

Development and optimization of intermediate release ketoprofen tablets by central composite design

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Abstract: In this study cost effective direct compression technique was used for the development and optimization of intermediate release (IntR) ketoprofen tablets using central composite design (CCRD). Fifteen different formulations (F1-F15) were developed using (X_1) microcrystalline cellulose (Avicel PH-102) (18-51%), (X_2) methocel K4M (0.1-25%) and (X_3) starch (1.5-18%) as selected variables while responses were % friability and Carr's Index (compressibility index). Powder blends of all formulations were evaluated using Angle of Repose, Carr's Index and porosity. Results of powder blends comply with USP standards and are classified as Fair Excellent. From F1-F15 only four formulations i.e. F6, F7, F14 and F15 were selected on acceptable weight basis, micromeritic properties and on the concentration of excipients. For the assessment of physico chemical properties of the optimized formulations different tests were performed. All results were found to be adequate range. *In vitro* assessment of the optimized formulations were also carried out in different dissolution media i.e. pH 1.2, phosphate buffer 4.5, pH 6.8 and pH 7.5. Release behaviour of F6, F7, F14 and F15 were estimated by using one - way ANOVA, model - independent, model dependent methods. Results of f_1 and f_2 showed that all the test formulations i.e. F6, F7, F14 were found to be similar with the reference formulation i.e. F15 at various dissolution media. Also all the formulations followed Hixson-Crowell kinetic model. The parameter n showed Anomalous transport (non - fickian diffusion). The mean dissolution time (MDT) was found to be in the range of 2.632-2.922. Results of ANOVA indicated no significant difference within and between formulations at different dissolution media as p values were found to be >0.05 . Also all the selected formulations were found to be stable at accelerated conditions.

Keywords: Direct compression, intermediate release, central composite design, micromeritic properties, anomalous transport, mean dissolution time.

INTRODUCTION

Micromeritic studies are usually carried out at an early stage of formulation development which helps to identify appropriate combinations of drug, excipients, and manufacturing processes which are required to design a stable dosage form. A good understanding of the association between the formulation ingredients, processing variables, and product performance is essential for product development. Determination of system's behaviour by the help of physico-chemical characteristics is very much difficult, generally when the product development process is carried out in a multidimensional space particularly in tablets and injectables or matrix devices (Hussain *et al.*, 1991). Scientists reported that the presence of drug and excipients in various ratios in formulations showed variations in relative density, powder porosity and finally in tablet disintegration (Hanif *et al.*, 2014).

Modified oral solid dosage forms are designed and developed to release the drug under specified dissolution medium (Rudnic and Schwartz, 2006). Those compounds

which exhibit different crystalline forms produce different physico-chemical features in the final product which may also affect the release behaviour of the dosage forms (Hanif *et al.*, 2014).

Tablets which are compressed by direct compression technique consisted of drug and adjuncts which did not need any primary treatment also this manufacturing method is very more economical as compared to other procedures (Lund, 1994).

For product formulation different experimental design studies are extensively used in industries. Scientists reported that the use of statistical models during the design of matrix formulations (Furlanetto *et al.*, 2006). Problems which are associated with the excessive concentrations of components rather than the use of central one was neutralized by using the rotatable central composite design (CCRD) technique. CCRD demonstrates the response of independent with dependent variables at various levels and also predicts the values (Hanif *et al.*, 2011). This technique helps to identify maximum responses particularly around center points due to its rotatable features (Zhang *et al.*, 2010).

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In the present study Ketoprofen was selected as model compound because it reduces joint swelling and is helpful in the managing the incidences of arthritis and rheumatoid arthritis (Dollery, 1991). It particularly binds with plasma albumin, in a stereoselective manner (Jamali and Brocks, 1990). Its half life is about 2 hrs (Delbarre *et al.*, 1976).

The aim of the present study is to develop and optimize intermediate release ketoprofen tablets using central composite design by the help of cost effective direct compression method. Different factors levels which are used in the formulations are shown in table 1 (A) and composition of IntR Ketoprofen formulations are presented in Table 1 (B). Assessment of micromeritic properties were also carried out. Ketoprofen intermediate release formulations were developed CCRD by altering the concentrations of Methocel K4M, Avicel PH102 and starch by using direct compression method. Behaviour of intermediate release formulations were also evaluated at different dissolution media. For this purpose different kinetic models were used to assess the release pattern.

