International Journal of Pharmacy and Biological Sciences-IJPBS™ (2021) 11 (2): 86-102
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Formulation Development and Evaluation of Sustained Release Matrix Tablet of Zaltoprofen

[1]Vaishali N. Tidke*, [2]Amanpreet Kaur,[3]Shrikant M. Madhekar
[4]Swati S. Rawat and [5]Renuka G. Pawar
[1, 3, 5]Lecturer Dr. Y S Khedkar College of Pharmacy Aurangabad
[2]Assistant professor in Oyster institute of Pharmacy, Aurangabad.
[4]Professor Vedprakash Patil College Aurangabad.

Received: 12 Jan 2021 / Accepted: 6 March 2021 / Published online: 01 April 2021
*Corresponding Author Email: vaishalitidke8@gmail.com

Abstract

Objective: The current work was focused to Formulate develop and evaluation of sustained release matrix tablet of Zaltoprofen. **Methods:** HPMC K100M and PVP K30 can be used in formulation of sustained release dosage form of slightly water-soluble drug. Zaltoprofen was considered as ideal drug for sustained release formulation. The sustained release matrix of Zaltoprofen were prepared by wet granulation technique in differ matrix polymers ratio. Pre formulation studies have been performed for the Active Pharmaceutical Ingredient. **Results**: Drug excipient compatibility studies have been performed and the tablets have been prepared in seven different formulations with the change in the ratios of excipients. These tablets are evaluated for various parameters including the release of drug by using dissolution studies. **Conclusion:** Hence the study resulted in the development of sustained release matrix tablet of comparable to the innovator product for Zaltoprofen which is stable.

Keywords
Zaltoprofen, Sustain release tablet, Matrix tablet.

*****

INTRODUCTION

Zaltoprofen, a non-steroidal anti-inflammatory drug, is given to patients suffering from lumbar pain, dental pain, osteoarthritis, frozen shoulder, musculoskeletal pain, post-operative pain, cervicobrachial syndrome and other inflammatory conditions. This drug has analgesic and antiphlogistic effects. The medicine is not recommended for patients having dysemia, peptic ulcer, asthma, ulcerative Crohn's disease, hypersensitivity and renal or hepatic problems. Zaltoprofen has the dose of 80 mg three times a day which reduce patient compliance and used in the treatment of rheumatoid arthritis, osteoarthritis, and other chronic inflammatory Pain conditions. ZLT has recently been reported to cause potent inhibition of cyclooxygenase-2 with fewer side effects on the gastro-intestinal tract than other non-steroidal anti-inflammatory drugs. However, if taken after food, the medicine may cause gastrointestinal discomfort. It should be taken at the same time each day for best results. The dosage should not be increased abruptly and must be taken at regular intervals. Drugs with half-life less than 2 hrs. should not be used because an exceptionally large dose will be required to maintain the release rate. Drugs with half-life in range of 2-4 hrs. make a good candidate for design of sustained release system.

MATERIAL AND METHODS

MATERIALS

Zaltoprofen was obtained from IPCA Mumbai. HPMC K4M, HPMC K15M, HPMC K 100M and MCC PH101, MCC PH 102 was obtained from LUPIN Ltd. Aurangabad. Lactose, Magnesium stearate, Talc, Iso propyl alcohol, PVP K30, Sodium hydroxide, Potassium dihydrogen phosphate was obtained from Research Lab, Fine Chem. Mumbai.

METHODS

Tablet Preparation

Zaltoprofen Sustained Release matrix tablets were prepared by Wet granulation technique. All the ingredients were passed through sieve # 60, mixed properly; the tablets were compressed at tableting machine using 11 mm flat circular punches to get the hardness of 6-8 kg/cm2. Then tablets are evaluated for in- vitro drug release.

PRE-FORMULATION STUDIES

Bulk Density

Accurately weighed quantities of samples of drugs and excipients were placed in 10 ml measuring cylinder. The volume occupied by the powder was determined without disturbing the cylinder and bulk density was calculated using the equation-

$$BD = \frac{M}{Vo}$$

Where M = Weight of sample (g)
Vo = Bulk volume(ml))

Tapped Density

After measuring the bulk volume, the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Initial volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb was consider as final tappedre volume. The tapped density (TD) was calculated by the following formula. (Result given in table 21)

$$TD = \frac{M}{Vb}$$

Where. M = Weight of sample (g)
Vb = Tapped volume (ml)

Haussner's Ratio

Haussner's ratio is an important character to determine the flow property of powder and granules. A Hausner ratio less than 1.25 indicates good flow and greater than 1.25 is an indication of poor flow. This can be calculated by the following formula (Result given in table 21).

$$\text{Haussner's Ratio} = TD/BD$$

Where, TD= Tapped density
BD = Bulk density

Carr's Index

The Carr's index is an expression that shows the compressibility of the powder. It was calculated by using the formula (Result given in table 21)

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{X } 100$$

Angle Of Repose

Improper flow of powder is due to frictional forces between the particles. The frictional force in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The lower the angle of repose, better the flow property.

EVALUATION OF TABLETS

Appearance

The thickness of tablet as a dimensional variable was evaluated. The tablet thickness was controlled within ±5% of average value. The color, odour and any other flaws like chips, cracks, surface texture, etc. are other important morphological characteristics were observed.

Hardness

Tablet hardness is defined as force required to crush the tablet in diametric compression test. The hardness was measured with Monsanto hardness tester. The tablets were placed diametrically between two plungers and the lower plunger was kept in contact of tablet to read as zero. The upper plunger was forced against a spring by turning the screw until tablet fractures. (Hardness was 8 ± 0.20 (Kg/cm2)

Thickness

The thickness of individual tablets was measured in triplicate using vernier caliper, which permits accurate measurement and provides information of the thickness variation between tablets. Thickness was 3.63±0.03 mm.

Friability

Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 minutes dropping the tablets through a distance of 6 inches with each revolution. The tablets were dusted and reweighed. This process was repeated for all formulations and the percentage friability was calculated by following formula. Friability was 0.13 %.

$$F = \frac{W1 - W2}{W1} \times 100$$

Where, F is friability,
WO is the weight of tablets before test
W is weight of tablets after test.

4.5 Weight Variation Test

The procedure mentioned in Indian Pharmacopoeia. Twenty tablets were selected randomly and

weighed. Average weight of the tablet was used determined. The tablets were weighed individually, and the weight variation was determined. The tablets meet the test if not more than 2 tablets are outside the limit and if no tablet differs by more than 2 times the limit. The weight variation was 398.4±1.91 .

Drug Content

Randomly selected 3 tablets from each batch were crushed in a mortar and pestle. The crushed powder equivalent to 400 mg of Zaltoprofen was taken in a 100 ml volumetric flask and dissolved in phosphate buffer pH 6.8. The volume was made up to the mark and filtered through Whattman filter paper No. 42. Make necessary dilution of solution. The concentration of Zaltoprofen was determined by measuring the absorbance at 340 nm.

***In -Vitro* Dissolution Studies**

The drug release rate from Zaltoprofen was determined using USP apparatus type II The dissolution test was performed using 900 ml of phosphate buffer pH 6.8, for 24 hrs at 37 ± 0.5°C and 100 rpm. A sample (5 ml) was withdrawn at a specific interval and replaced with fresh dissolution medium of same quantity. The samples were filtered through a Whattman filter paper. Absorbance of the solutions was measured at 340 nm.

Analysis of Samples.

Statistical Analysis by Design Expert Software

A 32 full factorial was selected for study of effect of independent variable on drug release. Two factors were evaluated at three level, HPMC K 100 M and PVP K 30 were selected as independent variables and % drug release was dependent variable

The data obtained from the factorial batches was treated by design expert software 8.0.7.1 and analysed statistically using analysis of variance. The data were also subjected to 3-D response surface methodology to study the interaction of HPMC K100M (X1) and PVP K30 (X2) on dependent variables. (Result given in table 26)

Stability Studies

The stability study of the selected optimized formulations was carried out according to ICH guidelines at accelerated (40 ±2°C/ 75 ± 5% RH) and room temperature condition for three month by storing the samples in stability chamber.

RESULTS AND DISCUSSION

Preformulation Studies

Drug Identification

Table 1: Characterization of Zaltoprofen

Sr.No.	Test	Specification	Result
1	Colour	White	Confirmed
2	Odour	Odourless	Confirmed
3	Physical state	Powder	Confirmed
4	Identification	FTIR	Positive
5	Melting point	135- 139ºc	138°c
6	Solubility	Soluble in methanol	Confirmed
	a. In water	Insoluble	0.038 mg/ml
	b. In phosphate buffer (pH 6.8.		0.099 mg/ml

Melting Point Determination:

The average melting point of Zaltoprofen was determined by digital melting point apparatus and was found to be 138^{0}C, which is in good agreement with reported melting point.

