Formulation development of intermediate release Nimesulide tablets by CCRD for IVIVC studies

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Abstract: Simple and cost effective study consisting of three steps, comparison of micromeritic properties of different blends i.e. placebo without API and Nimesulide containing, Use of central composite design (CCRD) for intermediate release Nimesulide tablets and stability results of three selected Nimesulide tablet formulations which were calculated by using R Gui. Different concentrations of Avicel, hydroxypropyl methyl cellulose (HPMC) and magnesium stearate were used as variables in central composite design and two types blend i.e., with or without Nimesulide were selected for bulk density, tap density, percentage compressibility; angle of repose and Hausner's ratio. Blending rate constant was performed after applying the different mixing times like 3, 6, 9 and 12 minutes. Twenty intermediate release formulations were designed and three formulations were chosen for compression by direct compression method on the basis of compressibility index. Physicochemical properties and best release pattern in four hours in different dissolution medium were successfully measured. Relative densities, porosity of tablets were compared with tensile strength of tablet and weight variation, hardness, friability and dissolution was performed by simple experiments. Presence of Nimesulide in the bulk increased all micromeratic tests while 9 minutes was best mixing time. The hardness of NM containing tablets increased with the increase of relative density. The release pattern was further analyzed by model dependent i.e. zero order, first order and Higuchi, Korse-meyer and Pappas, Hixson Crowell and model independent kinetic model i.e., f_2 value respectively. R Gui explained the F16 formulation shows the best result in stability studies with shelf life 72 months.

Keywords: Micromeritic properties, Intermediate release, central composite design, stability studies, model dependent and independent approaches.

INTRODUCTION

Micromeritic properties of powder blend are considered most important parameters for the tablets quality control tests. True density is considered as fundamental property because it is used not only for the accurate characterization of particle size, mechanical and physical nature of the powders but also used for porosity, hardness, tensile strength and elastic modules of tablets Ryshkewitch *et al.,* 1953; Spriggs *et al.,* 1961; Knudsen *et al.,* 1962). Powders used in different compositions have the different micromeritic properties. Presence of active ingredient and different ratios of the excipients shows the change in relative density, porosity and disintegration. Main problems in these calculations are the uses of the sensitive instruments and complex structure of Active ingredients e.g. crystalline, amorphous structure etc.

Different crystalline forms of active ingredients provide the advantages of formulation development while there are some unfavorable physicochemical properties of dosage form provide the ideas of different modified release pattern. Several examples of the suitability and accuracy of using one crystalline form of API inspite of another one are present in literature (Haleblian J *et al.,* 1969; Rollinger *et al.,* 2002). Nimesulide have the crystalline form and it is quite difficult to predict the compatibility of Nimesulide with excipients. Nimesulide consists of N-(4-Nitro-2-phenoxyphenyl) methane sulphonamide which showed the less compatibility and low solubility with most of the excipients. Furthermore sensitivity of porosimeter also converted the situation more difficult.

Statistical models have great importance in the pharmaceutical drug developments. Full factorial, fractional factorial and central composite designs are extensively used in new drug development as well as in optimized methods. Drawback of using extreme concentrations rather than central one was overcome by selecting the central composite rotatable design (CCRD) (Hanif *et al.,* 2011). Formulae of calculations for maximum, minimum and median values of excipients are reported in table 1 and software generated values are listed in table 2.

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In the present study comparison of micromeritic properties of two types of powder blends i.e., placebo blend and Nimesulide containing blend with intermediate release of NM tablets with successfully analyzed. Central composite design was applied for the new concept of intermediate release directly compressed NM tablet having different concentration of HPMC, Avicel and Magnesium stearate. Release pattern of the NM formulations were analyzed by model dependent and model independent method with the help of Microsoft Excel based program DD Solver. Three best intermediate release formulations were further analyzed on long term stability and results were analyzed by freely available R Gui software.

