 ml IPA under constant stirring till it dissolved. Granulation was carried out in PLM by adding above binding solution of povidone, adopting the following parameter.

i) Shifting Zaltoprofen was loaded in PLM and dry mixing for 15 minute.
ii) Binding solution was added for 10 minute at slow speed of PLM.
iii) Kneading continue for 20 minute at 242 rpm.

Wet shifting was carried out through sieve no #10 then the granules was dried by using rapid dryer for 90 minute at 30^0C. Dry shifting was done through sieve no #20.

Lubrication: Dried granules were blended with Mag. stearate, talc for 10 minute in blender.

Compression: Lubricated granules were compressed by 10 mm circular punch.

Table 1: Composition of S.R Formulation (Qty mg/Tab)

Ingredient	ZP1	ZP2	ZP3	ZP4	ZP5	ZP6	ZP7	ZP8	ZP9	ZP10	ZP11	ZP12
Zaltoprofen	240	240	240	240	240	240	240	240	240	240	240	240
MCC 101	40	40	40	40	40	40	40	40	40	40	40	40
Polyox WSR	150	---	---	75	75	---	100	25	25	75	37.5	37.5
HPMCK4M	---	150	---	75	---	75	25	100	25	37.5	75	37.5
HPMCK100LV	---	---	150	---	75	75	25	25	100	37.5	37.5	75
PVP K-30	10	10	10	10	10	10	10	10	10	10	10	10
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mag. stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**

Post-compression Evaluation of matrix tablets

Tablet thickness
Thickness of tablets is an important for uniformity of tablet size. Thickness will measure by using Vernier Calipers on six randomly selected samples [10].

Tablet Hardness
The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation will be measured by Monsanto hardness tester [11].

Friability
Friability is the measure of tablet strength. Roche friabilator is will be taken in use for testing the friability using the following procedure. Twenty tablets will be weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets will be weighed and the percentage loss in tablet will be determined [12].

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

Weight Variation
Twenty tablets will be weighed individually and the average weight will be determined. The % deviation will be calculated [13].

Uniformity of Content
Content of active ingredient in tablets will be taken at random, will be determined. 10 tablets will be weighed and average weight will be calculated. All tablets will be crushed and powder equivalent to 240 mg will be dissolved in 250 ml 6.8 phosphate buffer and shaken for 20 min. solution will be filtered and after suitable dilution using 6.8 phosphate buffer, absorbance will be measured spectrophotometrically against reagent blank. Amount of drug present in one tablet will be calculated [14].

Swelling Study
The swelling behaviour of tablet described as the water absorbing capacity. The tablets will be weighed individually (W_0) and placed separately in Petridis containing cellophane membrane and incubated at 37 ± 5 ^{0}C. At regular time intervals until 18 hours, the tablets will be removed carefully [15]. The swollen tablet will be then reweighed (Wt) and the % swelling will be calculated using the following formula:

$$\% \text{ swelling} = \{(W_t - W_0) / W_0\} \times 100$$

Where Wt is the weight of tablet at time t and W_0 is the initial weight of tablet.

Dissolution Studies [16]
The release rate of Zaltoprofen from matrix tablets will be determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test will be performed using 900 ml of 6.8 Phosphate buffer for 24 hour, at 37 ± 0.5

°C and 100 rpm. Aliquot volume will be withdrawn from the dissolution apparatus at specified time point, and the samples will be replaced with fresh dissolution medium. After filtration and suitable dilution the amount of drug release will be determined from the calibration curve.