FT-IR Spectral Studies

The FT-IR spectrum shown in Figure 4 of pure drug was found to be like the standard spectrum of Zaltoprofen. The spectrum of Zaltoprofen shows the following functional groups at their frequencies and is presented in Table 13 and FT-IR spectrum of optimized Formulation is given in Figure.

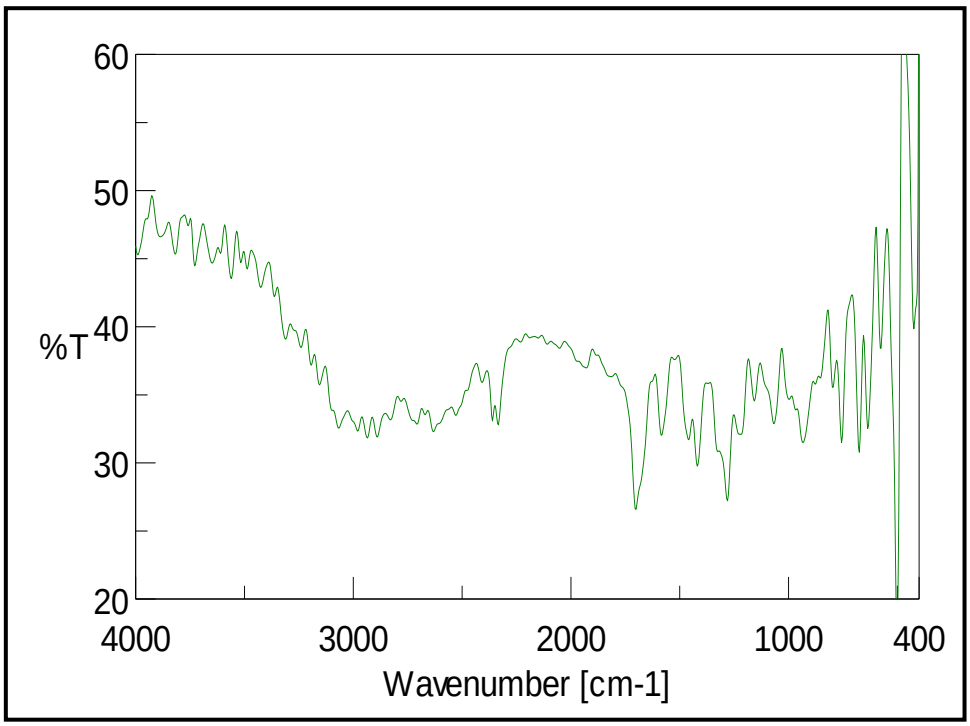

Figure 4: FIG 1: FTIR spectra of Zaltoprofen

Table 2: FTIR spectral obtained values of Zaltoprofen

Sr. no.	wave no cm^{-1}	Assignment
1	2981.41	Aromatic C-H stretching
2	2360.44	Arile C-H stretching
3	1700.91	C=O stretching
4	1280.5	C-O group Stretching.
5	1419.35	C-S-C stretching

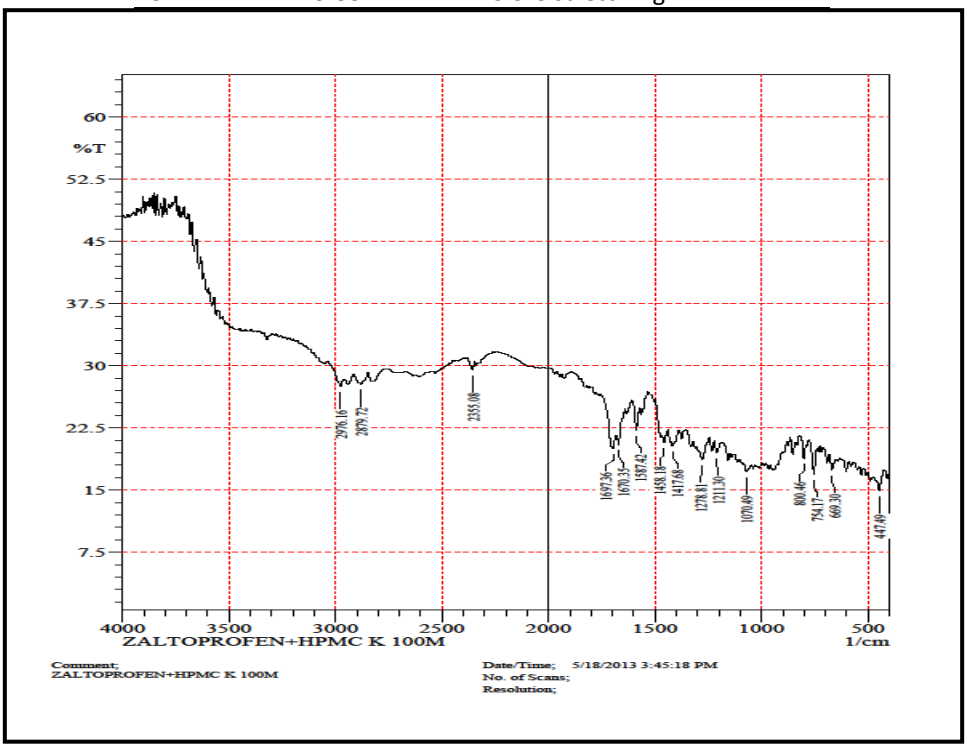

Figure 2: FTIR spectra of optimized formulation of Zaltoprofen

Table 3: FTIR obtained spectral values of optimized formulation.

Sr. no	wave no cm^{-1}	Assignment
1	2976.16	Aromatic C-H stretching
2	2355.08	Arile C-H stretching
2	1697.36	C=O stretching
3	1278.81	C-O group stretching.
4	1417.68	C-S-C stretching

The FT-IR spectrum of pure drug and FT-IR spectra of the optimized formulations showed that there is a negligible difference in the position of characteristics of absorption bands of the functional groups of the drug and the drug has remained in its normal form even when the formulations were prepared from it without undergoing any chemical interaction with the different polymers and other excipients used during the study. Thus, it is clear from FT-IR study that there is no interaction of the drug with the polymer and other excipients.

Differential Scanning Calorimetry:

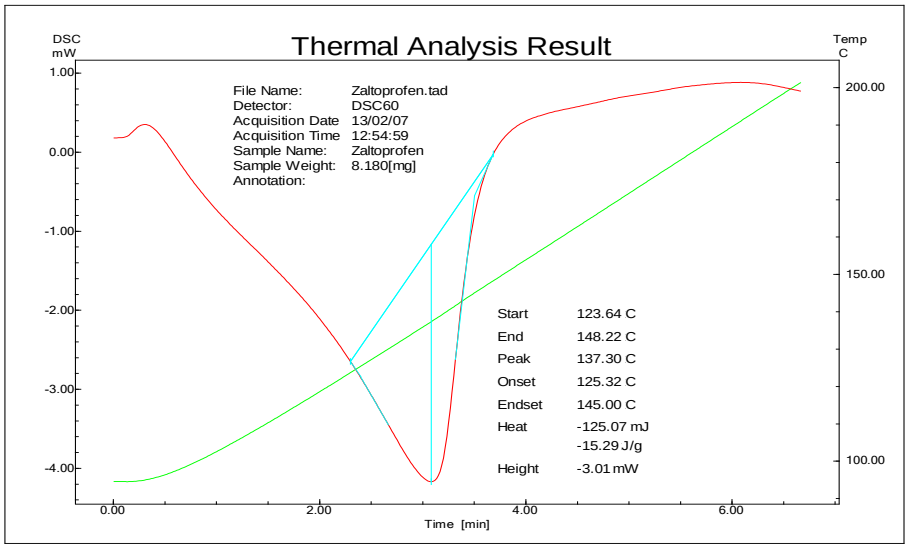

Figure 3: DSC thermogram of Zaltoprofen

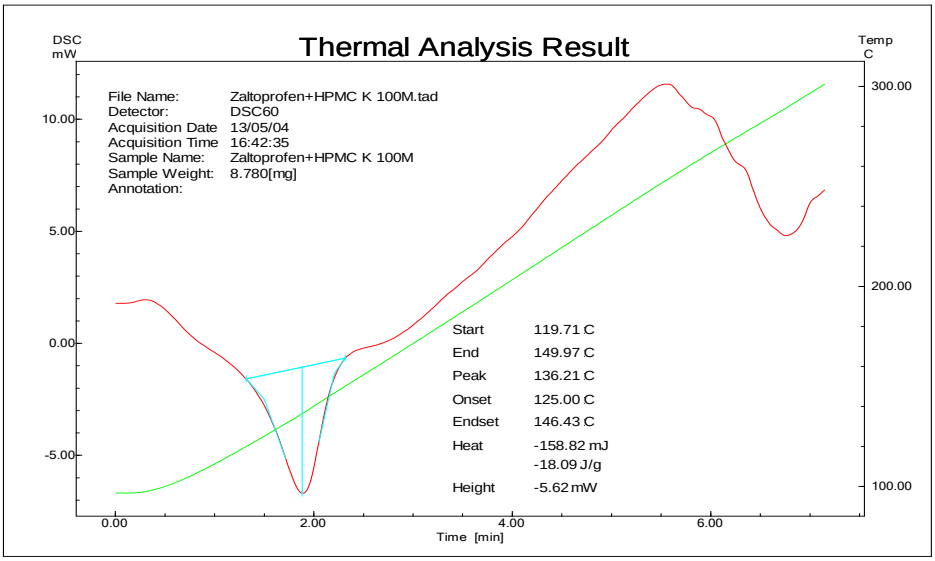

Figure 4: DSC thermogram of Zaltoprofen + HPMC K100M (1:1)

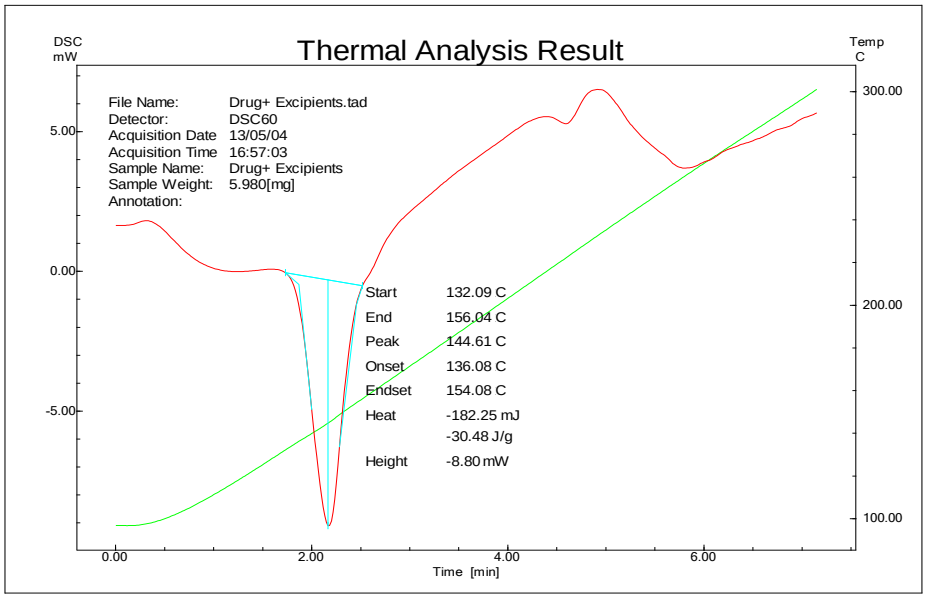

Figure 5: DSC thermogram of optimized Zaltoprofen formulation

Figure 6 is a DSC thermogram of pure Zaltoprofen and shows endothermic peak at 137.30°C and figure 7 is DSC thermogram of Zaltoprofen and HPMC K100M in 1:1 proportion and shows peak at 136.21°C, Figure 8 shows DSC analysis optimised formulation which shows endothermic peak at144ºC, this shows that there is no interaction between the drug and excipients. The DSC thermograms for pure drug sample and different formulations were taken during the present study. These thermograms help us to know any type of interaction of the drug with other substances in the process of formulation. In the present study, the melting point as obtained from endothermic peak of isotherm of the drug molecule was observed as 137.30 0C, which agrees with literature related to melting point of the drug. The comparative study of thermograms indicated that the drug even in its formulation form has not much deviated from the literature melting point appreciably indicating that the drug has not undergone any type of interaction with the other ingredients used for the formulation.

UV Spectra for Estimation of Zaltoprofen:

The UV spectrum of Zaltoprofen solution exhibited wavelength of absorbance maximum at 340 nm which complies with the reported.

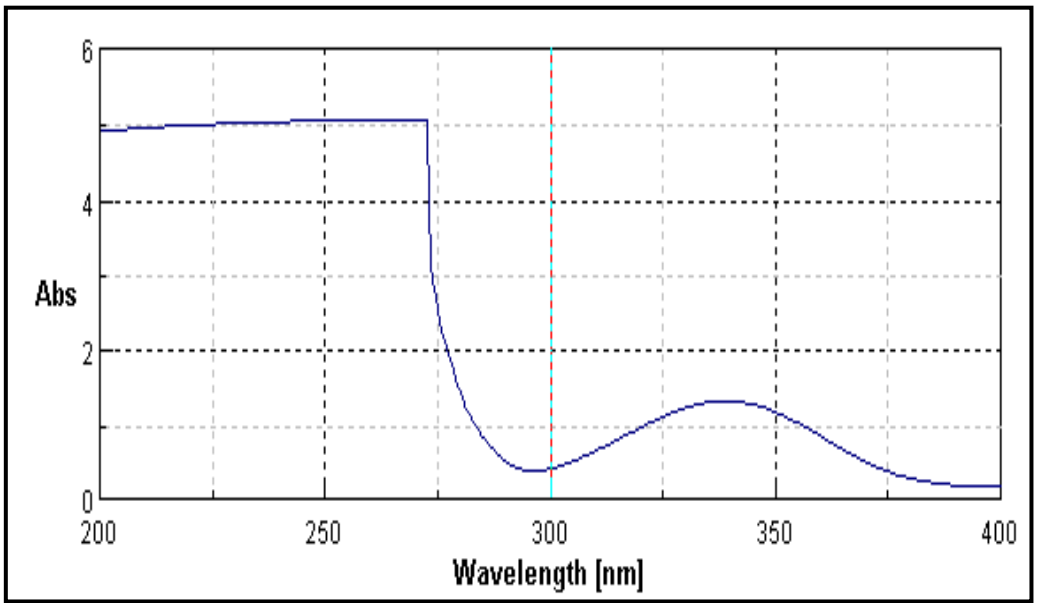

Figure 6: Spectra of Zaltoprofen in phosphate buffer of pH 6.8

Analytical Method Validation

Calibration Curve for The Estimation of Zaltoprofen:

The standard solution of Zaltoprofen was prepared by diluting stock solution in the range of 10-50 µg/ml. The standard calibration curve of Zaltoprofen was obtained by plotting the absorbance of the standard solution against its concentration measured at 340 nm. The standard solutions of Zaltoprofen showed linear curve with correlation coefficient of 0.999. The equation of line is y = 0.0099x +0.0082. The observations are shown in Figure 10 and Table 15.

Table 4: Standard calibration curve value

Concentration (µg/ ml)	Absorbance
10	0.108
20	0.205
30	0.308
40	0.405
50	0.505

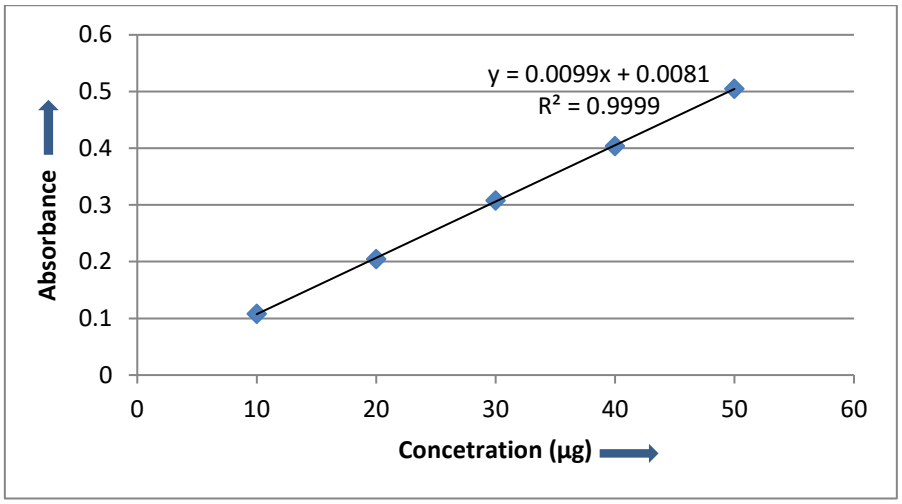

Figure 7: Standard calibration curve of Zaltoprofen

Method Validation

Developed method was validated and validation parameters are as follows.