MATERIALS AND METHODS

Ketoprofen was donated by Aventis Pharma (Pvt.), Pakistan while Methocel K4M (Colorcon Ltd., UK), Avicel PH -101 and starch (FMC Corporation, USA), magnesium stearate (Dow Chemical, USA) potassium dihydrogen phosphate, hydrochloric acid, methanol and sodium hydroxide (Merck, Damstabt, Germany) were purchased.

Multiple software's were used i.e. central composite design (CCRD) was successfully applied from Design Expert software, version 7.0.0, State-Ease, Inc., Minneapolis. While DD solver, Microsoft Excel and SPSS 17.0 (SPSS Inc) were used for the evaluation of release data.

Evaluation of micromeritic characteristics

Powder blends were evaluated by hausner's ratio (HR), angle of repose (α) and compressibility index (CI) as presented in Table 3. Following equations were used for the estimation of micromeritic features:

$$\text{Hausner ratio} = \frac{P_{\text{tapp}}}{P_{\text{bulk}}} \quad (1)$$

$$\text{Angle of Repose} = \tan^{-1} \frac{2h}{D} \quad (2)$$

$$\% \text{ Carr's Index} = \frac{P_{\text{tapp}} - P_{\text{bulk}}}{P_{\text{tapp}}} \times 100 \quad (3)$$

Where, P_{bulk} (bulk density), P_{tapped} (tapped density), H (height of heap) and D (diameter of heap).

Formulation design of intermediate release ketoprofen tablets

Fifteen different formulations of Ketoprofen intermediate release formulations (F1-F15) were designed using rotatable central composite method (CCRD) (Design Expert software, version 7.0.0) using three independent variables i.e., microcrystalline cellulose (Avicel PH-101) (X_1) (18-51%), methocel K4M (X_2) (12-25%) and magnesium stearate (X_3) (1-18%). Powder blends of all formulations were mixed through tumbling action. Powder blends were then compressed by single punch tablet machine (Korsch Erweka, Frankfurt Germany). Compression force was kept constant throughout the compression process. Composition of the formulations was presented as table 1(B).

Evaluation of tablet tensile strength

Tablet hardness tester (Fujiwara, Japan) was used for the assessment of crushing load. Following equation was used for its calculation:

$$T \text{ (MPa)} = \frac{2F}{\pi DH} \times \frac{1}{1000} \quad (4)$$

Where, F (N) is the crushing load, H (cm) is the thickness and D (cm) is the tablet diameter.

Disintegration and friability test

Disintegration test was performed using Basket Rack Assembly (Erweka ZT-2 Husenstamm, Germany). Tablets were subjected to distilled water (900mL) at $37 \pm 0.5^\circ\text{C}$. Friability test was conducted on friabilator (H.Jurgens GmbH and Co., Bremen, Germany) (USP, 2006).

Assessment of in vitro drug release

Release profiles of optimized formulations (F6, F7, F14 and F15) were estimated using 900mL of phosphate buffer pH 7.5 by using USP dissolution paddle method (apparatus II) (Erweka GmbH DT 600, Heusenstamm, Germany) at 50 rpm at $37 \pm 0.5^\circ\text{C}$. At 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hr approximately 10mL of sample were collected from each vessel and were replaced with fresh 10mL of dissolution media. The % drug release was measured at 260 nm (UV-1800 Shimadzu Corporation Kyoto, Japan) (BP, 2004).

Assessment of pharmaceutical assay

For assay assessment weighed and crushed twenty tablets from each formulation. Mean tablet weight was shaken with 75% of methanol (75%), ketoprofen were determined at 258 nm (BP, 2004) using UV-Visible spectrophotometer (Heliosa UV-Visible spectrophotometer 150, England).

Comparison of in vitro release profiles

The release profiles of the best optimized formulations were determined using 900mL of different dissolution media i.e. 0.1N HCl, phosphate buffer pH 4.5, pH 6.8 and pH 7.5 at $37 \pm 0.5^\circ\text{C}$. Apparatus II (Erweka DT 700,

Husenstamm, Germany) was used at 50 rpm. F15 was selected as reference formulation. Samples were drawn at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hrs from each vessel. UV-Visible spectrophotometer was used for the estimation of Ketoprofen at 276nm.

