Intermediate release formulations of diclofenac potassium tablets for IVIVC

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Abstract: In recent days response surface methodology (RSM) has widely been applied for development and optimization of cost effective formulations with required quality. Study comprised of three steps including micromeritic comparison of different powder blends of placebo and diclofenac potassium (DP), formulation designing with CCRD (Design Expert, version 7.0.0), and stability testing of selected formulations by using R Gui. Ten formulations (F11-F20) were developed using microcrystalline cellulose (Avicel PH-102) (X1) (13-72%), methocel K15M (X2) (6.59-23.4%) and magnesium stearate (X3) (1.32-4.68%), while responses were % friability and % drug release. Blending rate constant was determined at 3, 6, 9 and 12 minutes. The results of physicochemical parameters were found within acceptable limits. After *in vitro* testing at pH 1.2, pH 4.5 and pH 6.8, mechanism of drug release, kinetic analysis and statistical evaluation were carried out by model - independent, model-dependent and one-way ANOVA methods. Most formulations followed zero order kinetics at higher pH. Fickian release ($0.326 \leq n \leq 0.449$) was observed with β greater than 0.5 and less than 1. ANOVA indicated no significant variation within and between formulations as p-values were found to be $\wp$ 0.05.

Keywords: Diclofenac potassium, intermediate release, zero order, Hixon - Crowell and fickian

INTRODUCTION

Homogeneity of formulation, bulk flow and surface area - controlled procedures i.e. drug release and chemical reactivity are directly related to different micromeritic characteristics of the powders (Christianah and Harry, 2008). Most of the flow features are simultaneously affected by the variation in the particle sizes, shape, surface morphology, electrostatic charge and absorbed moisture content, which may occur from processing or formulation which might change the free flowing behavior of the powders. These features produce a significant impact on the product processibility and quality of the dosage form, which necessitate the development of the entirely new formulation (Khar *et al*., 2013; Hanif *et al*., 2014).

The formulation of the successful dosage form depends not only on the properties of the active compound but also on the selection of the excipients because it is important to maintain the product quality. Not only the excipients selection but also their concentration in the manufacturing formulation is based on the compatibility and functionality of the excipients and drug. Results of drug – excipients stability studies play an important role in understanding the selection of the dosage form, behaviour of the drug during stability and identify different degradation products etc. (Christianah and Harry, 2008; Khar *et al*., 2013).

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Various crystalline forms of the compounds play a major role in the product development procedures while the presence of unfavorable features produce different modified release behavior (Hanif *et al*., 2014). Diclofenac potassium (DP) is an effective non-steroidal anti-inflammatory compound (NSAID), which is used in the management of rheumatic syndromes (Chang *et al*., 2002). The solubility of potassium salt of diclofenac in water is high as compared to sodium salt. Therefore, diclofenac potassium formulations are indicated for the treatment of pain and especially used in the management of migraine (McNeely and Goa, 1999) for which a rapid onset of action is vital (Diener, 2005).

Statistical models play an important role in the pharmaceutical product development. They are considered as powerful and effective tools in the design of different pharmaceutical dosage forms. These models have been successfully used in the development of various kinds of modified release tablet dosage form (Furlanetto *et al*., 2006). Central composite design (CCRD) is used extensively in the development of new drug product as well as in different optimized methods (Hanif *et al*., 2014). In the present study factors levels used in the optimization of intermediate formulations are presented in table 1 (A). Also the micromeritic features of two types of powder blend i.e. Diclofenac potassium containing blend and placebo blend were compared. Central composite design was successfully applied for the development of intermediate release DP tablet using

various concentration of Methocel (K15M), Avicel PH102 and Magnesium stearate. Tablets were compressed by direct compression method. Drug release pattern of intermediate release tablets were assessed by one-way ANOVA using Tukey's post hoc test, model – independent and model – dependent methods. Shelf life of optimized formulations was also determined at long term and accelerated conditions.

MATERIALS AND METHODS

Diclofenac potassium (DP) was gifted from Hilton Pharma (Pvt.) Ltd while Hydroxypropyl methyl cellulose (Methocel K15M) (Colorcon Ltd., UK), Avicel PH-102 (FMC Corporation, USA) and Magnesium stearate (Dow Chemical, USA) were purchased.

Different software was used i.e. central composite design was successfully applied from Design Expert software, version 7.0.0, State-Ease, Inc., Minneapolis. Microsoft Excel, DD solver and SPSS 17.0 (SPSS Inc) were used for the assessment of drug release data and Stab from R Gui software was used for the estimation of shelf life.

Blending Rate Constant

Blending rate constant was also assessed for estimating the precise mixing time. Twenty tablets were selected randomly from each formulation, 6 to 9 min were selected as mixing time as mentioned in 2(A). Following equation was used to calculate the blending rate constant:

$$RSD\ \% = (S.D)/Mean \times 100 \quad (1)$$

S.D is the standard deviation.

Assessment of micromeritic properties

Diclofenac potassium containing blends and placebo blends were assessed for hausner's ratio (HR), angle of repose (α) and compressibility index (CI) as shown in table 2(B). Following equations were used for the determination of micromeritic properties:

$$\text{Hausner ratio} = \rho_{tap} / \rho_{bulk} \quad (2)$$

$$\text{Angle of Repose} = \tan^{-1} 2h / D \quad (3)$$

$$\%\ \text{Carr's Index} = (\rho_{tap} - \rho_{bulk}) / \rho_{tap} \times 100 \quad (4)$$

Where, p_bulk and p_tappedwere bulk and tapped density respectively while H is the height of heap and D is the diameter.