Table 5 : Validation parameters

Parameter	Limit [43]	Results
Range	--	05 -100 µg/ml
Coeff. of correlation	$R^2 > 0.9997$	0.9999
Accuracy	98 – 102	100.17±1.01
Repeatability	%RSD < 2	0.925
Intraday precision	%RSD < 2	0.124
Inter day precision	%RSD < 2	0.114
LOD	-	0.433 (µg/ml)
LOQ	-	1.31 (µg/ml)

From the above result, it is seen that all the values of parameters evaluated are within the limits given by ICH guideline.

Formulation Study

Precompression Studies

Precompression study of drug such as bulk density, tapped density carr,s index, Hausner Ratio, angle of repose, which are given below.

Table 6 : Flow properties of Zaltoprofen and excipients

Drug/ Excipients	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)
Zaltoprofen	0.5±0.02	0.90±0.08	44.99±1.82	1.81±0.05	41.25±0.95
HPMC K4M	0.28±0.03	0.35±0.003	29.29±0.11	1.22±0.05	37.24±0.6
HPMC K15M	0.26±0.03	0.38±0.02	26.90±1.28	1.35±0.08	33.65±0.73
HPMCK100M	0.27±0.013	0.35±0.004	22.14±0.80	1.35±0.026	36.87±0.81
MCC 101	0.32±0.03	0.34±0.05	17.98±0.06	1.29±0.08	26.83±2.34

Preliminary Batches:

Using direct compression method preliminary batches were studied with various polymers like HPMC K4M, HPMC K15M in concentration range of 10%, 15%, 30% drug release was studied up to 12 hr.

Table 7: Drug release profile of preliminary trial batches of direct compression

TIME (hrs)	K 4M 10% DF1	K 4M 30% DF2	K15M 10% DF3	K 15M 15% DF4
0	4.5	3.8	2.265	3.909
1	28.55	15.2	17.08	22.713
2	48.34	21.4	25.09	27.85
3	60.78	29.4	29.67	30.66
4	71.2	30.3	36.08	56.02
5	78.73	34.2	60.0	61.39
6	87	36.81	69.42	77.5
7	92	41	72.5	66.21
9	-	76.09	76.23	78.5
10	-	88	85.69	85
12	-	-	97.05	92

From above preliminary trial batches it was observed that when HPMC K 4M was used 10% and 30% in batches DF1 and DF2 respectively, most of drug got released in 9-10 hrs. There was no retardation of drug release. When higher grade of HPMC i.e., K 15 M was used in 10% and 15% concentration for batch DF3 and DF4 respectively, still there was up to 85% drug release in 10 hrs. This may be due to less polymer linking in lower viscosity grade polymer.

It was also observed that batches DF1 to DF4 had poor powder flow, indicting use of wet granulation method required in process. Therefore, further trials were conducted using wet granulation method.

Table 8: Drug release profile of preliminary batches by wet granulation using HPMC K 15 M and HPMC K 100 M polymer.

TIME (hrs)	K 15M 10% (10% lactose) F1	K 15M 10% (05%Lactose) F2	K 15M 15 % (05%Lactose) F3	K15M15% (Without Lactose) F4
0	5.2	3.1	3.20	1.1
1	25.9	19.2	17.80	12.8
2	51.3	35.5	25.66	17.5
3	56.9	55	44.16	35.22
6	83.8	80.4	60.5	44.81
9	98.6	103	67.33	52.6
12		-	97	81.5

(All values are mean, n=2)

Above preliminary trial batches were prepared by wet granulation method. Batches F1 and F2 both had HPMC K15 M, but F1 had 10 % Lactose while F2 had 05%. F1 batch showed more drug release in first 3hrs as compared to F2. According to the guidelines there must be 15-30% drug releases in first 1 to 2 hrs[i]. If this guideline is considered, F1 batch would result in rapid drug release before completion of 24 hours[ii].

Batch F3 and F4 contains HPMC K 15 M 15%, F3 contains 05 % Lactose and F4 batch is without Lactose. In F4 batch drug release in first 1 to 2 hrs is less and F3 shows drug release according to guidelines so 05% concentration is continued for further batches. The flow of granules prepared was particularly good.

Table 9: Drug release profile of preliminary trial batches using HPMC K 15 M and K 100 M polymer by wet granulation (using 5% lactose).

TIME (hrs)	K 15 M 30% F5	K 100 M 7% (PVP - 3%) F6	K 100 M 7% F7	K 100M 10% F8	K 100 M 12.5% F9	K 100 M15% F10
0	3.43	3.2	5.9	8.4	8	8.7
1	14.8	27.4	25.8	19.05	13.21	10.56
2	18.3	37.8	33.4	30.5	22.27	11.45
3	21.8	41.6	36.3	33.34	24.05	16.92
6	32.1	45.5	41.5	35.27	29.4	20.77
9	42.7	54.16	45	41.15	32.7	25.3
12	50.83	60	52.2	48.27	35.79	33.54
24	**90.38**	**92.5**	**95.83**	76.83	62.20	48.8

(all values are mean, n=2) From the above data, batch F5 and batch F6 shows drug release above 80% but tablets of F5 shows floating after 8 to 9 hrs and batch F7, F8, F9 which contains HPMC K 100 M 10%, 12.5%, 15% respectively, shows drug release less than 80% so F6 batch was selected for factorial designs.

Evaluation Of Final 3^2 Factorial Design

The above study reveals that 7 % of HPMC K100M with 5% of PVP K-30 is sufficient to provide good drug release profile for 24 hours. Thus, 3^2 factorial designs containing formulation batches bearing polymer concentration in the range of 7 to 12 % HPMC K100M and binder concentration i.e., PVP K-30 in the range of 3-7% were formulated.

Table 10: Flow properties of final granular blend of factorial batches

Formulation Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)
ZF1	0.250	0.292	14.4	1.168	26.82
ZF2	0.274	0.306	10.5	1.116	28.39
ZF3	0.269	0.340	20.89	1.263	30.25
ZF4	0.272	0.313	13.15	1.151	32.49
ZF5	0.267	0.290	8.152	1.088	30.24
ZF6	0.276	0.312	11.47	1.129	29.50
ZF7	0.34	0.36	15.7	1.05	28.45
ZF9	0.32	0.38	15.8	1.2	28.8

The characterization of flow properties of powder blend is important in tablet compression. The blend with good flow properties gives uniform die fill and consequently it gives the uniform tablet weight.

The angle of repose can be correlated with type of flow of powder or granules. The angle of repose 20 to 30^0 indicates the good flow while the angle of repose more 30º indicates poor flow properties and angle of repose below 20^0 indicates excellent flow properties. The angle of repose was found to be within the range of 20º to 33º indicating good flow ability.

The bulk density and tapped density of granules or powder are important parameters in the compressibility of the granules or powder. The bulk density was between 0.25 to 0.43 gm/cm^2 and tapped density was found 0.29 to 0.50 gm/cm The Hauser ratio is another parameter indicating the flow properties. It was found to be 1.11 to 1.26. The value of ratio below 1.25 indicates good while above 1.25 indicates the poor flow. The Carr's index is indicator of compressibility. It was found to be 10 to 15 %. The values below 20 % shows good compressibility and above it shows poor compressibility.

Evaluation Of Zaltoprofen SR Matrix Tablets

The tablets from the factorial batches were evaluated for different evaluation parameters of tablets.

1. Appearance

The tablets from all factorial batches were white, circular, and flat faced. The surface texture was smooth. The thickness of tablets of factorial batches was 3 to 4 mm and it was found to be within limit of deviation from average value (not more than 5%).

2. Hardness and friability

The hardness and friability are two important characteristics to be evaluated for handling and transportation properties of the tablets. The friability of tablets was less than 0.5% which indicates good handling and transportation characteristics. The hardness of tablets was found to be 7 to 9 Kg/cm^2.

3. Weight variation

According to I.P., for Tablet weighing 400 mg or more, not more than two tablets differ from the average weight by 5% deviation. The percent deviation in weight variation from average value for all formulation of factorial design batches were within limit. The weight variation within limits indicates uniformity in tablet compression and consequently content of drug in a tablet.