Calculation:

$$\% \text{ Zaltoprofen Dissolved} = \frac{A_T}{AS} \times \frac{Wstd}{100} \times \frac{5}{50} \times \frac{900}{5} \times \frac{P}{LC} \times 100$$

Calculation of Dissimilarity (F_1) & Similarity (F_2) Factor

Dissimilarity factor (f_1)

It was calculated in the comparison with reference or with the innovator product to know the dissimilarity. The dissimilarity factor (f_1) should be always less than 15 (f_1<15).

$$f_1 = \frac{\sum R_t - T_t}{\sum R_t} \times 100$$

Similarity factor (f_2)

The similarity factor (f_2) was defined as the logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products. This was calculated to compare the test with reference release profiles [17]

$$f_2 = 50 \times \log 10 \times \frac{1}{\sqrt{1 + 1/n \times \sum (R_t - T_t)^2}} \times 100$$

Where, n= numbers of sampling points, the similarity factor (f_2) should be always greater than 50 (f_2>50)

Drug Release Kinetics: To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order as cumulative amount of drug released vs time, first order as log cumulative percentage of drug remaining vs time, and

Higuchi's model as cumulative percentage of drug released vs square root of time.

Stability Studies of the Standardized Formulations

The stability studies will be carried out on the most satisfactory formulations as per ICH guidelines. The most satisfactory formulation sealed in aluminium packaging and will be kept in humidity chamber maintained at 25 ± 2 °C / 60 ± 5 %RH and 40 ± 2 °C / 75 ± 5 % RH for 1 month. At the end of studies, samples will be analyzed for the drug content, in vitro dissolution and other physicochemical parameters.

RESULTS AND DISCUSSION

DSC

Thermogram of pure ZPF is depicted in Fig. 1. Pure ZPF displayed endothermic peak at 137.95°C corresponding to its melting point. In the thermogram one endothermic peak were at 137.95°C.

FTIR study

The FTIR spectra of pure ZPF, excipient and formulation in figure 2 to 7. Pure ZPF presents characteristic infrared spectra in the region of 3400-2400cm^{-1} explains carboxylic acid (COOH) functional group, while 1280 cm^{-1} suggests C-O group. It also exhibits characteristic infrared spectra in the C=O stretching region of functional carbonyl group band at 1700 cm^{-1}, showing its crystalline nature. The characteristic acid carbonyl stretching band at 1700 cm^{-1} of pure ZPF appeared unchanged in physical mixture and complex.

Particle size analyzer

Particle size analyzes was done using Malvern apparatus by dry method (fig. 8). The size of the 50, 90 and 100% w/w particle was 6.488, 15.963 and 282.508 m^2/g

Evaluation of Tablets

The physical attributes of the tablet were found to be satisfactory. Typical tablet defects, such as capping, chipping, and picking, were not observed, the compression was done with 10 mm standard concave punches. Results for other physical evaluations were also found to be within an acceptable range. For instance, weight variation ranges for all formulation are from 449 to 452. Hardness of the tablet was found to be 4.22 to 5.81. Thickness was found to be fixed during the compression cycle; values were 3.16 to 3.51 respectively. The range of Friability of the batches was calculated 0.216 to 0.781 which was well within the acceptable range of 1% and indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed.

Percentage Swelling Study

All the tablets have different hydration profiles, as they hydrated gradually and swell more as the conc. of Polyox WSR 303 and HPMC k–4M increases, reaching a maximum point after 24 hr. Most of the tablet reached between 25 to 30 % hydration with the first two hour. The fastest hydration rate was obtained from batch ZP3, ZP7, ZP8, ZP10 that hydrated above 57 % within 24 hour. High amount of water uptake may be due to quick hydration of the Polyox WSR 303, HPMC k-4M and HPMC k-100LV and swelling rate of the tablets increasing with increase in the concentration of Polyox WSR 303 and HPMC k-100LV in tablets. These findings can be correlated with the hydrophillicity of cellulose derivatives, which usually varies according to the kind of degree of substitution and to some extent with the polymer viscosity grade.

Calculation of theoretical drug release (TDR)

The pharmacokinetic parameters of Zaltoprofen were utilized for the calculation of theoretical drug release profile for 24 hours dosage form. The Loading dose for sustained release Zaltoprofen was calculated using following equation and was found to be 54.153 mg.