Preparation of placebo tablets

Powder blends were mixed 9 minutes using tumbling method. Blend was then compressed by direct compression method using single punch tablet machine (Korsch Erweka, Frankfurt, Germany). Tablets were manufactured in the range of 150-250mg having different hardness and thickness. Concentrations of different excipients were mentioned in table 1(B).

Formulation design of intermediate release diclofenac potassium tablet

A total of 10 Diclofenac potassium intermediate release (IntR) formulations (F11-F20) were prepared using randomized rotatable central composite method (CCRD) (Design Expert software, version 7.0.0) using three different independent variables i.e., (X1) microcrystalline cellulose (Avicel PH-102) (13-72%), (X2) methocel K15M (6.59- 23.4%) and (X3) magnesium stearate (1.32-4.68%). Powder blends of F11- F20 were mixed through tumbling action. All the blends were compressed by single punch tablet machine (Korsch Erweka, Frankfurt Germany). During the manufacturing compression force was kept constant. Composition of the formulations was presented as table 1(B).

Evaluation of tablet tensile strength

For the estimation of crushing load, tablet hardness tester (Fujiwara, Japan) was used. It is calculated by following equation:

$$T\ (MPa) = (2F)/\pi DH \times 1/1000 \quad (5)$$

Where, F (N) = crushing load, H (cm) and D (cm) are the thickness and diameter of the tablet respectively.

Relative density

Thickness (cm), mass and diameter (cm) of the Diclofenac potassium (DP) and placebo tablets were determined by vernier caliper and Sartorius balance (Blanco MJ *et al*., 2004). Relative densities and densities of tablets were calculated by following equation:

$$P_t = (P\ tablet)/(P\ Powder) \quad (6)$$

$$P_t = M / (\pi hd\ 2\ /4\ ) \quad (7)$$

P = is the density in g / cm3

Tablets porosity

The % porosity of the tablet □ % was determined from the true density (ρ) g/cm^{3}of the tablets by following formula:

$$\square(\%) = [(1-M)/V_p\ ] \times 100 \quad (8)$$

The thickness and diameter for the determination of tablet volume were calculated with the help of micrometer.

Disintegration test

Disintegration test was carried out on six tablets of each formulation using Basket Rack Assembly (Erweka ZT-2 Husenstamn, Germany), all the tablets were subjected to 900mL distilled water at 37 + 0.5°C (USP, 2009).

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

Factors		Units	Levels X				
			-β	-1	0	+1	+β
X1	Avicel PH102	%	13	25	42.5	60	72
X2	HPMC (K15M)	%	6.59	10	15	20	23.4
X3	Magnesium stearate	%	1.32	2	3	4	4.68

Table 1(B): Composition of IntR diclofenac potassium formulations using central composite design

Formulations	(Avicel PH 102)	(HPMC K15M)	(Mag. Stearate)	(Avicel PH 102)	(HPMC K15M)	(Mag. Stearate)	Tablet weight
	X1 (%)	X2 (%)	X3 (%)	X1 (mg)	X2 (mg)	X3 (mg)	(mg)
F11	60.0	10.0	2.00	120.0	20	4	194
F12	50.0	12.0	2.00	100.0	24	4	178
F13	60.0	20.0	2.00	120.0	40	4	214
F14	71.9	15.0	3.00	144.0	30	6	230
F15	42.5	15.0	4.50	85.0	30	9	174
F16	60.0	10.0	3.00	120.0	20	6	196
F17	42.5	8.0	3.00	85.0	16	6	157
F18	42.5	15.0	1.50	85.0	30	3	168
F19	25.0	10.0	4.00	50.0	20	8	128
F20	45.0	15.0	3.00	90.0	30	6	176

Table 2(A): Determination of blending rate constant of diclofenac potassium IntR

Formulations	Assay (%)			
	3 (min)	6 (min)	9 (min)	12 (min)
Batch 1	103.76	99.96	100.79	103.23
Batch 2	100.45	98.11	98.13	98.34
Batch 3	97.12	102.94	101.88	97.67
SD	3.320	2.436	1.928	3.035
MEAN	100.443	100.336	100.266	99.746
%RSD	3.305	2.428	1.923	3.042
*ln*RSD	1.133	0.933	0.675	0.983
Blending Rate Constant (K_b)			0.023 (min^{-1})	

Table 2(B): Micromeritic properties of IntR formulations of diclofenac potassium & placebo (N=3)

Formulations	Hausner's Ratio	Carr's Index (%)	Flow Rate (min)	Porosity	Angle of Repose (θ)	Comments* (USP, 2007)
F11	1.48	32.75	1.85	0.48	54.85	Very Poor
F12	1.15	13.67	1.75	0.52	31.46	Good
F13	1.17	15.06	1.72	0.61	34.20	Good
F14	1.49	33.01	1.62	0.63	57.75	Very Poor
F15	1.55	35.74	1.69	0.61	59.98	Very Poor
F16	1.19	16.12	1.84	0.50	36.67	Fair
F17	1.45	31.12	1.58	0.63	47.51	Poor
F18	1.61	37.81	1.60	0.65	63.23	V,V Poor
F19	1.38	27.84	1.73	0.57	48.59	Poor
F20	1.23	19.11	1.77	0.55	38.70	Fair
Placebo	1.22	23.27	1.02	0.69	35.63	Fair