Analysis of in vitro release

Model-independent method

Difference factor (f_1) and similarity factor (f_2) were used for the comparison of test and reference product profiles. (f_1) and (f_2) were calculated using below equations:

$$f_1 = \left[\frac{\sum_{t=1}^n (R_t - T_t)}{\sum_{t=1}^n R_t} \right] \times 100 \quad (5)$$

$$f_2 = 50 \times \log \left\{ 1 + \left(\frac{1}{N} \sum (R_i - T_i)^2 \right)^{-0.5} \right\} \times 100 \quad (6)$$

Where, R_i and T_i = the % release of reference and test products and n = no of samples (Koester *et al.*, 2004).

Model- dependent methods

Different kinetic models were used for the assessment of release behaviour (Costa and Lobo, 2001; Hixson and Crowell, 1931; Higuchi, 1961; Langenbucher, 1972; Vudathala and Rogers, 1992) as shown in table 5.

STATISTICAL ANALYSIS

One – way ANOVA was used to analyze different release profiles statistically at various dissolution media as presented in Table 8.

Drug release mechanism

The release mechanism of intermediate ketoprofen formulations were estimated by Korsmeyer Peppas equation:

$$\frac{M_t}{M_\infty} = Kt^n \quad (7)$$

M_t / M_∞ = is the release in fraction,, k = is the kinetic constant, t = is the compound release time and n = is an exponent (Koester *et al.*, 2004).

Mean dissolution time (MDT)

Mean dissolution time (MDT) was determined as follows:

$$MDT = \left(\frac{n}{n+1} \right) k^{-1/n} \quad (8)$$

Where, n and k were obtained from Korsmeyer Peppas model (Möckel and Lippold, 1993).

Stability studies

Stability studies were conducted using international guidelines (ICH, 2003). Best formulations i.e., F6, F7, F14 and F15 were placed at $40^\circ\text{C} \pm 2^\circ\text{C}$ and $75\% \text{ RH} \pm 5\%$

RH (accelerated conditions) for 6 months in humidity chamber to assess the stability of the formulations. Shelf life was determined using Stab from R Gui soft ware.

RESULTS

In the present study different Intermediate release (IntR) formulations were manufactured using Central composite design (Barmpalexis *et al.*, 2009; Aslan 2008; Shivakumar *et al.*, 2008) as presented in Table 1(A) and (B). Flow properties of all fifteen different formulations (F1 and F15) were conducted. Micromeritic assessments were carried out using Hausner's ratio (Eq. 1), angle of repose (Eq. 2) and compressibility index (Eq. 3) as shown in Table 2. In this study results of weight variation, thickness and hardness variations of F6, F7, F14 and F15 were found to be in the range of $236.51 \pm 0.17 \text{ mg}$ - $297.32 \pm 0.33 \text{ mg}$, $2.88 \pm 0.15 \text{ mm}$ - $3.58 \pm 0.06 \text{ mm}$ and $6.22 - 7.94 \text{ kg}$ respectively. Also, the tensile strength (Eq. 4) of selected formulations were found to be in the range of $62.2 - 67.1$ as shown in Table 3. Friability and disintegration results are also summarized in Table 3 and were found within acceptable limits. Results of analysis of variance (ANOVA) were presented in Table 4. Data of release profiles were fitted to various kinetic models as presented in Table 5. Release kinetics was measured using model independent and dependent approaches. F15 was selected as a reference formulation while remaining formulations i.e. F6, F7 and F14 were selected as test formulations. Values of f_1 and f_2 at pH 1.2 were ranged of 1-3 and 84.433 - 90.236, at phosphate buffer pH 4.5 values were 0 - 4 and 81.923 - 86.813, at pH 6.8 and pH 7.5 f_1 and f_2 were ranged of 1 - 3 and 0 - 4, 84.748 - 93.438 and 73.895 - 97.511 respectively as presented in Table 6. Ketoprofen release mechanism was presented in Table 7. Mean dissolution time (MDT) (Eq.8) were found to be F6 (2.632 hrs), F7 (2.918 hrs), F14 (2.842 hrs) and F15 (2.922 hrs). MDT was assessed by using DD-Solver an add - in program for Microsoft Excel™ 2007 (Microsoft Corporation, USA). In the present study one – way ANOVA was applied using Tukey's post hoc test to evaluate the *in vitro* behaviour within and among the four selected formulations at different dissolution media at 0.05 level of significance (Table 8). Shelf life of intermediate formulations were calculated to be 33.11 - 35.09 months.