Table 1: Relationship between coded and actual values of a variable (Box and Wilson, 1951)

Code	Actual value of variable
-β	x_{min}
-1	$[(x_{max} + x_{min})/2] - [(x_{max} - x_{min})/2\alpha]$
0	$[(x_{max} + x_{min})/2]$
+1	$[(x_{max} + x_{min})/2] + [(x_{max} - x_{min})/2\alpha]$
+β	x_{max}

x_{max} and x_{min} maximum and minimum values of x respectively, $\alpha = 2^{k/4}$; k=number of variables (in this study; $\alpha = 1^{3/4} = 1.682$)

MATERILS AND SOFTWARES

Nimesulide was gifted by PharmEvo, Pakistan, microcrystalline cellulose (Avecil PH 102), hydroxypropyl methylcellulose (HPMC) both were purchased from Colorcon Asia Pacific, Singapore and magnesium stearate purchased from local market. All of the other material used in the experiment was analytical grade.

Software used were DD Solver an adds on program in Microsoft Excel and *R* Packages (R Gui 2.13) were used for stability analysis. Central composite was applied from Design-Expert® version 7, Stat-Ease, Inc., Minneapolis

Bulk and tapped densities

Bulk and tapped densities were calculated by using glass cylinders with following equations.

$$P_b = \frac{M}{V_b} \quad (1)$$

$$P_t = \frac{M}{V_t} \quad (2)$$

$$\text{Compressibility index (\%)} = \frac{P_t - P_v}{P_t} \times 100 \quad (3)$$

Where ρ is density of the powder blend while "t" and "b" showed it's tapped and bulk values.

Blending rate constant

Dose uniformity of the tablets was analyzed by using simple experiment of blending rate constant. Thirty (30) tablets from each formulation were selected randomly and assay of 20 tablets were used to calculate the results in the range of 85% to 115% by repeating the experiment three times.

Following equation was used for the calculations of RSD %

$$\text{RSD\%} = \frac{\text{S.D}}{\text{Mean}} \times 100 \quad (4)$$

S.D is the standard deviation.

Preparation of placebo tables

Placebo tablets were prepared by direct compression method on single punch machine (Korasch, Japan). Powder mixture was blended 9min with barrel mixer. Tablets of 330-470 mg weight with different thickness were prepared by taking different concentration of excipients compositions as listed in table 3.

Preparation of nimesulide tablets

Among twenty formulations three F11, F16 and F20 were selected for compression by using single punch machine (Erweka, korasch, Japan) by direct compression technique. Powder of Avicel PH 102 (50-70%), HPMC (5-15%) and Magnesium stearate (1-5%) all were in their acceptable ranges (Rowe RC *et al.,* 2007) and were accurately weight, mixed with tumbler mixer for 9 minutes by and compress tablets by keeping weight constant of 400±70mg.

Measurement of tablet tensile strength

Tablet hardness tester (Tablet Tester, FUJIWARA, Japan) was used for the calculations of crushing load. The tensile strength (T) was calculated using the following equation:

$$\text{T (MPa)} = \frac{2\text{F}}{\pi \text{DH}} \times \frac{1}{1000} \quad (5)$$

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

Relative density

Mass, thickness (cm) and diameter (cm) of the Nimesulide and placebo tablets were calculated by Sartorius weighing balance and vernier caliper respectively (Blanco MJ *et al.,* 2004). Densities and relative densities of tablets were calculated by using equation 6 and 7 respectively

$$P_t = \frac{M}{\pi h d^2 / 4} \quad (6)$$

$$\text{P}_\text{t} = \frac{\text{P tablet}}{\text{P Powder}} \quad (7)$$

Pis the density in gm/cm^3

Porosity of tablets

The percentage porosity of the tablet ε (%) was calculated from the true density ρ (g/cm^3) of tablets and true density of powders ρ (g/cm^3) using the following equation:

$$\varepsilon(\%) = \left(\frac{1-M}{V_p}\right)\times 100 \quad (8)$$

The diameter and thickness of tablet for calculation of tablet volume were measured with a micrometer. The tablet volume was calculated from the diameter and thickness.

Disintegration time

Basket rack USP disintegration time assembly was used for the estimation disintegration time of NM tablets. Water was used as disintegrated medium at temperature of 37±0.5°C.

Dissolution studies

Nimesulide releases patterns were carried out by using a USP dissolution apparatus II (DT 600, Erweka, Japan). Tablets (n=6) were placed gently in USP dissolution apparatus II (Paddle method) having 900 ml of dissolution media at 37±0.5°C with rotating at 100 rpm. Different dissolution medium were 0.1M HCL (pH 1.2) and Phosphate buffer solution of pH 4.5, 6.8, 7.2 used. Approximately 5 ml aliquot of each medium was withdrawn at different time intervals; filtered by 0.45µm syringe filter, equal amount of fresh medium was added and drug concentrations were measured by UV spectrophotometer (UV-1601, Shimadzu, Japan) at 297nm. HPLC method for the estimation of Nimesulide concentration in intermediate release tablets was already reported by Hanif *et al.* (2011).