Table 2(C): Physicochemical tests of DP formulations

CODE	Weight Variation (mg)	Thickness (mm)	Hardness (kg)	Friability (%)	Disintegration Time (min)	Porosity of Tablet (%)	Tensile Strength (N)	Relative Density (gm/cm^3)	Assay (%)
F12	178±3.65	2.78±0.17	6.52-7.91	0.63	12.5	4.80	65.2	19.94	101.54±0.23
F13	214±3.65	2.57±0.26	6.22-7.53	0.53	11.2	5.10	62.2	19.60	100.84±0.24
F 16	196±3.99	2.91±0.23	7.25-7.96	0.89	14.5	4.41	72.5	21.89	99.92±0.31
F 20	176±3.41	2.49±0.22	6.78-7.47	0.67	12.0	4.99	67.8	18.60	100.97±0.39

Table 3: Results of ANOVA for RSM

	Sum of		Mean	F	p-value
Source	Squares	df	Square	Value	Prob> F
Friability					
Model	991.0	9	110.11	18.300	< 0.0001
X1 avicel	39.25	1	39.25	6.523	0.0287
X2 HPMC	450.25	1	450.25	74.831	< 0.0001
X3 magnessium stearate	30.71	1	30.71	5.105	0.047
Residual	60.16	10	6.016		
Lack of Fit	60.168	7	8.595		
Pure Error	0	3	0		
Cor Total	1051.1	19			
Drug Release at 12 hrs					
Model	0.833	9	0.092	13.60	0.0002
A-X1 avicel	0.372	1	0.372	54.77	< 0.0001
B-X2 HPMC	0.075	1	0.075	11.02	0.0077
C-X3 magnessium stearate	0.069	1	0.069	10.26	0.0094
Residual	0.068	10	0.0068		
Lack of Fit	0.068	7	0.0097		
Pure Error	0	3	0		
Cor Total	0.901	19			

Table 4: Equations of model dependant methods used to evaluate the drug release kinetics of IntR DP tablets

MODEL DEPENDENT	Zero order kinetics	$Q_t = K_0\, t$
	First order kinetics	$\mathrm{Log\ Q = LogQ_0 - \frac{kt}{2.303}}$
	Weibull model	$\mathrm{m = 1 - exp\left[-\frac{(t-Ti)^{\beta}}{\alpha}\right]}$
	Hixson–Crowell model	$\mathrm{Q_0^{1/3} \quad Q_t^{1/3} = K_{HC} \times t}$
	Baker and Lonsdale model	$\frac{3}{2}\left[1-(1-F)^{2/3}\right]-F = kt$
	Higuchi model	$\mathrm{Q = kt^{\frac{1}{2}}}$

Pharmaceutical assay

Assay of intermediate release DP tablet was carried out by high performance liquid chromatography method (HPLC). Mobile phase consisted of methanol - monobasic sodium phosphate (0.01M) using equal volume of ortho phosphoric acid (0.01M) in (70:30) ratio, orthophosphoric acid (10%) was used to adjust pH 2.5, flow rate was maintained at 1mL min^{-1} using reverse phase (C18) column at 254 nm (USP, 2009).

Dissolution test

The % drug release of intermediate release diclofenac potassium (DP) tablet was carried out using paddle apparatus (II) (Erweka DT 700, Husenstamm, Germany) at 50 rpm. For this purpose 900mL of phosphate buffer pH 6.8 was used, temperature was maintained at 37°C + 0.5°C. The % release was determined by UV- Visible spectrophotometer (UV-1800 Shimadzu Corporation Kyoto, Japan) at 276nm (USP, 2009).

Comparison of dissolution profiles

The release profiles of three selected intermediate release DP formulations were compared using 900mL of three different dissolution media i.e. pH 1.2, phosphate buffer pH 4.5 and pH 6.8 at 37+0.5°C. Apparatus II (Erweka DT 700, Husenstamm, Germany) at 50 rpm was used. F 12 was used at reference product. Samples were drawn at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hr from each vessel and estimated by UV- Visible spectrophotometer at 276nm.

Table 5: similarity factor and differential factor of diclofenac potassium IntR formulations

Formulations	f_1	f_2
pH 1.2		
F13	7.16	69.32
F16	12.07	59.26
F20	5.72	74.12
Phosphate buffer pH 4.5		
F13	6.32	67.02
F16	9.10	58.15
F20	6.22	71.02
Phosphate buffer pH 6.8		
F13	4.93	69.03
F16	11.34	53.70
F20	3.03	80.34

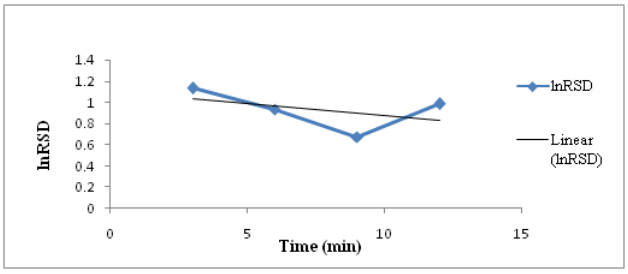

Fig. 1: Blending rate constant of IntR DP (N=3)

Analysis of in vitro data

Model-Independent Method

Model – independent method consisted of difference factor (f1) and similarity factor (f2). FDA endorsed both equations for the comparison of drug release profile. For the determination of f1 and f2 values Microsoft Excel TM 2007 (Microsoft Corporation, USA) was used. Difference factor (f1) and similarity factor can be calculated as:

$$f_1 = \left[\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right] \times 100 \qquad (9)$$

Where n = no of samples, Rt and Tt = the % drug release of the reference and test formulations (Koester *et al*., 2004).

$$f_2 = 50 \times \log\{[1+(1/N)\sum(Ri-Ti)^2]^{-0.5}\} \times 100 \qquad (10)$$

Where, Ri and Ti= the % drug release of reference and test formulations and n = no of samples (Koester *et al*., 2004).