DISCUSSION

The optimization technique based on RSM method particularly includes different statistical experimental designs which are assessed by using certain controlled equations. Therefore, Central composite design (CCRD), factorial design and contour plots completely evaluated the factors by persuading the results by altering them concurrently (Arulsudar *et al.*, 2005; Zahran *et al.*, 2003).

Table 1(A): Factors levels used in the optimization of intr ketoprofen formulations

Factors		Units	Levels X				
			- β	-1	0	+1	+ β
X ₁	Avicel PH101	%	18.182	25	35	45	51.817
X ₂	HPMC (K4M)	%	0.113	5	12.574	20	25.113
X ₃	Starch	%	1.591	5	10	15	18.409

Table 1(B): Composition of intr ketoprofen formulations using central composite design

Formulations	(Avicel PH 101)	(HPMC K4M)	(Starch)	(Avicel PH 101)	(HPMC K4M)	(Starch)	KETO	MG-ST	Tablet weight
	(%)			(mg)			(mg)		
	X ₁ (%)	X ₂ (%)	X ₃ (%)	X ₁ (mg)	X ₂ (mg)	X ₃ (mg)	mg		
F1	25	5	5	38.846	7.769	7.769	100	1	155.384
F2	45	5	5	101	11.222	11.222	100	1	224.444
F3	25	20	5	50.5	40.4	10.1	100	1	202
F4	45	20	5	151.5	67.333	16.833	100	1	336.666
F5	25	5	15	45.909	9.181	27.545	100	1	183.636
F6	45	5	15	129.857	14.428	43.285	100	1	288.571
F7	25	20	15	63.125	50.5	37.875	100	1	252.5
F8	45	20	15	227.25	101	75.75	100	1	505
F9	18.182	12.5	10	30.958	21.283	17.026	100	1	170.268
F10	51.817	12.5	10	203.784	49.158	39.327	100	1	393.270
F11	35	1	10	65.462	1.870	18.703	100	1	187.037
F12	35	25.113	10	118.280	84.869	33.794	100	1	337.944
F13	35	12.5	1.591	69.437	24.799	3.156	100	1	198.393
F14	35	12.5	18.408	103.692	37.033	54.539	100	1	296.265
F15	35	12.5	10	83.176	29.705	23.764	100	1	237.647

Table 2: Micromeritic properties of intr formulations of ketoprofen formulations (N=3)

Formulations	Angle of Repose (θ)	BULK Density (g/cm ³)	TAPPED Density (g/cm ³)	Hausner's Ratio	Carr's Index (%)	Porosity	Comments* (USP, 2007)
F1	42.56	0.49	0.66	1.346	25.757	0.346	Passable
F2	37.25	0.47	0.59	1.255	20.338	0.255	Fair
F3	43.59	0.43	0.58	1.348	25.862	0.348	Passable
F4	34.59	0.49	0.61	1.244	19.672	0.244	Fair
F5	33.59	0.48	0.57	1.187	15.789	0.187	Good
F6	37.59	0.45	0.54	1.2	16.666	0.2	Fair
F7	42.59	0.40	0.51	1.275	21.568	0.275	Passable
F8	38.95	0.46	0.56	1.217	17.857	0.217	Fair
F9	37.58	0.51	0.62	1.215	17.741	0.215	Fair
F10	37.54	0.45	0.55	1.222	18.181	0.222	Fair
F11	33.25	0.48	0.56	1.166	14.285	0.1666	Good
F12	32.55	0.48	0.54	1.125	11.111	0.125	Good
F13	38.49	0.46	0.58	1.260	20.689	0.260	Fair
F14	37.25	0.51	0.63	1.235	19.047	0.235	Fair
F15	32.65	0.56	0.64	1.142	12.5	0.142	Good