***In vitro* kinetics**

Model independent approaches

Similarity and dissimilarity factors f_2 and f_1 respectively were calculated by using the following formulas.

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

$$f_2 = 50\times\log\{[1+\left(\frac{1}{n}\right)\sum_{j-1}^{n}|R_t - T_j|^2]^{-0.5}\times 100\} \quad (10)$$

Model Dependent approaches

Followings are the formulae of some model dependent approaches

Zero order release

$$Q = K_o t \quad (11)$$

Where Q is the drug release at time t. K_o is the zero order rate constant and t is the time (Hanif *et al.,* 2011).

First order release

$$\ln Q = \ln Q_o - Kt \quad (12)$$

The drug release at time t is Q; initial drug release is Q_o at time t_0 and K is the first order rate constant.

Higuchi release kinetics

$$Q = K_H t^{1/2} \quad (13)$$

Where k is the release rate constant, t is the time and Q is the drug release.

Hixson and crowell cube root law

$$Q_o^{1/2} - Q_t^{1/2} = K_{HC} t \quad (14)$$

Where Q_o the initial amount of drug in the pharmaceutical dosage form is Q_t is the remaining amount of drug in the pharmaceutical dosage form at time t and K_{HC} is constant showing surface to volume relation.

Korse mayers and peppas model

$$\frac{M_t}{M_\infty} = Kt^n \quad (15)$$

is the fraction drug release ate time t, n is the diffusion exponent, values of 0.5<n<1 for anomalous, n=1 for case II or zero order and n>1 for super case II transport. This model is used for those polymeric dosage forms where drug release mechanism is not well known and more than one phenomenon is involved (Hanif *et al.,* 2011).

Stability studies

Accelerated stability studies for three best selected formulations under the ICH guidelines were performed for six months and the results were analyzed by using R Gui Software (ICH 2003). Lower accepted assay range of intermediate release NM tablets was 93% and shelf life of formulation was calculated.

RESULTS

Micromeritic properties of two types of powder blend i.e. Nimesulide containing and placebo were analyzed and found within pharmacopeial limits. Central composite design was applied for the selection of equal amount of excipients in both cases as shown in table 3. Blending rate constant was found to be 9 minutes. Comparison of Nimesulide containing powder blend with placbo are shown in table 4. All physicochemical properties of tablets were within range as shown in table 5. First order release rate was observed in selected formulations as shown in table 6. Response surface methodological graphs are shown in fig. 1 while Nimesulide release rate in different buffer mediums are shown in figs. 2 to 5.

DISCUSSION

Results revealed that presence of crystalline Nimesulide in the blends changed the micromeritic properties of powder blend similar findings were also reported by Michel *et al.* in 2008 while studying the effect of API in

Table 2: Independent variables with different levels used in formulations

Name	Units	X_{min}	X_{max}	-1	+1	0
Avicel PH 101	%	48.54	75.45	54	70	62
HPMC	%	5.79	14.20	7.5	12.5	10
Mag. Stearate	%	1.31	4.68	2	4	3

Table 3: Formulations according to central composite design and release pattern of NM intermediate release tablets

Formulations	Avicel PH 102 (%)	Mag. Stearate (%)	HPMC K4M (%)	Avicel PH 102 (mg)	Mag. Stearate (mg)	HPMC K4M (%)	Nimesulide (mg/tab)	Tablet (mg)
F11	52.23	2.61	5.12	208.92	10.44	20.48	100.00	339.84
F12	58.07	2.41	11.33	232.28	9.64	45.32	100.00	387.24
F13	59.23	2.41	11.02	236.92	9.64	44.08	100.00	390.64
F14	62.00	2.41	11.00	248.00	9.64	44.00	100.00	401.64
F15	57.69	3.61	13.06	230.76	14.44	52.24	100.00	397.44
F16	54.11	3.25	14.56	216.44	13.00	58.24	100.00	387.68
F17	61.31	3.61	8.17	245.24	14.44	32.68	100.00	392.36
F18	56.85	5.02	12.69	227.40	15.06	50.76	100.00	393.24
F19	59.32	2.41	14.53	237.28	9.64	58.12	100.00	405.04
F20	67.42	4.82	12.53	269.68	19.28	50.12	100.00	439.08