Model- dependent methods

Drug release data were fitted into various kinetic models i.e. First Order, Zero-Order, Weibull model, Higuchi model, Korsmeyer Peppas and Hixson – Crowell cube root law and Baker and Lonsdale model (Hanson *et al*., 1982; Costa and Lobo, 2001; Hixson and Crowell, 1931; Higuchi *et al*., 1963; Langenbucher, 1972; Vudathala and Rogers, 1992; Korsmeyer *et al*., 1983). DD-Solver an add- in program for Microsoft Excel TM 2007 (Microsoft Corporation, USA) was used to analyzed kinetic models.

STATISTICAL ANALYSIS

One – way ANOVA with Tukey's post hoc test was to statistically analyze the release profiles at various dissolution media. SPSS 20.0 (SPSS Inc) was used to analyze the data.

Mean Dissolution Time (MDT)

Mean dissolution time (MDT) of three best formulations according to the following formula:

$$MDT = (n/(n+1))\, k^{-1/n} \qquad (11)$$

Where, n and k were derived from Korsmeyer Peppas model (Mockel and Lippold, 1993).

Stability studies

Stability studies were carried out using the guidelines of International Committee on Harmonization (ICH, 2003). Four best formulations i.e., F12, F13, F16 and F20 were placed at 30°C±2°C and 65% RH ±5% RH (room temperature) for 12 months and at 40°C±2°C and 75% RH ±5% RH (accelerated conditions) for 6 months at humidity chamber to estimate the shelf life of selected formulations. Shelf lives were calculated using Stab from R Gui software.

RESULTS

The present study was aimed to determine the appropriate compositions of excipients to optimize the intermediate (IntR) formulations using response surface methodology. Different responses were assessed including friability and drug release Q12 hr with different levels of excipients.

Micromeritic evaluations of two different blends of powder i.e. diclofenac potassium and placebo were carried out and found acceptable. Central composite rotatable design was used for the selection of excipients in both cases as presented in table 1(A)-1(B). Powder blends assessment and physico-chemical quality evaluation of the optimized test products were also performed and summarized in table 2 (B) - 2(C) respectively.

Release profiles of selected formulations were fitted into different kinetic models (table 4 and 6) and (fig. 3-4). Results of drug release were analyzed by model – independent and one - way ANOVA method as mentioned