4. Drug content

The drug content of the nine formulations was found to be between 97 to 103 % (i.e. variation of ±3%). The value ensures good uniformity of the drug content in the tablet. Thus, all the physical parameters of the compressed matrices were found to be practically within control.

5. Thickness

The thickness of tablet was found to be in between 3 to 4 mm.

Table 11: Tablet evaluation of factorial batches

Formulation	Appearance	Weight variation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug Content (%)
ZF1	White, circular,11mm flat faced	397.9±0.78	7.63± 0.15	0.16	3.59±0.02	99.76
ZF2	White, circular,11mm flat faced	399±1.01	7.63±0.07	0.12	3.68±0.01	97.77
ZF3	White, circular,11mm flat faced	397.5± 1.96	7.5± 0.15	0.12	3.62±0.017	98.76
ZF4	White, circular,11mm flat faced	397.2±1.86	8±0.20	0.20	3.59±0.020	99.28
ZF5	White, circular,11mm flat faced	398.4±1.91	8 ± 0.20	0.13	3.63±0.03	98.28
ZF6	White, circular,11mm flat faced	398.3±2.50	8.03± 0.25	0.23	3.61±0.015	100.80
ZF7	White, circular, 11mm flat faced	398.85±1.94	8.23± 0.02	0.13	3.66±0.03	98.78
ZF8	white, circular, 11mm flat faced	399.33±2.02	7.66±0.15	0.33	2.61±0.01	98.38
ZF9	white, circular 11 mm flat faced	398.45±2.29	7.86 ± 0.05	0.14	3.54± 0.025	99.77

(All values are mean ± S.D, n=3)

***In-vitro* Drug Release Study**

The drug release rate from Zaltoprofen (n=3) was determined using USP apparatus type II. The dissolution test was performed using 900 ml of phosphate buffer pH 6.8, for 24 hrs at 37 ± 0.5°C and 100 rpm. A sample (5 ml) was withdrawn at a specific interval and replaced with fresh dissolution medium of same quantity. The samples were filtered through a Whattman filter paper. Absorbance of the solutions was measured at 340 nm. The drug release and drug release kinetics were calculated by PCP disso ver. 3.0. The cumulative percentage drug release of factorial batches is reported in the Tables 23, 24 and 25.

Table 12 : Cumulative percent drug release of formulation ZF1 to ZF3

Time	Cumulative percent drug release		
(Hrs)	ZF1	ZF2	ZF3
0	2.94±0.45	3.74±0.160	3.25±0.32
1	10.94±0.11	13.10±0.75	11.48±0.34
2	14.98±0.90	18.28±1.00	15.88±1.17
3	19.11±0.04	19.95±0.75	20.98±1.85
6	24.55±1.15	29.30±1.85	29.88±0.05
9	29.23±0.068	32.64±2.07	30.92±1.27
12	33.56±1.48	35.16±0.59	35.64±0.98
24	68.67±0.94	62.12±1.91	69.67±1.92

(All values are mean ± SD, n=3)

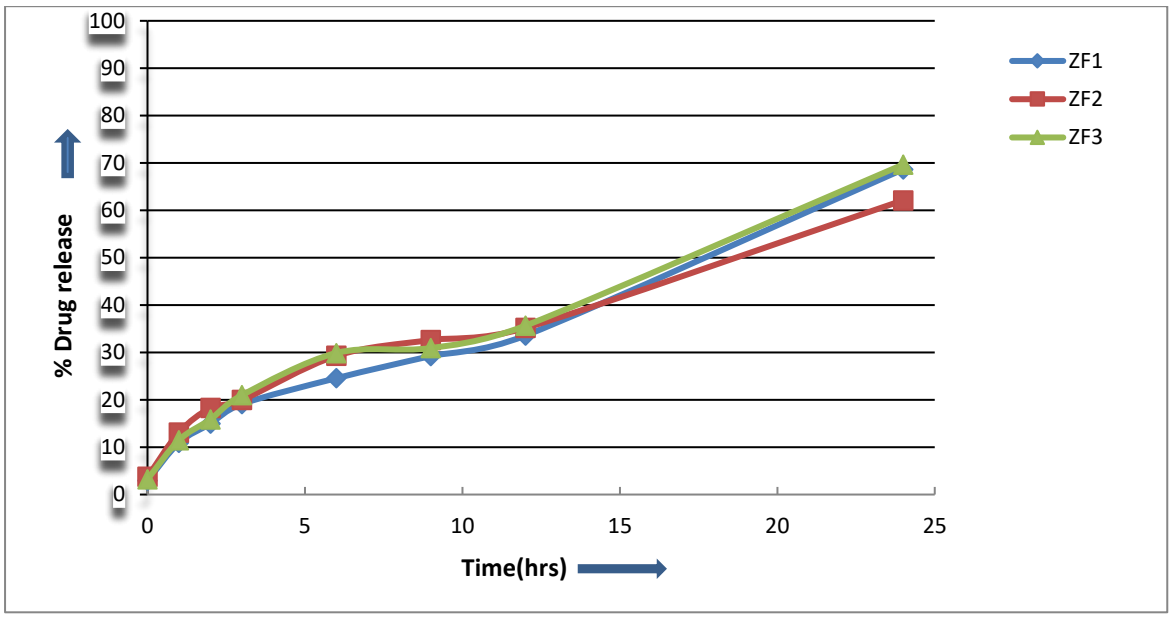

Figure 8: Cumulative percent drug release of formulation ZF1 to ZF3

Table 13: Cumulative percent drug release of ZF4 to ZF6

Time(hrs)	Cumulative percent drug release		
	ZF4	ZF5	ZF6
0	3.71±0.50	4.52±0.73	2.92±0.56
1	15.69±1.41	15.03±0.77	13.12±2.10
2	20.98±1.95	19.73±1.61	20.29±1.65
3	24.72±0.75	25.95±0.55	25.38±0.74
6	33.44±2.03	34.014±1.21	32.98±0.74
9	38.85±1.15	38.47±1.76	37.89±2.05
12	48.78±0.56	52.07±2.54	52.54±1.90
24	85.038±1.63	81.27±1.94	78.33±0.98

(All values are mean ± SD, n=3)

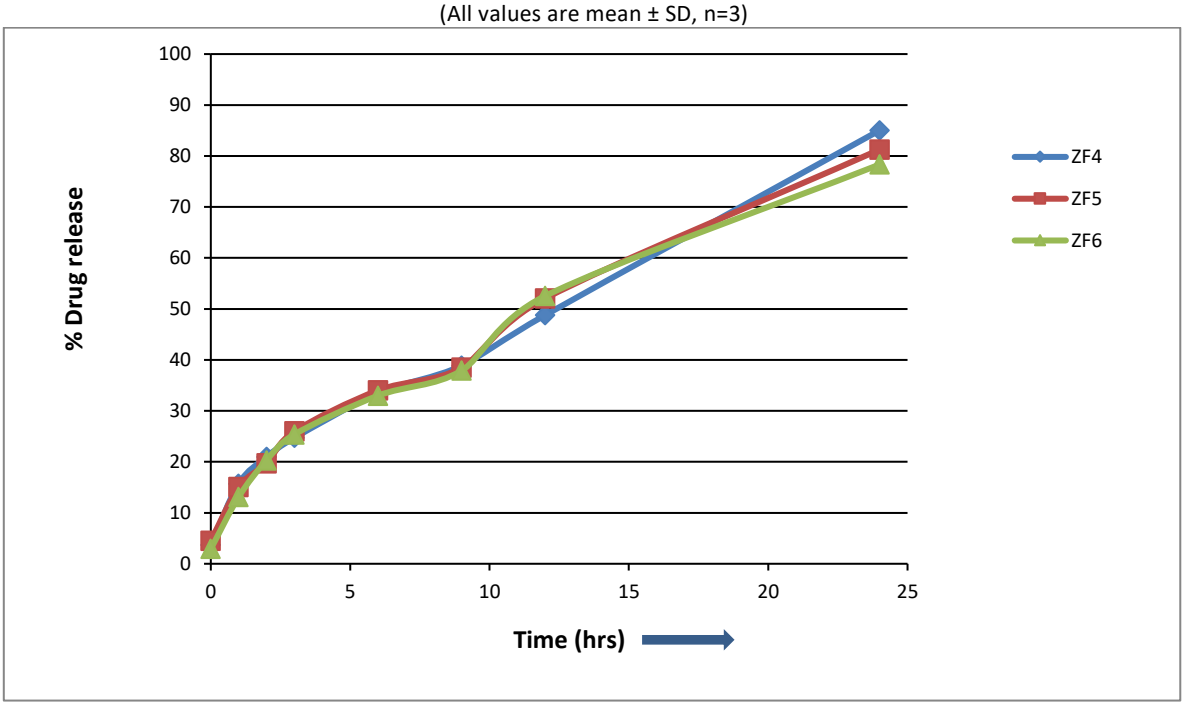

Figure 9: Cumulative percent drug release of formulation ZF4 toZF6

Table 14: Cumulative percent drug release of formulation ZF7 to ZF9

Time(hrs)	Cumulative percent drug release		
	ZF7	ZF8	ZF9
0	3.90±0.30	4.032±0.21	4.39±0.47
1	18.01±0.95	16.69±2.70	18.53±0.64
2	21.65±0.89	21.71±1.49	23.057±0.49
3	28.97±2.74	26.79±1.75	31.46±3.36
6	34.89±0.96	35.88±1.45	40.33±0.48
9	46.85±3.80	43.05±3.07	47.39±1.52
12	58.85±0.21	58.82±5.33	53.24±1.52
24	94.78±0.77	92.22±1.35	97.00±1.57