Micromeritic of Powder Blends

The powder blends were categorized as Fair – Excellent were selected for studies. Results of Hausner's ratio, compressibility index (CI) and angle of repose were found

in the range of 1.125 - 1.142, 11.111 - 25.862 and 32.55 - 43.59 respectively. Four different formulations i.e. F5, F11, F12, F15 showed good flow properties while F1, F3 and F7 showed passable properties. Variations in flow

Table 3: Physicochemical evaluation of intermediate release formulations

Formulations	Weight Variation (mg) (n=20)	Thickness (mm) (n=20)	Hardness (kg) (n=20)	Friability (%) (n=10)	Disintegration Time (min) (n=6)	Tensile Strength (N)(n=10)	Assay (%) (n=20)	Dissolution (%) (n=6)
F2	225.44±0.12	3.23±0.05	6.51-7.21	0.56	11.5	65.1	99.11 ±0.01	97.01 ±0.01
F3	201.22±0.15	2.93±0.13	6.53-6.89	0.61	12.8	65.3	98.27±0.02	99.51± 0.02
F5	182.61±0.17	2.88±0.15	6.68-7.64	0.48	11.8	66.8	99.23±0.11	97.51± 0.01
F6	289.27±0.15	3.56±0.27	6.66-7.58	0.64	13.1	66.6	99.15±0.08	98.55± 0.02
F7	251.62±0.13	3.26±0.07	6.53-7.12	0.49	12.7	65.3	98.43±0.07	99.67± 0.01
F12	335.12±0.18	3.88±0.10	6.88- 7.11	0.52	13.4	68.8	99.01±0.15	98.58± 0.07
F13	199.24±0.19	2.93±0.03	6.54-7.91	0.47	11.7	65.4	99.29±0.44	97.43± 0.05
F14	297.22±0.33	3.58±0.06	6.71-7.89	0.61	12.5	67.1	98.02±0.09	97.13± 0.11
F15	236.51±0.17	3.32±0.11	6.22-7.84	0.58	13.2	62.2	99.88±0.77	99.16± 0.34

Table 4: Results of ANOVA for CCRD

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Friability					
Model	0.368	9	0.040	3.493	0.0909
A-MCC	0.101	1	0.101	8.688	0.0320
B-HPMC	0.162	1	0.162	13.897	0.0136
C-STARCH	0.014	1	0.014	1.206	0.3221
Residual	0.058	5	0.011		
Cor Total	0.427	14			
Carr's Index					
Model	172.493	3	57.497	7.087	0.0064
A-MCC	82.173	1	82.173	10.129	0.0087
B-HPMC	89.942	1	89.942	11.086	0.0067
C-STARCH	0.3782	1	0.378	0.046	0.8330
Residual	89.239	11	8.112		
Cor Total	261.733	14			

Table 5: Equations of model dependent methods¹⁴⁻¹⁸

MODEL DEPENDENT	Zero order kinetics	$Q_t = K_0 t$
	First order kinetics	$\text{Log } Q = \text{Log } Q_0 - \frac{kt}{2.303}$
	Weibull model	$m = 1 - \exp \left[- \frac{(t-T_1)^n}{a} \right]$
	Hixson-Crowell model	$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t$
	Baker and Lonsdale model	$\frac{3}{2} [1 - (1 - F)^{2/3}] - F = kt$
	Higuchi model	$Q = kt^{1/2}$

characteristics are due the variation in the compositions of different formulations (Bolhuis and Chowhan, 1996; Bolhuis & Armstrong, 2006). Porosity of different powder blends were found to be in the range of 0.125 - 0.348 as presented in Table 2. Different scientists reported the consequences of the properties of API on physicochemical characteristics of various formulations (Di Martin *et al.*, 2005; Michel de *et al.*, 2008).