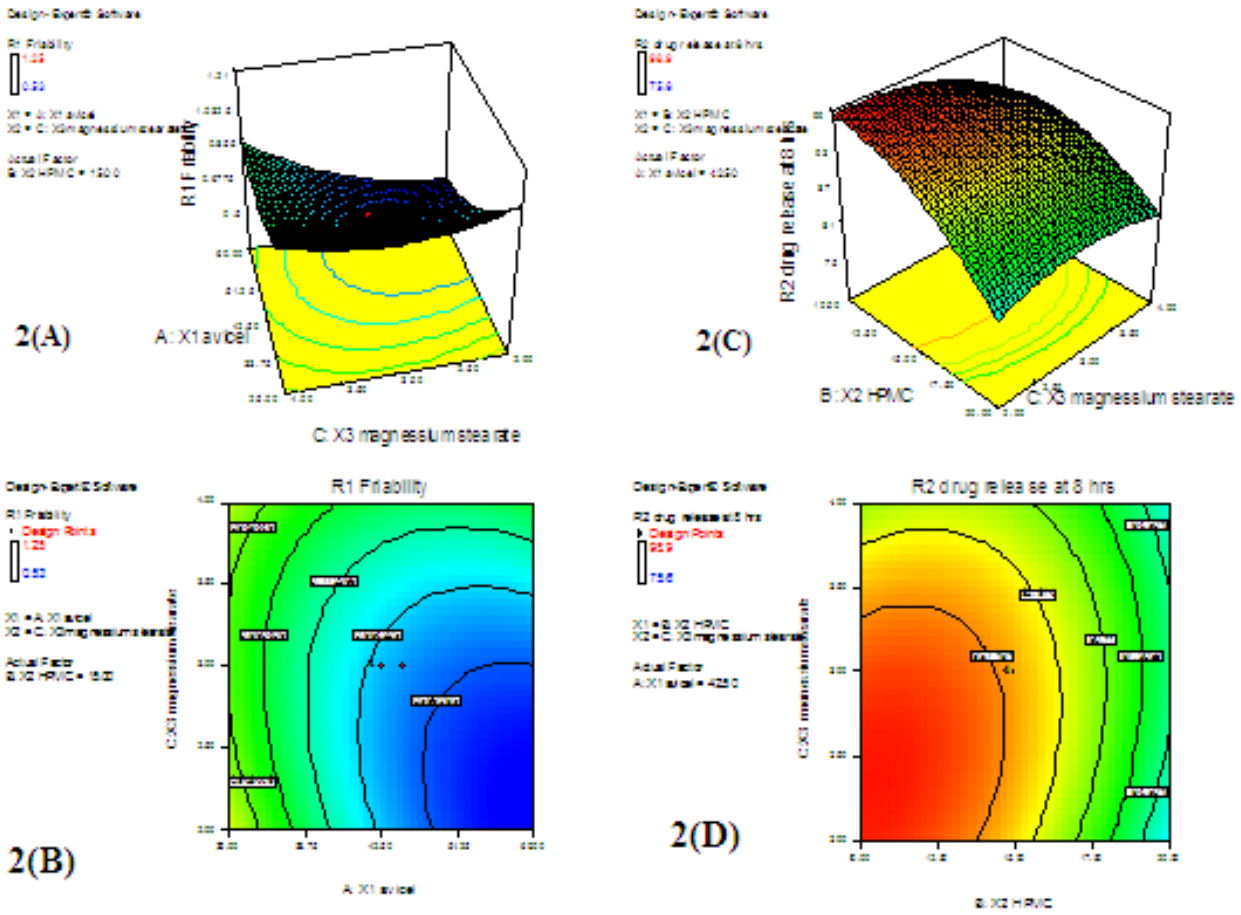

Fig. 2: RSM and Contour Plots of IntR for % friability (2(A), 2(B)) and Drug Release (2(C), 2(D))

in table 5 and 7 respectively. 3D graphs of RSM, Contour plots of % friability and % drug release are presented in fig. 2. Response surface quadratic model was analyzed by ANOVA as shown in table 3.

DISCUSSION

The optimization process based on response surface methodology (RSM) includes statistical experimental designs, which are analyzed under a set of controlled equations. Central composite design, factorial design and contour plots help in studying the factors persuading the responses by varying them simultaneously (Arulsudar *et al*., 2005: Zahran *et al*., 2003). Intermediate release (IntR) formulations were prepared with three variables (table 1(A)-1(B)). Central composite design was effectively used in different studies for optimization (Barmpalexis *et al*., 2009; Aslan, 2008; Shivakumar *et al*., 2008).

Micromeritic of powder blends

Blending rate constant was determined 0.023 min-1 for IntR formulations, while least %RSD values were found in the range of 6 to 9 minutes (table 2(A), figs. 1). Flow properties of ten selected formulations were shown in table 2(B), Hausner's ratio was found in the range of 1.15 to 1.61, compressibility index (CI) 13.67 to 37.81% and angle of repose 31.46o to 63.23o. F12 and F13 showed good flow properties while F16 and F20 showed fair flow properties. Micromeritic differences in trial batches were may be due to variable composition of formulations with respect to excipients and polymer ratio like hydroxypropyl methyl cellulose (HPMC) which showed direct relations with CI and inverse relation with angle of repose, while microcrystalline cellulose (avicel PH 102) exhibited direct relation with CI and hausner's ratio (Bolhuis & Chowhan, 1996; Bolhuis & Armstrong, 2006). Results also revealed that presence of DP in the powder blends altered the micromeritic behavior. Change in CI, porosity and flow properties with increased in bulk density and poured tapped density were observed with placebo as shown in table 2(B). Authors also reported the effect of API on physicochemical and micromeritic properties of different formulations (Di Martino *et al*., 2005); Michel *et al*., 2008; Hanif *et al*., 2014).

Table 6: in vitro model dependent kinetic studies of intermediate release diclofenac potassium tablets

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	K_H ($hr^{-1/2}$)	r^2	K_{KP} (hr^{-n})	n	r^2	K_{HC} ($hr^{-1/3}$)	r^2	K_{BL}	r^2	A	β
pH 1.2																
F-12	0.958	6.75	0.982	0.123	0.992	23.48	0.981	40.81	0.359	0.945	0.055	0.987	0.029	0.987	3.699	0.643
F-13	0.907	7.04	0.964	0.143	0.981	25.51	0.992	30.11	0.408	0.948	0.038	0.994	0.016	0.994	3.224	0.638
F-16	0.883	9.20	0.959	0.203	0.966	30.38	0.982	36.31	0.389	0.938	0.053	0.987	0.024	0.991	2.489	0.636
F-20	0.868	7.16	0.952	0.158	0.961	26.72	0.979	32.65	0.390	0.929	0.041	0.985	0.018	0.989	2.942	0.637
pH 4.5																
F-12	0.951	8.67	0.994	0.217	0.994	30.82	0.994	32.72	0.439	0.990	0.055	0.986	0.026	0.986	2.580	0.720
F-13	0.950	9.00	0.993	0.243	0.995	32.29	0.997	35.80	0.447	0.990	0.060	0.989	0.030	0.986	2.377	0.730
F-16	0.878	10.7	0.977	0.323	0.960	36.62	0.988	45.91	0.361	0.954	0.077	0.993	0.040	0.995	1.837	0.691
F-20	0.951	8.67	0.994	0.217	0.994	30.82	0.994	32.72	0.449	0.990	0.055	0.986	0.026	0.986	2.580	0.720
pH 6.8																
F-12	0.926	9.83	0.991	0.341	0.988	36.13	0.997	43.09	0.407	0.988	0.080	0.991	0.042	0.987	1.988	0.792
F-13	0.937	9.37	0.995	0.318	0.990	35.23	0.998	42.29	0.408	0.995	0.075	0.992	0.040	0.983	1.899	0.740
F-16	0.913	11.6	0.992	0.457	0.974	40.80	0.997	52.86	0.352	0.985	0.104	0.996	0.059	0.986	1.396	0.720
F-20	0.900	8.30	0.984	0.314	0.961	34.12	0.992	48.87	0.326	0.970	0.071	0.992	0.041	0.986	1.591	0.639