(All values are mean ± SD, n=3)

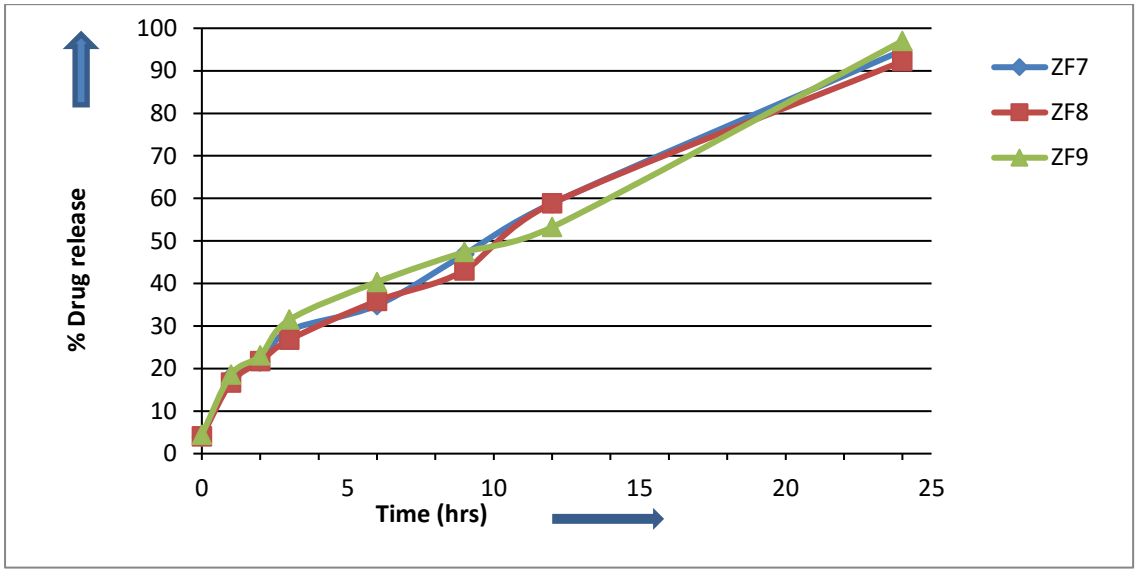

Figure 10: Cumulative percent drug release of formulation ZF7 toZF9

In preliminary studies, HPMC K4M, HPMC K15M and HPMC K100M were evaluated as retarding agent for SR preparation. HPMC K4M, HPMC K15M, HPMC K100M were evaluated at concentration Range 10 to 30%, It was found that, HPMC K4 M and K 15 M could not to retard release up to 24 hrs, but HPMC K 100 M could retard release up to 24 hr. Therefore, for factorial batches, HPMC K100 M was selected.

The factorial batches were designed using HPMC K100M and PVP K30 as independent variables and drug release as dependent variables The independent variables were studied at three levels. Formulations ZF1, ZF2 and ZF3 containing 13% of HPMC K100M with more amount of polymer shows more crosslinking which resulted in wetting of tablet in dissolution medium less radially and 68%, 62.12% and 69.67% drug releases respectively in 24 hrs. In case of formulations ZF4, ZF5 and ZF6 containing 10% of HPMC K100M as it is in less compared to above batches less wetting time to tablet and the less the cross linking due to less amount of polymer than above batch so the drug release found that 85.03, 81.27 and 78.33 % in 24 hrs which was more as compared to above batches. In case of ZF7, ZF8 and ZF9 containing 7 % of HPMC K100M the drug release from above batches founded to 94.78, 92.22 and 97.00 % respectively at the end of 24 hrs.

Binder has significant effect on drug release in IR tablet. While planning for optimized batches, it was thought that PVP K 30 would have impact on drug release but after dissolution study of optimized batches, it was seen that PVP K 30 does not contribute significantly to drug release. It is quite possible that polymer plays major role in controlling drug release.

Kinetic Analysis of Drug Release

To analyse the mechanism of drug release from the tablet the *in vitro* dissolution data was fitted to zero order, first order, Higuchi release model, Hixson and Crowell dissolution method and Korsmeyer and Peppas model by using PCP Disso Version 3 software, and the model with the higher correlation coefficient was considered to be the best model. The observations are summarized in following table.

Table 15: Drug release kinetics of factorial batches

Formulations	R value					Best fit model	Parameter of equation	
	Zero Order	First order	Matrix	Korsmyer and peppas	Hixon Crowell		k	N
ZF1	0.9381	0.9769	0.9621	**0.9800**	0.9718	Korsmeyer and peppas	0.5340	10.3
ZF2	0.9556	0.9549	**0.9810**	0.9783	0.9329	Matrix	0.5043	12.65
ZF3	0.9209	0.9740	0.9707	**0.9818**	0.9677	Korsmeyer and peppas	0.5261	11.12
ZF4	0.9341	0.9733	0.9757	**0.9844**	0.9824	Korsmeyer and peppas	51.99	13.97
ZF5	0.9073	0.9865	0.9865	**0.9888**	0.9799	Korsmeyer and peppas	0.5180	14.10
ZF6	0.9018	0.9884	0.98881	**0.9902**	0.9767	Korsmeyer and peppas	0.5392	13.2
ZF7	0.9052	0.9762	0.9841	**0.9847**	0.9749	Korsmeyer and peppas	0.5355	14.2
ZF8	0.9180	0.9762	0.9803	0.9802	**0.9862**	Hixon Crowell	0.5422	15.08
ZF9	0.9632	0.9393	**0.9758**	0.9733	0.9488	Matrix	0.5690	17.4

The result of drug release kinetic data showed that the batches ZF1, ZF3,ZF4, ZF5, and ZF7 follows Korsmeyer Peppas model while ZF2 and ZF9 follows Matrix release model and ZF8 batch shows Hixon Crowell release model. The drug release rate is rapid initially followed by progressively slow drug release through the matrix by the drug in the outside layer exposed to dissolution medium is dissolved first and then diffuse out of matrix.

The value of 'n' between 0.5 and 1 indicates the slow release of the drug from the matrix may be due to the formation of viscous gel of HPMC. The n values were found to be between 0.5 to 1 indicating that the mechanism is diffusion controlled or the anomalous drug release transport indicating nonfickian diffusion in all factorial batches. The factorial batch ZF9 was selected as an optimum batch with the drug release 97.0 % within 24 hours.

Analysis Of Data By Design Expert Software

The 3^2 factorial design was selected to study the effect of independent variables HPMC K 100M (X_1) and PVP K 30 (X_2) on dependent variable Y1, Y2 and Y3. A statistical model incorporating interactive and polynomial term was utilized to evaluate the responses.