Physico-chemical evaluation of intermediate release formulations

From fifteen different formulations only nine formulations i.e. F2, F3, F5, F6, F7, F12, F13, F14 and F15 were selected on acceptable weight basis and micromeritic properties. From nine formulations only four best formulations were selected for further studies i.e. F6, F7, F14 and F15 while F1, F2, F3, F5 and F13 were excluded due to the concentration of excipients

Table 6: Similarity factor and differential factor of ketoprofen formulations

FORMULATIONS	f_1	f_2
pH 1.2		
F15 and F6	3	84.433
F15 and F7	2	87.208
F15 and F14	1	90.236
Phosphate buffer pH 4.5		
F15 and F6	0	86.813
F15 and F7	2	83.536
F15 and F14	4	81.923
Phosphate buffer pH 6.8		
F15 and F6	1	90.245
F15 and F7	1	93.438
F15 and F14	3	84.748
Phosphate buffer pH 7.5		
F15 and F6	4	73.895
F15 and F7	0	97.511
F15 and F14	4	77.278

particularly of methocel K 4M, Avicel PH 101 and Starch and also due to their unacceptable weight. All the formulations were compressed by direct compression method using single punch tablet machine. The quantity of the methocel used in the controlled release formulations produce a great impact on different physico-chemical properties of the tablets i.e. friability, hardness and *in vitro* release pattern (Korsmeyer *et al.*, 1983). Scientists reported that high concentration of methocel in matrix tablets results in increase in tablet hardness. Similarly, addition of microcrystalline cellulose (MCC) showed increase in force of cohesion (Monajjemzadeh *et al.*, 2013). It was also found that alteration in compression force produced variation in tablet porosity and hardness (Velasco *et al.*, 1999). In the present study the disintegration test was performed and the results were found to be in acceptable limits. The % friability of the best optimized formulations were found to be in the acceptable limits as shown in Table 3. Predicted values of % friability were presented in Eq. 9:

$$Y_1 = 2.071955 - 0.04351X_1 - 0.05337X_2 - 0.04069X_3 + 0.000917X_1X_2 - 0.00037X_1X_3 + 0.0003X_2X_3 + 0.000388X_1^2 + 0.000135X_2^2 + 0.002825X_3^2 \quad (9)$$

Predicted values of % friability were found to be in excellent relation with the actual values as shown in above Eq.9. Barakat *et al.*, in 2009 found that high concentrations of methocel in carbamazepine matrix tablets results in slow drug release from the tablets. Similarly, Ghimire *et al.*, in 2010 reported that the use of high concentration and also the high viscosity grade of methocel in the formulations further increase in gel layer strength which may results in reduced water penetration into the dry matrix tablet. Similar results were also reported by Huma *et al.*, in 2016. In the present study predicted values of Carr's Index was shown in Eq.10:

$$Y_2 = 34.823156 - 0.2453X_1 - 0.34833X_2 - 0.03328X_3 \quad (10)$$

Actual values of Carr's Index showed excellent correlation with the predicted values. The assay assessment was carried on the optimized formulations and the results were found to be in the range of $98.02 \pm 0.09\%$ - $99.88 \pm 0.77\%$. The results of % drug release were found to be $97.13 \pm 0.11 - 99.16 \pm 0.34\%$ as shown in Table 3. Among four selected formulations (F6, F7, F14 and F15), F15 was selected as a best formulation due to its acceptable weight and its excellent physico-chemical behaviour.

Ketoprofen release kinetics

In this study, ketoprofen release pattern of the best optimized IntR formulations were estimated at different dissolution medium i.e. at pH 1.2, phosphate buffer 4.5, 6.8 and 7.5. Release profiles at pH 7.5 are shown in Figure (1). Qazi *et al.*, in 2013 used different kinetic models to determine the release behaviour of Diltiazem HCl sustained release tablets. For F6, F7, F14 and F15 formulations, r^2 values of Zero and First order at pH 1.2 were ranged of 0.9571 - 0.9912 and 0.9916 - 0.9967, at phosphate buffer pH 4.5; r^2 were ranged of 0.9689 - 0.9828 and 0.9873 - 0.9964, at pH 6.8 and 7.5 values were 0.9686 - 0.9735 and 0.9499 - 0.9799 respectively as presented in Table 7. Sankalia *et al.*, in 2008 used zero-order kinetics for the determination of release behaviour of glipizide matrix formulations. For Higuchi model, consecutive values of r^2 at pH 1.2, 4.5, 6.8 and 7.5 were found to be in range of 0.9786 - 0.9958, 0.9870 - 0.9957, 0.9944 - 0.9959 and 0.9944 - 0.9968 respectively as presented in Table 7. Bravo *et al.*, in 2002 found zero order kinetics for the matrix tablet of diclofenac sodium with excellent r^2 values. For Baker-Lonsdale model r^2 values were 0.9559 - 0.9864 at pH 1.2, 0.9638 - 0.9787 at phosphate buffer pH 4.5, 0.9705 - 0.9731 at pH 6.8 and 0.9633 - 0.9842 at pH 7.5. Weibull model was also used to evaluate the release kinetics of ketoprofen IntR