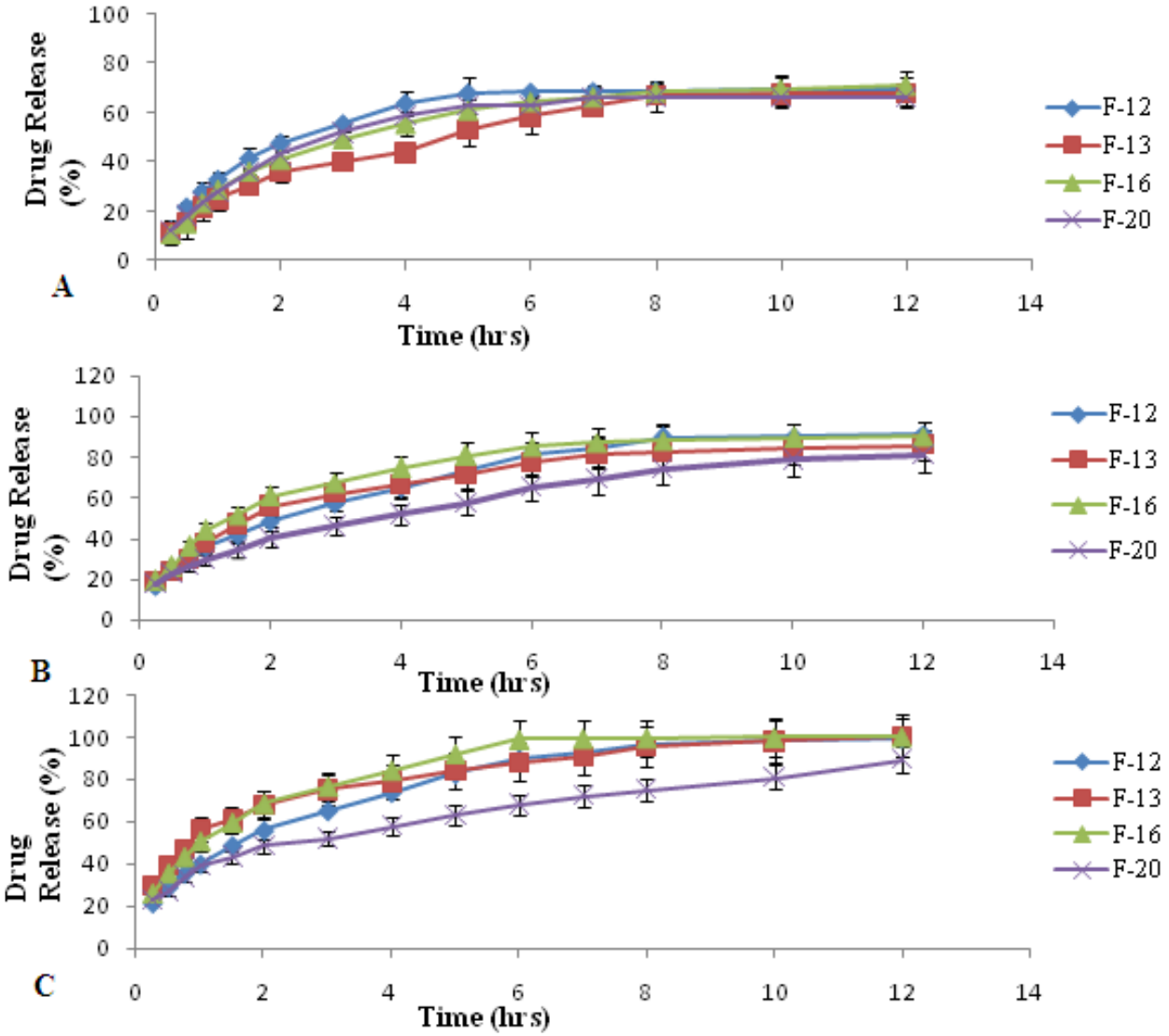

Fig. 3: % Drug Release of Diclofenac Potassium Intermediate Release Formulations With 1% SLS (A) pH 1.2 Solution (B) Phosphate Buffer pH 4.5 (C) Phosphate Buffer pH 6.8

Physico-Chemical evaluation of intermediate release tablets

In this study results of weight variation, thickness and hardness variations for F12, F13, F16 and F20 were in the ranged of 176±3.41to 214±3.65mg, 2.49 ±0.22 - 2.91± 0.23 mm and 6.22 – 7.25 kg respectively (table 2 (C). Microcrystalline cellulose (PH 102) has increased the cohesion forces of the powder blend owing to have high porosity and fine particle size while the methocel increases the hardness of the compacted mass (Monajjemzadeh *et al*., 2013). Scientists stated that variations in applied forces for compression may alter the tablet porosity with less effect on the release pattern (Velasco *et al*., 1999). Tensile strength (Eqn. 5), porosity (Eqn. 8) and relative density (Eqn. 6) of DP were also determined and found in acceptable ranges as given in table 2(C).

In present study % friability values of F12, F13, F16 and F20 were observed to be satisfactory (table 2(C)). Three dimensional (3D) response surface (RSM) and contour plots of % friability (fig. 2 (A), (B)) showed that high concentrations of PH 102 (X1) and methocel K15M (X2) resulted in acceptable values of % friability. Predicted values of friability are shown in Eq. 12:

R1(Y1)= +3.03380 -0.052149 * X1 - 0.050609 * X2 - 0.44479 * X3 -6.11989E-005* X1 * X2 +5.23523E-003 * X1 * X3 - 0.013667 * X2 * X3+3.23579E-004 * X12 +2.60663* X2 2 +0.084399 * X32 (Eqn. 12)

Good correlation was found between the actual and predicted values of % friability (fig. 2). Methocel in higher concentrations enhance the gel network bonding and declines the water penetration which results in low diffusion coefficient and prolong release pattern (Ghimire