Table 16: Summary of statistical design

Factor	Name	Units	Type	Actual value		Coded value	
				Lowest	Highest	Lowest	Highest
X1	HPMC K 100	%	Numerical	7	13	-1	+1
X2	PVP K 30	%	Numerical	3	7	-1	+1

Table 17: Summary of responses

Responses	Name	Units	Obs.	Analysis	Min	Max	Mean	Model
Y1	DR at 1hr	%	9	Polynomial	10.9	18.5	14.7	Linear
Y2	DR at 12 hr	%	9	Polynomial	33.56	58.85	46.20	Linear
Y3	DR at 24 hr	%	9	Polynomial	62.12	96.38	79.25	Linear

Table 18: Analysis of variance for Y1

Source	Sum of Squares	Degree of Freedom	Mean square	F values	P- value prob >F	Model significant/Nonsignificant
Model	58.83	2	26.41	21.19	0.0019	Significant
X1- HPMC K 100 M	52.33	1	52.33	41.99	0.0006	
X1X2	0.49	1	0.49	0.40	0.5526	
Residual	7.48	6	1.25			
Cor Total	60.30	8				

Table 19: Analysis of variance for Y2

Source	Sum of Squares	Degree of Freedom	Mean square	F values	P- value prob >F	Model significant/Nonsignificant
Model	728.65	2	364.33	24.39	0.0013	Significant
X1- HPMC K 100 M	724.02	1	724.02	48.47	0.0004	
X1X2	4.63	1	4.63	0.31	0.5979	
Residual	89.63	6	14.94			
Cor Total	818.28	8				

Table 20: Analysis of variance for Y3

Source	Sum of Squares	Degree of Freedom	Mean square	F values	P - value prob >F	Model significant Nonsignificant
Model	1158.771	2	579.39	64.60	< 0.0001	Significant
X1- HPMC K 100 M	1145.95	1	1145.95	127.77	<0.0001	
X1X2	12.82	16	12.82	1.43	0.2270	
Residual	58381	8	8.97			
Cor Total	1212.58					

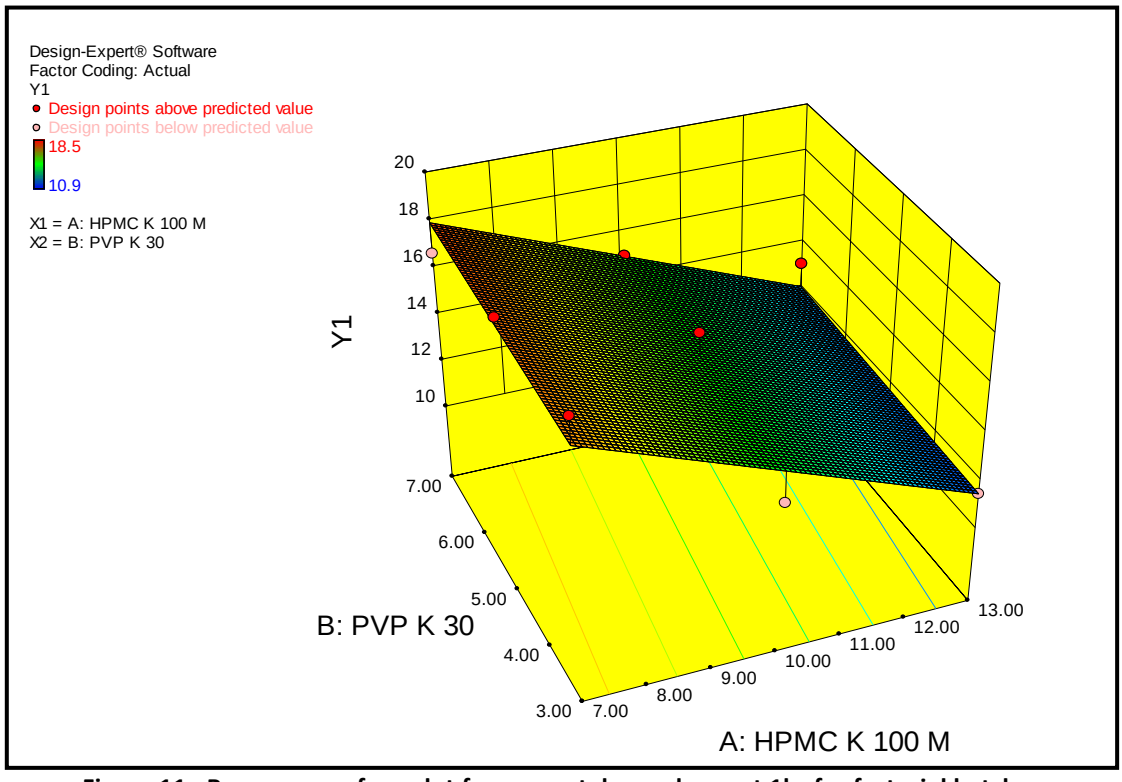

Figure 11 : Response surface plot for percent drug release at 1hr for factorial batches

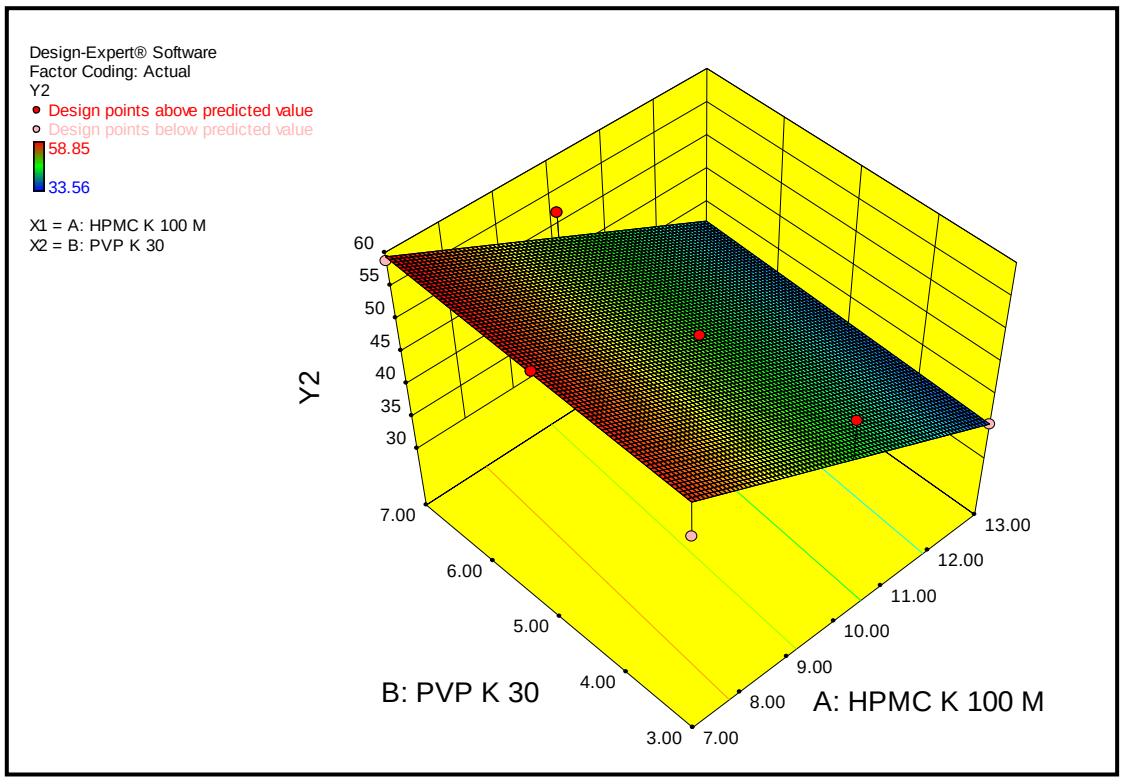

Figure 12: Response surface plot for percent drug release at 12 hr for factorial batches