Table 7: Kinetic models of intr formulations

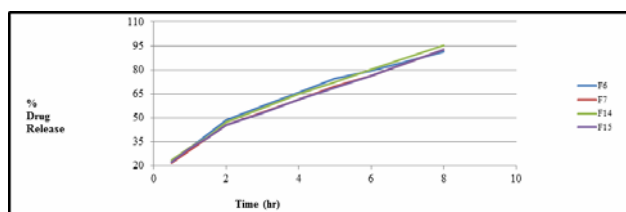
CODE	Zero Order		First Order		Higuchi		Korsmeyer Peppas		Hixson-Crowell		Baker-Lonsdale		Weibull model		
	r^2	K_0 (hr ⁻¹)	r^2	K (hr ⁻¹)	r^2	$\frac{K_H}{(hr^{-1/2})}$	r^2	$\frac{K_{KP}}{(hr^{-n})}$	n	r^2	$\frac{K_{HC}}{(hr^{-1/3})}$	r^2	K_{BL}	r^2	β
pH 1.2															
F6	0.9912	6.609	0.9926	0.108	0.9786	21.274	0.9961	13.172	0.731	0.9950	0.031	0.9559	0.010	0.9808	5.524
F7	0.9681	6.723	0.9916	0.116	0.9952	22.361	0.9965	20.381	0.549	0.9872	0.033	0.9827	0.011	0.9937	5.006
F14	0.9571	6.506	0.9923	0.111	0.9958	21.715	0.9963	20.402	0.534	0.9843	0.031	0.9864	0.010	0.9985	5.174
F15	0.9764	6.555	0.9967	0.111	0.9943	21.760	0.9986	18.476	0.584	0.9932	0.031	0.9794	0.010	0.9949	5.120
pH 4.5															
F6	0.9717	7.809	0.9940	25.926	0.9949	0.152	0.9969	22.699	0.570	0.9928	0.041	0.9739	0.016	0.9915	4.287
F7	0.9689	7.794	0.9964	26.262	0.9957	0.154	0.9978	23.875	0.550	0.9927	0.042	0.9787	0.016	0.9929	4.095
F14	0.9828	7.547	0.9873	24.907	0.9891	0.140	0.9942	19.049	0.633	0.9914	0.038	0.9638	0.014	0.9806	4.456
F15	0.9798	7.493	0.9876	25.399	0.9870	0.143	0.9918	20.119	0.614	0.9890	0.039	0.9658	0.015	0.9769	4.070
pH 6.8															
F6	0.9735	8.282	0.9888	0.174	0.9944	28.090	0.9956	25.141	0.557	0.9902	0.046	0.9724	0.019	0.9829	3.715
F7	0.9720	8.381	0.9926	0.178	0.9952	28.270	0.9969	25.240	0.558	0.9932	0.047	0.9725	0.020	0.9869	3.763
F14	0.9731	8.661	0.9943	0.187	0.9959	28.931	0.9986	25.512	0.565	0.9957	0.049	0.9705	0.021	0.9885	3.777
F15	0.9686	8.399	0.9935	0.177	0.9949	28.123	0.9964	25.414	0.553	0.9931	0.047	0.9731	0.019	0.9891	3.883
pH 7.2															
F6	0.9499	8.997	0.9943	0.249	0.9966	32.796	0.9972	35.131	0.465	0.9940	0.062	0.9842	0.031	0.9875	2.688
F7	0.9762	9.053	0.9818	0.225	0.9949	31.761	0.9959	28.316	0.556	0.9896	0.057	0.9650	0.027	0.9698	2.945
F14	0.9761	9.353	0.9820	0.248	0.9968	33.017	0.9979	29.619	0.553	0.9923	0.062	0.9634	0.031	0.9687	2.785
F15	0.9799	8.948	0.9799	0.222	0.9944	31.583	0.9961	27.172	0.572	0.9890	0.056	0.9633	0.027	0.9655	2.889