Table 7: Statistical analysis of in-vitro drug release

Formulations	Dissolution Medium	Source of variation	df	Mean Square	F	Sig.
F12, F13, F16 and F20	pH 1.2	Between Groups	3	440.703	0.833	0.482
		Within Groups	52	528.831		
		Total	55			
	pH 4.5	Between Groups	3	161.830	0.893	0.357
		Within Groups	52	631.511		
		Total	55			
	pH 6.8	Between Groups	3	947.686	1.615	0.197
		Within Groups	52	586.949		
		Total	55			

et al., 2010). Rasul *et al* discussed the matrix formation and complexity associated with higher concentration of HPMC resulted in extended release (Rasul *et al*., 2010). 3D RSM and counter plots of % drug release are presented in (fig. 2 (C), (D)) and predicted values of % drug release were shown in Eq. 13:

R2 (Y2) = 72.07966+0.19536 * X1 +1.76346 * X2 +12.97831* X3+0.011950 * X1 * X2 -0.11135 * X1 * X3 +0.41668 * X2 * X3 -1.66726E-003 * X1 2 - 0.15872 * X22 - 2.69251 * X32 (Eqn. 13)

Intermediate release metoprolol, naproxen and nimesulide formulations were also reported for IVIVC studies (Sirisuth and Eddington, 2002; Hanif *et al*., 2014). Rettig and Mysicka also discussed release patterns of polymer controlled formulations and their used in IVIVC studies (Rettig and Mysicka, 2008). Analysis of variance (ANOVA) was also used to evaluate the difference of results as presented in table 3. The assay of optimized formulations was found to be in the range of 99.92 ± 0.31 to 101.54 ± 0.23% as shown in table 2 (C). In current study direct compression technique was used to compress the tablets. F12 due to its excellent micromeritic and physico-chemical behaviour was chosen as best formulation.

Diclofenac potassium release kinetics

In the present study, release profiles of the optimized IntR formulations were assessed at pH 1.2, phosphate buffer 4.5 and 6.8 (fig. 3 (A), (B) and (C)). Data was fitted to different kinetic models (table 4). These models are selected by considering the specific features related to drug – polymer systems (Shoaib *et al*., 2006). For F12, F13, F16 and F20 formulations, Zero and First order values of r^2 were 0.868 to 0.958 and 0.952 to 0.998 in dissolution medium of pH 1.2, phosphate buffer pH 4.5; r^2 were 0.873 to 0.951and 0.968 to 0.994, in pH 6.8 the results were 0.900 to 0.936 and 0.983 to 0.994 respectively as shown in (table 6 and fig. 4 (A)). Shoaib *et al* also discussed the release behaviour of ibuprofen matrix products and shown to fitted Zero-order kinetics with r^2 value of 0.9672 (Shoaib *et al.,* 2006). Higuchi model r^2values were 0.961 to 0.992 at acidic pH 1.2, 0.960 to 0.995 with phosphate buffer pH 4.5, 0.960 to 0.990 with pH 6.8. Intermediate diclofenac potassium showed First order release at pH 1.2, 4.5 and 6.8. F12 also followed the Zero order kinetics at higher pH. Intermediate formulations also fitted to Hixon Crowell and Weibull models and showed the r^2 values in the range of 0.929 to 0.948 and 0.987 to 0.994 at 1.2. While these values were 0.954 to 0.990 and 0.985 to 0.986 at 4.5 and 0.970 to 0.994 and 0.983 to 0.986 at 6.8 respectively (table 6 and fig.4 (B), (D) and (E)). Bravo *et al* evaluated the release pattern of matrix formulation of diclofenac sodium, with highest r^2 values for Zero-order followed by Higuchi and First-order model (Bravo *et al.,* 2004). Baker and Lonsdale equation was also used to assess the drug release behaviour and showed r^2 values in order of0.985-0.994, 0.986-0.993 and 0.991-0.996 at pH 1.2, 4.5 and 6.8.βwere greater than 0.5 and less than 1 in each case. Curve shape was observed steep slope at first and then flat surface at variable pH conditions which may be due to $\beta > 0.5 \Re 1$ (table 6). Other investigators also explained shape factor using Weibull model and effect of shape and geometry after calculating the coefficient of variation (Sathe *et al.*, 1996, Polli *et al.,* 1997, Yuksel *et al.,* 2000; Dash *et al.,* 2010).

Drug release mechanism

Drug release mechanism was evaluated using Korsmeyer and Peppas model. Values of *n* were found less than 0.45 in all cases and showed fickian diffusion, controlled due to presence of matrix forming hydrophilic polymer HPMC. For this purpose data of first 60 % was used in Korsmeyer – Peppas model (table 4) to determine the release mechanism by calculating the values of *n*, at pH 1.2, 4.5 and pH 6.8(table 6 and fig. 4 (C)).

Mean dissolution time (MDT) (Eq.11) of F12, F13, F16 and F20 were found to be 2.465 hrs, 2.136 hrs, 1.742 hrs and 3.345 hrs respectively. MDT was determined by using DD-Solver an add - in program for Microsoft Excel ™ 2007 (Microsoft Corporation, USA).