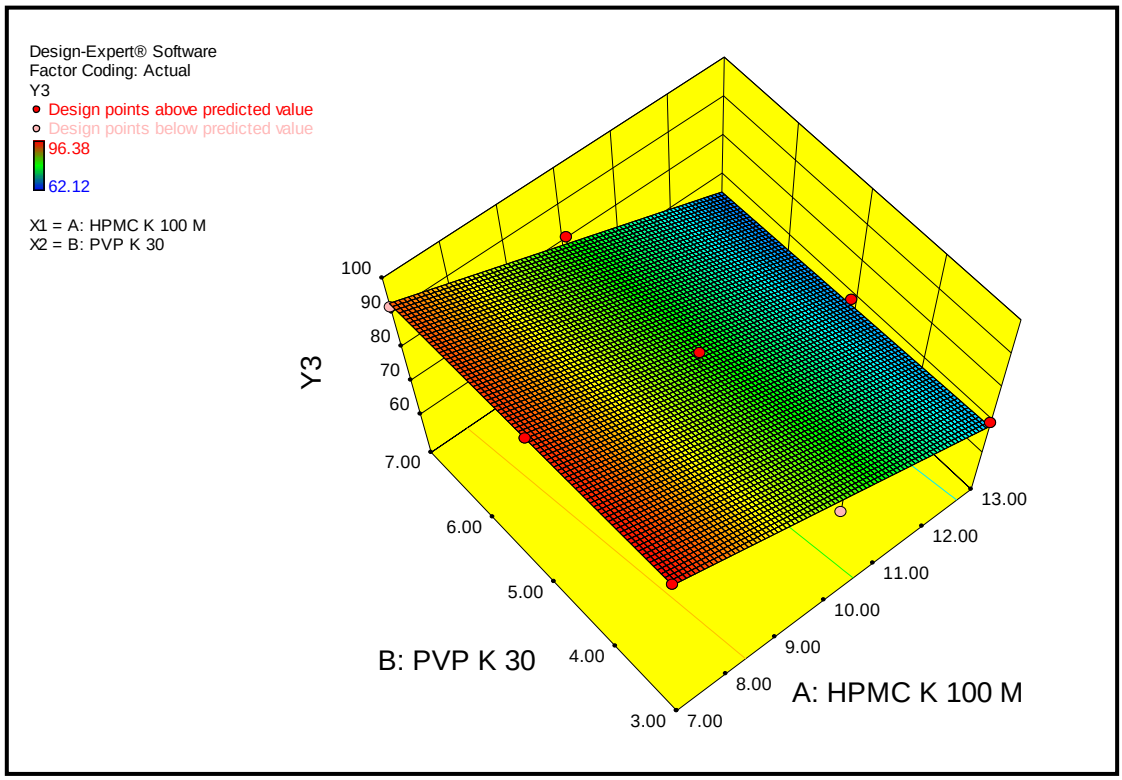

Figure 13: Response surface plot for percent drug release at 24hr for factorial batches

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$Y=b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11}X_1^2+b_{22}X_2^2$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i(b_1, b_2, b_{12}, b_{11} and b_{22})is the estimated coefficient for the corresponding factor X_i (X_1, X_2, X_{12}, X_{11} and X_{22}), which

represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

The equation conveyed to study of effect of variable. the regression coefficient values are estimate of model fitting. The polynomial equation can also be used to draw conclusion considering the magnitude of coefficient and the mathematical sign it carries, that is positive or negative.

Final equation in terms of coded factor

Y1= + 14.72-2.95*HPMC K 100 M+0.29*PVP K30

R^2 =0.8347

Final equation in terms of actual factors:

Y1 =+23.85222-0.98444 * HPMC K 100 M+0.1433*PVP K 30

Final equation in terms of coded factors:

Y2 =+47.56 -10.9* HPMC K 100 M + 0.88* PVP K 30

R^2=0.8540

Final equation in terms of actual factors:

Y2 =+81.97639 -3.6616* HPMC K 100 M +0.43917 * PVP K30

Final equation in terms of coded factors:

Y3=+80.94-13.82*HPMC K 100 M -1.46* PVP K 30

R^2= 0.9408

Final equation in terms of actual factors:

Y3 =+130.66194 -4.60667* HPMC K 100 M -0.73083* PVP K 30

Response Surface Plot

The linear model obtained from the regression analysis used to build a 3-D graph in which the responses are represented by curvature surface as a function of independent variable can be directly visualized from response and independent variable can be directly visualized from response surface plot.

The response surface plot was generated using design expert 8.0.7.1 software presented in figure 16,17 and figure 18. The effect of independent variable X1 and X2 on the responses Y1 Y2 and Y3 was studied .

Graphical presentation of data helps to show the relationship between the response and the in depended on variable. The information given by graph complies with mathematical equation obtained from statistical analysis.

The response plot showed that various combination of independent variable X1 and X2 and may satisfy and specific requirement while taking into consideration various factor involved in dosage form.

ANOVA Study

Analysis of variance of dissolution study data of all formulation was carried out Table 28, 29 and 30shows ANOVA for the dependent variable Y1 AND Y2 respectively. Coefficient X1 and X2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both variables on the selected responses. ANOVA and multiple regression analysis were done using Design Expert 8.0.7.1 software

Stability Studies

The stability studies were carried out for the selected optimized formulation at 40°C, ±2°C/75% ± 5% RH and room temperature for three months. Table 31 shows the values of post-compressional parameters and Table 34 shows dissolution profile after stability studies at above temperature and humidity conditions. Tablets did not show any physical changes (hardness and friability) during the study period and the drug content was found 93.72 % at 40 ± 2°C/ 75±5% RH at the end of three months. At room temperature drug content was found to be 95.79%. This indicates that tablets are stable at room temperature.

Table 21: Formula of optimized batch for stability study

Ingredients	Quantity (mg) /tablet
Zaltoprofen	240
HPMC K100M	28
PVP K30	3% solution in IPA
MCC PH101	104
Lactose	20
Magnesium Stearate	4
Talc	4
Total Weight	400

Table 22: Physico-chemical evaluation of selected matrix tablet before and after stability study

ICH conditions	Appearance		Drug content (%)		% Drug Release	
	Before	After three months	Before	After three months	Before	After three months
40 ±2°C/ 75 ± 5% RH	White flat faced.	No Change	99.77	93.72	96.38	90.61
Room Temp.	circular	No Change		95.75		92.70

CONCLUSION

Suitable analytical method based on UV-Visible spectrophotometer was developed for Zaltoprofen in phosphate buffer at λ_{max} 340 nm. The polymer selected for the sustaining the release i.e., HPMC K100M is compatible with the Zaltoprofen Sustained release matrix tablets of Zaltoprofen were successfully prepared using HPMC K100M and PVP K30 in IPA and other excipients. The tablets were successfully evaluated for pharmacopoeial and non-pharmacopoeial tests. The study revealed optimized formulation ZF9 followed linear kinetic models. Thus, an attempt to design an effective and rugged formulation technology was feasible with minimizing side effects and improved patient compliance.

CONFLICT OF INTEREST: Authors declared no conflict of interest.

REFERENCE:

[1] Aulton, M. E. Eds. *Pharmaceutics: The Science of Dosage Form Design*, Churchill Livingstone: Edinburgh, 2005, pp 25

[2] United States Pharmacopoeia 2008, The official compendia of standards the United States pharmacopeial convention, Twinbrook Prkway, Rockville, *vol1*, Asian edition, pp 813-814

[3] Aulton, M. E. Eds. *Pharmaceutics: The Science of Dosage Form Design*, Churchill Livingstone: Edinburgh, 2005, pp 358-359

[4] Code Q2A, Text on Validation of Analytical Procedures. Consensus Guideline, ICH Harmonised Tripartite Guidelines, 1994, pp 1-5.

[5] Code Q2B, Validation of Analytical Procedures: Methodology. ICH Harmonised Tripartite Guidelines. Geneva, Switzerland: 1996, pp 1-8.

[6] Azharuddin M.; Kmath K.; Pillai S.S.; Formulation and evaluation of controlled release matrix tablet of antihypertensive drug using natural and synthetic hydrophilic polymer*, research in biotechnology*,2011, *2(4),* 26-32.

[7] Veuba M.L.; Veiga F.; Sousa J.J; Pina M.E.; Influence of cellulose ether polymer on ketoprofen release from hydrophilic matrix tablet, *European Journal of pharmaceutics and Biopharmaceutics,*2004, *58*, 51-59.

[8] Sharma A.; Shukla T.; Indoria M.D.; Design development and evaluation of Acelofenac sustain release matrix tablets, *International Journal of Drug Development and Research,*2011, *3(1),* 307-312.

[9] Kannan S.; Manivannam R.; Formulation and evaluation of sustain release tablet of Acelofenac using hydrophilic Matrix system, *International Journal of Pharma Tech Research,* 2010,*2(3*), 1775-1780.

[10] Aulton, M. E. Eds. *Pharmaceutics: The Science of Dosage Form Design*, Churchill Livingstone: Edinburgh, 2005, pp 355-356

[11] Lachmann, L.; Lieberman, H. A.; Kanig, J. L; Theory and Practice of Industrial Pharmacy" Varghese Publishing House: Bombay, 1991, pp 183-184.

[12] Bolourtchian, N.; Hadidi, N.; Foroutan, S. M. Shafaghi, B. Formulation and Optimization of Captopril Sublingual Tablet Using D-Optimal Design, *Iranian J. Pharma. Research*, 2008, *7 (4),* pp 259-267.

[13] Lewis, G.A.; Mathieu, D.; Phan-Tan-Luu, R. *Pharmaceutical Experimental Design*, Marcel Dekker: New York, 1999, pp 33-38.

[14] Indian Pharmacopoeia, Ministry of Health and Science Welfare, Government of India, New Delhi, *Volume II*, 1996, pp 1647-1648.

[15] Code Q1A (R_2), Stability testing of new drug substances and product, ICH Harmonised Tripartite Guidelines, Feb 6, 2003.