Here, the formulation should release 54.153 mg (22.56 %) of drug in 1 hour like conventional tablet and 185.847 mg (77.44%) per hour up to 24 h thereafter.

In Vitro Dissolution Studies

To achieve the good dissolution profile, the tablet should be formulated so that it releases the drug in a predetermined and reproducible manner. By considering the drug's biopharmaceutic and pharmacokinetic profile, one can determine the required release from the tablet 5 and Figure 1 shows the in vitro drug release profile of Zaltoprofen. It was found that ZP7 and ZP8 19.6% and 21.4% of the drug was released during the first hour, which is in accordance with the conventional dose of 80-mg tablet. During the initial 6 hours, ~45% of the drug was released. After 6 hours, the release rate increased slightly, until the 21st hour, and then release slowed but continued until the 24-hour mark. Hence, a sustained-release pattern was observed throughout the 24-hour dissolution study. The in vitro release behaviour of Zaltoprofen SR was also compared with the theoretical (predictive) profile and found to be quite similar;

Drug Release Kinetics

It was found that the in vitro drug release of Zaltoprofen SR (ZP7) was best explained by Higuchi's equation, as the plots showed the highest linearity ($r^2 = 0.995$), followed by Hixon crowel model ($r^2 = 0.975$) first order ($r^2 = 0.918$) and zero order ($r^2 = 0.910$). This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's kinetics).

Table 2: Sieve Analysis of S.R Granules (% Retain)

Formulations	# 20	# 40	# 60	# 80	# 100	Receiver
ZP1	8	25	28	5	7	27
ZP2	21	25	32	4	7	11
ZP3	52	32	11	1	1	3
ZP4	52	28	12	1	2	5
ZP5	45	24	27	1	1	2
ZP6	33	28.5	22.5	4.5	5	6.5
ZP7	15.5	45	28.5	4	2.5	4.5
ZP8	15.5	28.5	27	6.5	8	14.5
ZP9	17	26.5	28	7.5	6.5	14.5
ZP10	15	26	26.4	7	8	17.6
ZP11	19	28	24	9	5	15
ZP12	17	25	23	9	8	18

Table 3: Post-Compression Evaluation of S.R Tablet

Formulations	Hardness (Kg/cm^2)	Thickness (mm)	Friability %	Weight Variation %w/w	Drug content (%)
ZP1	4.22 ± 0.62	3.21 ± 0.62	0.216	449 ± 0.97	99.92
ZP2	4.71 ± 0.59	3.31 ± 0.48	0.324	450 ± 0.92	98.99
ZP3	4.83 ± 0.38	3.39 ± 0.51	0.323	450 ± 1.27	99.45
ZP4	5.38 ± 0.67	3.46 ± 0.64	0.128	451 ± 0.87	99.82
ZP5	5.81 ± 0.85	3.16 ± 0.42	0.124	449 ± 1.11	99.68
ZP6	4.92 ± 0.29	3.44 ± 0.68	0.194	450 ± 0.95	98.89
ZP7	5.39 ± 0.57	3.15 ± 0.27	0.284	450 ± 0.82	98.88
ZP8	4.62 ± 0.46	3.19 ± 0.52	0.168	451 ± 0.99	99.2
ZP9	5.16 ± 0.92	3.51 ± 0.69	0.363	449 ± 0.94	99.95
ZP10	4.72 ± 0.51	3.49 ± 0.64	0.781	450 ± 0.81	99.01
ZP11	4.69 ± 0.56	3.41 ± 0.61	0.659	449 ± 0.74	98.61
ZP12	4.71 ± 0.46	3.5 ± 0.67	0.572	449 ± 0.88	97.67

Mean ±S.D (n=6)

Table 4: Percentage Swelling Study

Time (Hr)	ZP1	ZP2	ZP3	ZP4	ZP5	ZP6	ZP7	ZP8	ZP9	ZP10	ZP11	ZP12
0	0	0	0	0	0	0	0	0	0	0	0	0
2	25	21	29	19	16	25	31	25	21	22	24	20
4	34	29	37	23	19	35	42	31	28	29	31	28
6	42	36	44	27	24	46	51	47	36	38	41	39
16	49	42	51	31	29	53	59	51	41	44	49	47
24	54	49	57	39	32	57	62	60	55	59	56	54