Model – independent method; f_1 (difference factor) (Eq. 9) and f_2 (similarity factor) were also utilized to analyzed the drug release data (Eq. 10). Dissolution profile of F12 (reference formulation) was compared with the optimized formulations (F13, F16 and F20). At phosphate buffer pH

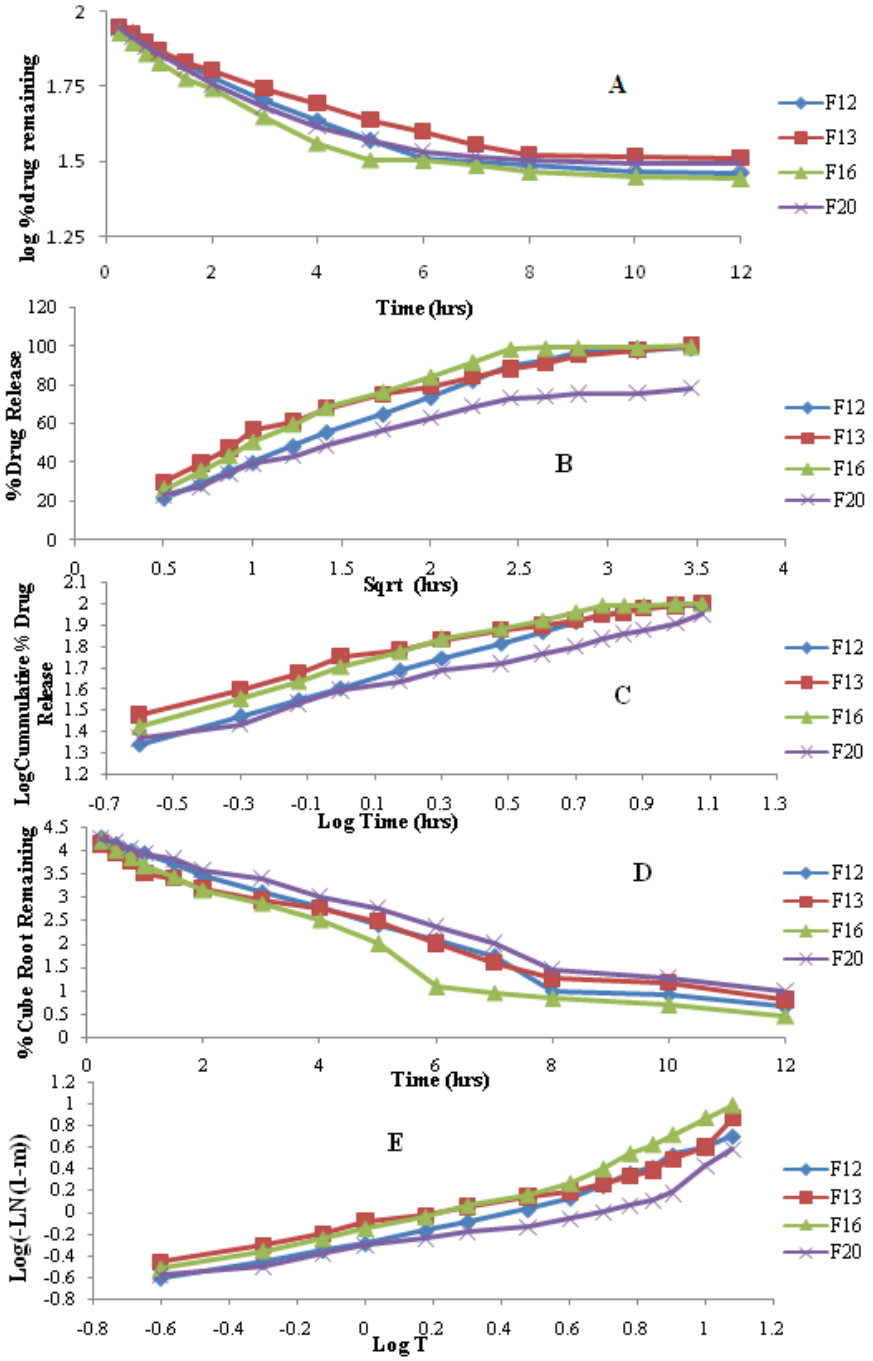

Fig. 4: Model dependent Release Kinetics of IntR Formulations in Phosphate Buffer pH 6.8 (A) First Order (B) Higuchi (C) Korsmeyer Peppas (D) Hixon plot (E) Weibull Model

6.8, f_2 values were 69.32, 59.26 and 74.12 at pH 1.2, 67.02, 58.15 and 71.01 at pH 4.5 and 69.03, 53.70 and 80.34 at pH 6.8. While values of f_1 are summarized in table 5

Statistical evaluation

In this study Tukey's post hoc test was applied using one – way ANOVA to analyze the *in vitro* release profiles of optimized formulations in selected dissolution media and variation within and between the formulations (F12, F13, F16 and F20) is also determined at 0.05 level of significance. F12 was chosen as reference formulation. Results indicated no significant variation within the formulations, as P values were found to be 0.482 (pH 1.2), 0.357 (pH 4.5) and 0.197 (pH 6.8) (table 7). Statistical evaluation was carried out by SPSS 20.0 (SPSS Inc).

Stability test

No physical changes were found during stability studies. Shelf life at accelerated conditions for intermediate formulations F12, F13, F16, and F20, were in order of 34.88, 31.32, 28.76, 33.24 months. Similarly the estimated shelf lives of the optimized formulations after long term studies were found in the range of 33.26 - 38.42 months. Shelf life was calculated by *R*-Gui software version 2.15.2.

CONCLUSION

Intermediate release formulations of DP were successfully developed by rotatable central composite design for IVIVC studies. Hydrophilic polymer methocel K15M effectively control the release for 12 hrs. Placebo and DP formulations were also compared. Physicochemical attributes were assessed and release profiles of optimized formulations were further compared using model dependent and independent methods.

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