Table 4: Micromeratic properties of powder and physical properties of tablets

Sr. No.	Properties	Placebo	With NM
1	Bulk volume (cm^3)	7	8
2	Bulk mass (gm)	4	4.36
3	True Volume (cm^3)	5.8	6
4	Bulk density (gm/cm^3)	0.57	0.54
5	True density (gm/cm^3	0.68	0.72
6	Car's Index (%)	19.2	25
7	Porosity	0.26	0.23
8	Angle of repose	35.41	36.2
9	Flow rate (min)	0.03	1.82

Table 5: Physicochemical properties of intermediate release NM tablets

Formulations	Friability (%)	Weight Variation (mg)	Hardness (kg)	Disintegration time (minutes)	Porosity of tablet (%)	Tensile strength (N)	Relative density (gm/cm^3)	Thickness (mm)
Limits	< 1	± 5%	3-10 Kg					
F11	0.96	342±1.564	6.23-7.53	5.12	2.5	62.3	12.05	3.56±0.85
F16	0.42	400±2.548	6.52-8.11	6.12	3.45	65.2	12.41	4.12±0.56
F20	0.96	450±1.854	6.51-7.42	6.24	2.40	65.1	14.24	4.89±0.45

physicochemical properties of tablets (Michel *et al.,* 2008).

Increased in bulk density due to decreased void spaces in case of NM containing blend, greater tap density due to crystalline nature of NM which compressed excipients with structured manner, increased flow properties due to NM affinity with magnesium stearate while decreased angle of repose due to affinity of NM with excipients was observed and their difference with placebo were shown in table 4 (Di Martin *et al.,* 2008; Narendra *et al.,* 2005).

The problem of exact amount of API in the Nimesulide formulations was overcome by applying the simple experiment of blending rate constant through assay method. The Relative Standard Deviation (RSD %) was found 14.02, 6.254, 4.023 and 2.123 for 3, 6, 9 and 12 minutes respectively. Among four blending time 9 minutes were the best time for the analysis of accurate amount of NM because RSD% was less than 6% which is the basic criteria for the tablets and capsule dosage form (Rasul *et al.,* 2010). After selecting the blending time the further process of blending was fixed at 9 minutes.

Table 6: *In vitro* model dependent approaches of intermediate release NM tablets

	Zero Order		First Order		Higuchi model		Korsmeyer Peppas			Hixson-Crowell	Weibull model		
	R^2	$K(hr^{-1})$	R^2	$K\ (hr^{-1})$	R^2	$K_H\ (hr^{-1/2})$	R^2	$K\ (hr^{-n})$	n	$K\ (hr^{-1/3})$	R^2	R^2	β
pH 1.2													
F11	0.817	0.278	0.995	0.008	0.973	5.058	0.975	5.784	0.476	0.002	0.997	0.998	1.387
F16	0.930	0.257	0.996	0.006	0.979	4.602	0.975	3.363	0.556	0.002	0.995	0.997	1.126
F20	0.813	0.275	0.995	0.007	0.971	4.969	0.971	5.047	0.497	0.002	0.996	0.996	1.252
pH 4.5													
F11	0.878	0.314	0.951	0.019	0.951	5.959	0.973	23.812	0.248	0.003	0.988	0.999	2.614
F16	0.890	0.302	0.983	0.015	0.961	5.690	0.981	18.391	0.287	0.003	0.996	1.000	1.227
F20	0.884	0.312	0.957	0.018	0.956	5.917	0.976	22.378	0.258	0.003	0.989	0.999	2.618
pH 6.8													
F11	0.921	0.318	0.899	0.037	0.932	6.160	0.973	39.984	0.158	0.003	0.974	0.989	1.125
F16	0.941	0.304	0.957	0.020	0.967	5.798	0.991	26.922	0.220	0.003	0.990	0.997	0.801
F20	0.912	0.316	0.908	0.032	0.938	6.110	0.975	36.645	0.173	0.003	0.976	0.990	1.338
pH 7.4													
F11	0.914	0.299	0.936	0.031	0.928	5.798	0.968	38.468	0.154	0.003	0.969	0.987	0.319
F16	0.915	0.275	0.931	0.014	0.959	5.247	0.973	25.964	0.208	0.003	0.951	0.968	0.384
F20	0.923	0.287	0.915	0.025	0.932	5.533	0.959	35.431	0.161	0.003	0.951	0.968	0.285