Table 5: Percentage Cumulative Drug Release

Time (Hr)	ZP1	ZP2	ZP3	ZP4	ZP5	ZP6	ZP7	ZP8	ZP9	ZP10	ZP11	ZP12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	36.2	41.8	50.3	26.4	31.6	40.2	19.6	21.4	29.4	22.6	28.4	32.5
2	59.8	60.4	71.9	40.1	44.5	52.7	26.5	31.5	38.7	33.5	40.4	43.9
6	70.8	71.9	89.3	59.6	58.2	65.3	42.2	46.2	52.9	47.8	57.9	60.5
12	81.2	82,5	96.7	76.4	78.5	80.2	68.6	69.2	72.9	69.5	71.7	78.1
18	92.8	94.9	99.2	88.7	89.6	91.7	81.9	82.5	89.2	84.7	89.3	88.3
24	99.5	99.8	99.9	99.7	99.5	99.5	97.4	98.2	98.3	99.6	99.5	99.6

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Table 6: Calculation of Similarity (*F*2) & Dissimilarity (*F*1) factor

Formulation	*FI*	*F2*
ZP7	4.9	74.63
ZP8	5.29	72.87
ZP10	6.09	69.68

Table 7: Comparatative Data of TDR and Formulation ZP7

Time (Hr)	% TDR	ZP7
0	0	0
1	22.56	19.6
2	29.03	26.5
6	41.98	42.22
12	61.41	68.6
18	82.94	81.9
24	100	97.4

Table 8: Drug Release Kinetics for ZP7 Formulation

Formulation	Zero order	First order	Higuchi	Hixson Crowell
ZP7	0.91	0.918	0.995	0.975