Table 8: Statistical analysis of *in vitro* release

Formulations	Dissolution Medium	Source of variation	Sum of Squares	df	Mean Square	F	Sig.
F6, F7, F14 and F15	pH 1.2	Between Groups	14.289	3	4.763	0.017	0.997
		Within Groups	9046.512	32	282.703		
		Total	9060.801	35			
	pH 4.5	Between Groups	26.608	3	8.869	0.023	0.995
		Within Groups	12171.081	32	380.346		
		Total	12197.689	35			
	pH 6.8	Between Groups	8.790	3	2.930	0.006	0.999
		Within Groups	14788.978	32	462.156		
		Total	14797.768	35			
	pH 7.5	Between Groups	52.242	3	17.414	0.032	0.992
		Within Groups	17204.408	32	537.638		
		Total	17256.650	35			

formulations, r^2 value for F14 at pH 1.2 was 0.9985, at phosphate buffer pH 4.5 r^2 value for F7 was 0.9929, at pH 6.8 r^2 value for F15 was 0.9891 and at pH 7.5 r^2 value for F6 was found to be 0.9875, also value of β was found to be < 1 for F6, F7, F14 and F15 at four different dissolution media. Also all the formulations were found to be best fitted to Hixson-Crowell kinetic model as shown in table 7.

Also Model – independent method was utilized for the assessment of release profiles using f_1 (difference factor) and f_2 (similarity factor) Eq. (5 and 6). Similarly, Muhammad *et al.*, 2012 in compared reference brand of cefuroxime axetil with the test products using f_2 (similarity factor). Different scientists assessed drug release pattern by utilizing model – independent method (Dash *et al.*, 2010; Shoaib *et al.*, 2010; Huma *et al.*, 2016) as shown in Table 6.

**Fig. 1:** % Drug Release of Intermediate Release Ketoprofen Formulations at pH 7.5.

Ketoprofen release mechanism

In the present study mechanism of ketoprofen intermediate release tablets were estimated by using Korsmeyer and Peppas model (Eq. 7) and exponent values (n) was also used to estimate the release mechanism of IntR formulations, consecutive r^2 values at different dissolution media i.e. at pH 1.2, phosphate buffer 4.5, 6.8 and 7.5 were ranged of 0.9961 - 0.9986, 0.9918 - 0.9978, 0.9956 - 0.9986 and 0.9959 - 0.9979. Values of n of all the formulations were found in the range of 0.465 - 0.731 at different dissolution media

indicating Anomalous transport (non - fickian diffusion) as shown in Table 7 which indicated that drug release was controlled by both mechanisms i.e. erosion and diffusion (Peppas, 1985). Jan *et al* in 2011 reported that Ketoprofen sustained release formulations showed zero order release pattern. Savaşer *et al* in 2005 used this model for the determination of release pattern of diclofenac sodium tablets.

Statistical evaluation

Statistical assessment was carried out by SPSS 20.0 (SPSS Inc). F15 was used as a reference product while remaining formulations were selected as test formulations. Results showed no significant difference in all formulations i.e. F6, F7, F14 and F15, as P value at pH 1.2, phosphate buffer pH 4.5, pH 6.8 and pH 7.5 were found to be 0.997, 0.995, 0.999 and 0.992 respectively as presented in Table 8.

Stability test

The shelf life of selected Ketoprofen IntR formulations were estimated at accelerated conditions i.e. $40 \pm 5^\circ\text{C}$ and $75 \pm 5\%$ RH in a humidity chamber²⁰ using stab package of R.Gui version 2.12. The shelf life of F6, F7, F14 and F15 were ranged of 33.11 - 35.09 months.

CONCLUSION

Intermediate release ketoprofen tablets were successfully developed and optimized by using central composite design by direct compression method. Physico-chemical properties and *in vitro* release were assessed and results were analyzed by model dependent and independent methods.

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