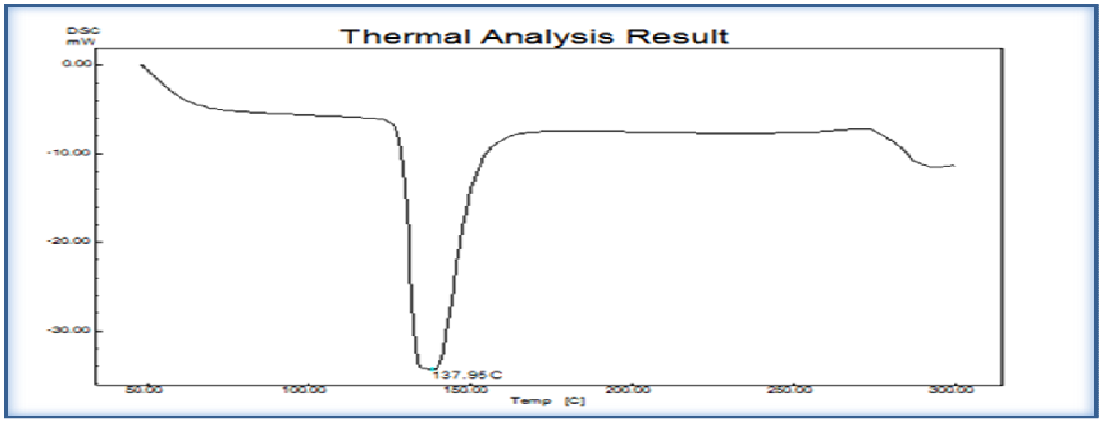

Figure 1: DSC thermogram of pure Zaltoprofen

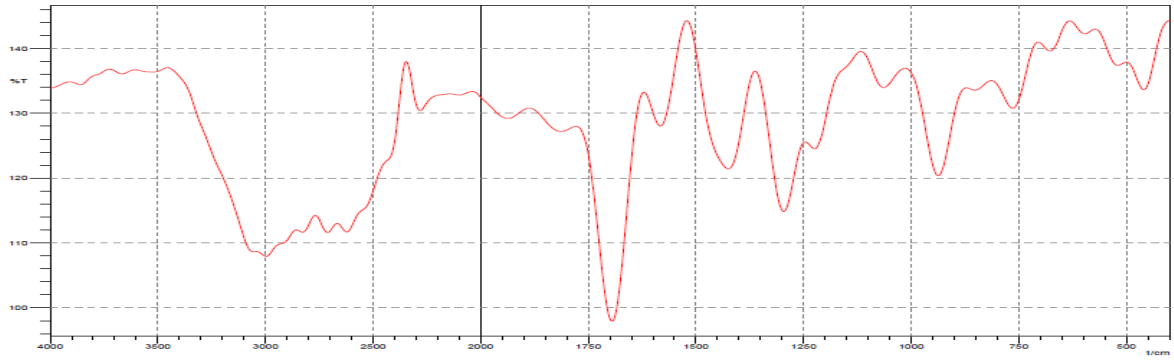

Figure 2: FTIR Spectra of pure Zaltoprofen

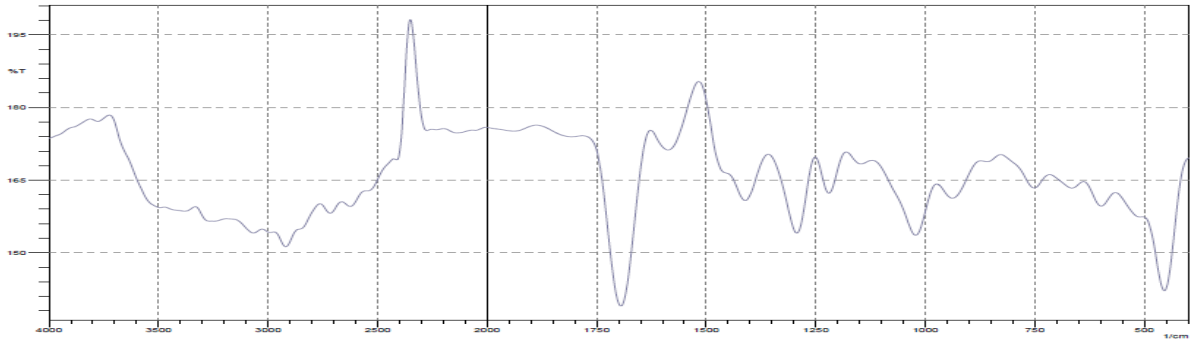

Figure 3: FTIR Spectra of pure Zaltoprofen + MCC 101

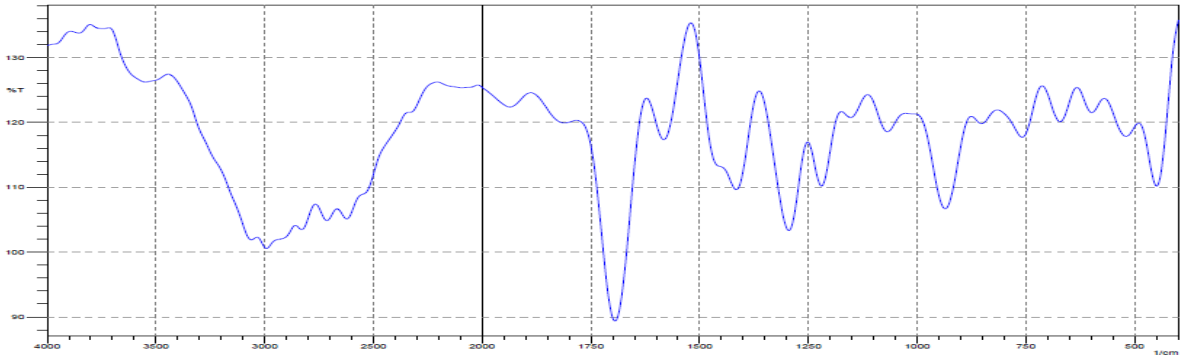

Figure 4: FTIR Spectra of pure Zaltoprofen + HPMC K-4M

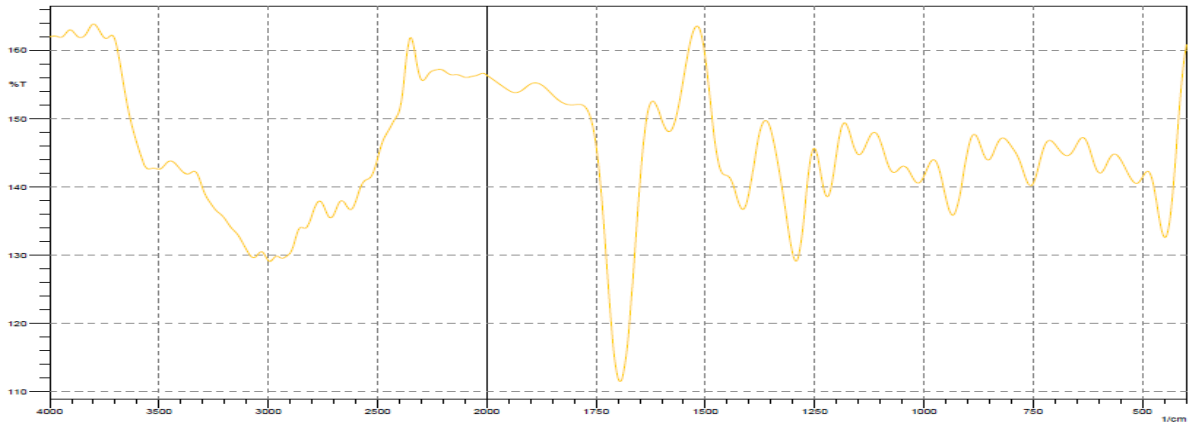

Figure 5: FTIR Spectra of pure Zaltoprofen + PVP K-30

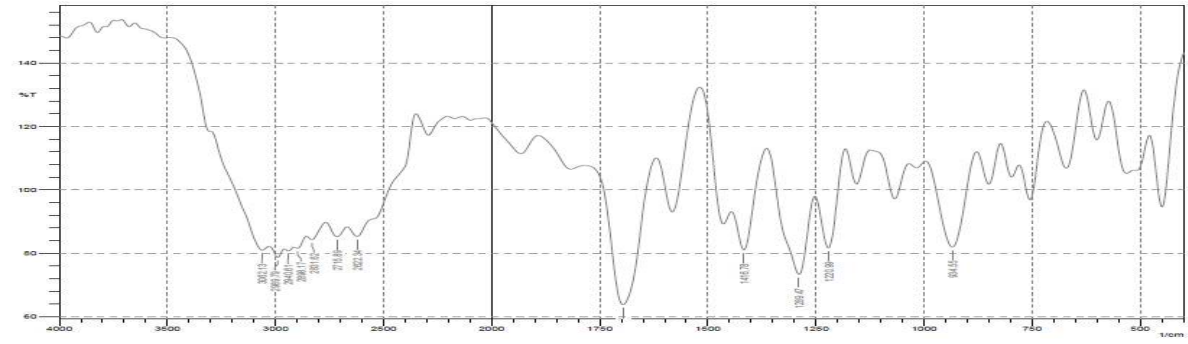

Figure 6: FTIR Spectra of pure Zaltoprofen + HPMC K-100LV

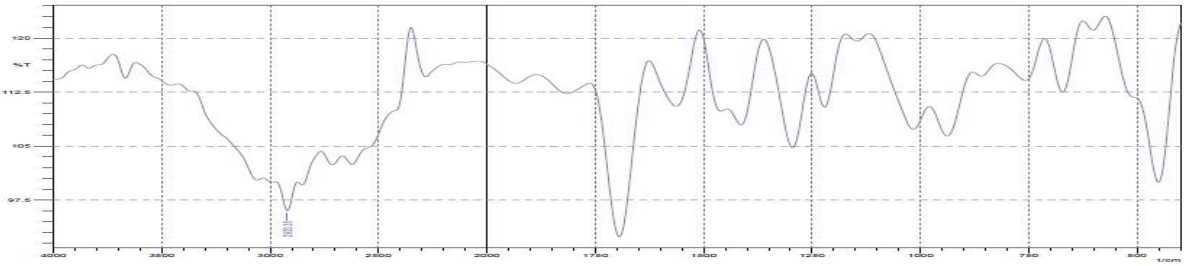

Figure 7: FTIR Spectra of pure Zaltoprofen + Polyox WSR

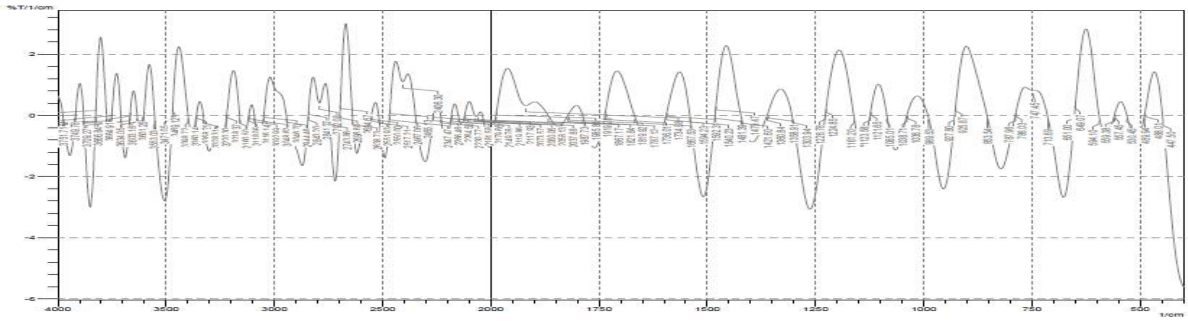

Figure 8: FTIR Spectra of Formulation ZP7

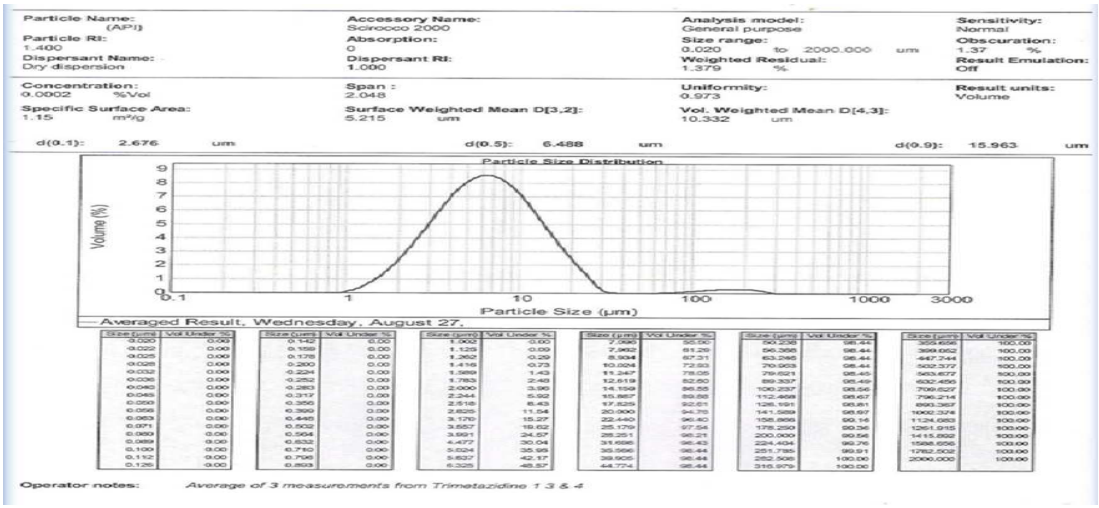

Figure 9: Particle size measurement of pure drug

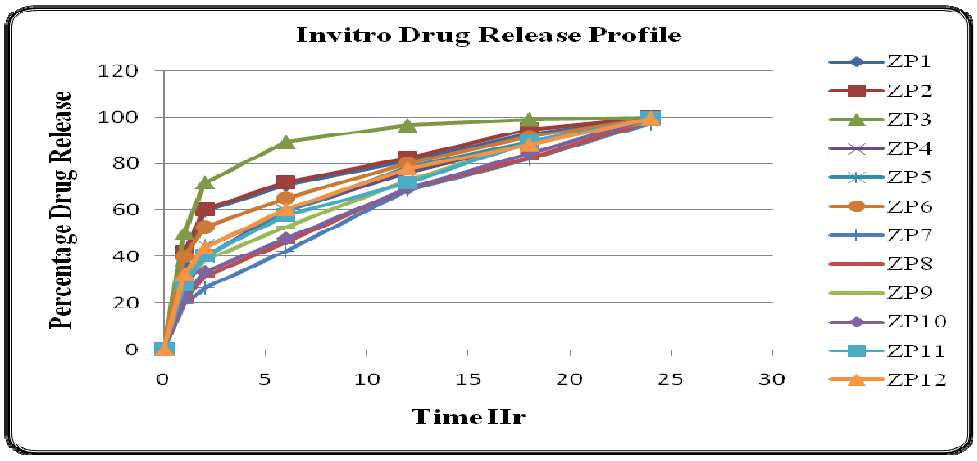

Figure 10: Invitro drug release profile of batch ZP1 to ZP12

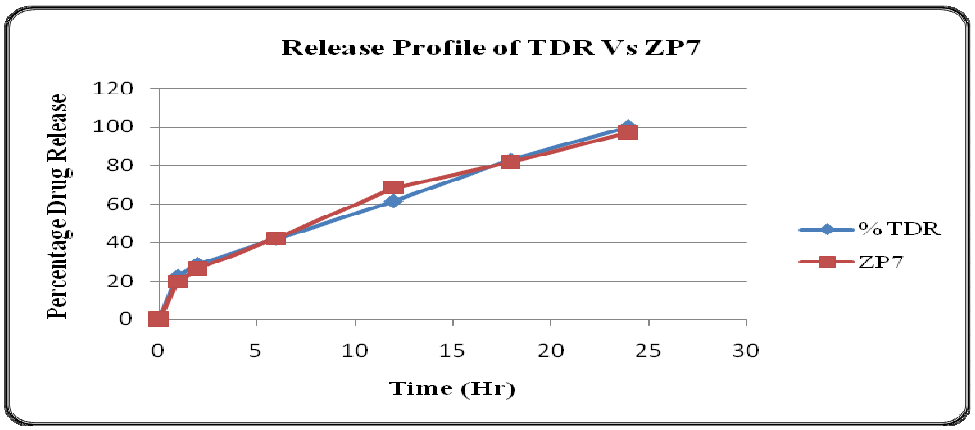

Figure 11: Comparative drug release profile of TDR Vs ZP7

CONCLUSION

In vitro drug dissolution of different formulations is carried out for 24 hours, Formulation ZP7 show 97.4% drug release. Drug release kinetics follow the Higuchi model, which shows continuous and uniform drug release for extended period of time, an attribute highly desirable for any sustained release formulation. *F*1 and *F*2 value of all formulations are calculated, from these value optimize batch was selected. Determining *in-vitro* drug release from the various formulations being developed as well as the optimized formulation ZP7 in order to its maximum similarity factor and greater R^2 value. Stability studies on the optimized sustained release tablet formulation (ZP7)

at three different stability storage conditions 40 ± 2 °C and 75 ± 5 % RH for 1 month. Good storage stability as assessed by short term stability studies as per ICH guidelines.

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