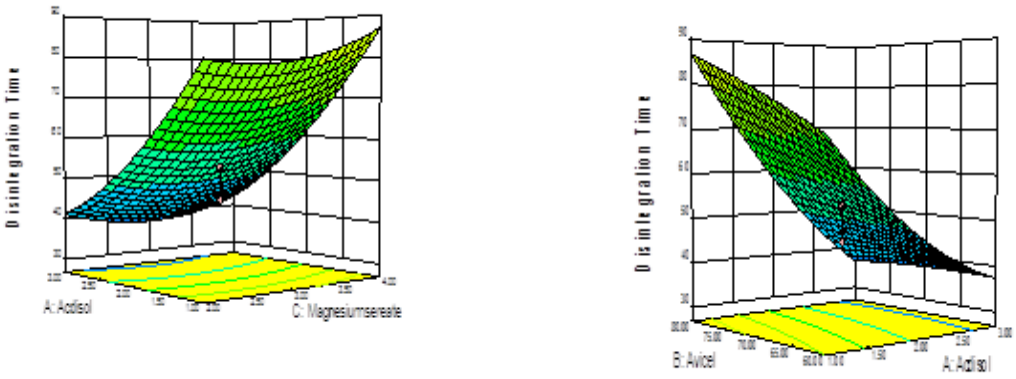

Fig. 1: Effect of different excipients on disintegration time of intermediate release Nimesulide tablets (RSM Presentation)

Concentration of water soluble HPMC showed great importance in all physical parameters like hardness, weight variation, friability and also in drug release pattern in 0.1 M HCL and buffers of pH 4.5, 6.8 and 7.4 with 1% sodium Lauryl sulphate. Three formulations F11, F16 and F20 showed the best release pattern due to HPMC concentration 5, 10 and 12.5% respectively. Response surface methodology graphs shown in fig. 1 cleared the effect of crosscarmellose sodium on disintegration time. Presence of crosscarmellose sodium had direct effect on disintegration time (Korsmeyer *et al.,* 1983).

Prepared tablets of Placebo and Nimesulide were compared by physical properties of tablets like weight variation, hardness, relative density, thickness, friability and disintegration. Hardness and disintegration time increased while friability decreased due to crystalline nature of Nimesulide however other properties almost had negligible change. All physicochemical parameters were within acceptable limits as shown in table 5. Similar results were also reported Hanif *et al.,* in 2011 by explaining the physicochemical properties of immediate release Nimesulide tablets. Tablet tensile strength, relative density and porosity were also found in satisfactory limit as shown in table 3.

Dissolution studies have monotonic nature and were used in the analysis of best optimized formulations like release pattern and comparison with the reference brand. Release of Nimesulide decreased with the increased of HPMC due to matrix formation and increased complexity as shown in figs. 2-5 (Rasul *et al.,* 2010). It was concluded that F16 showed the best results due to adopting all the parameters like physicochemical, quality control and stability studies. The results revealed that model independent approaches are more discriminative as compare to model in dependent approaches.

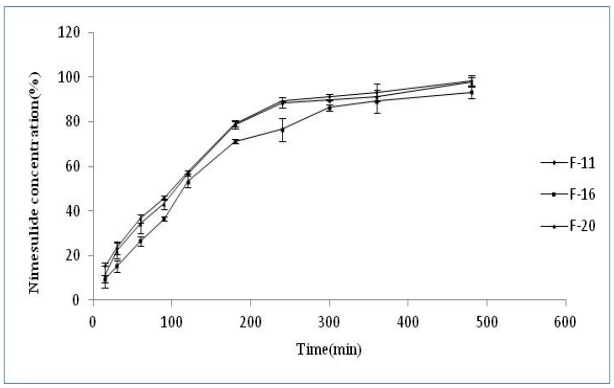

Fig. 2: NM (%) release from intermediate release formulations at different pH 1.2 with 1% SLS (n=6)

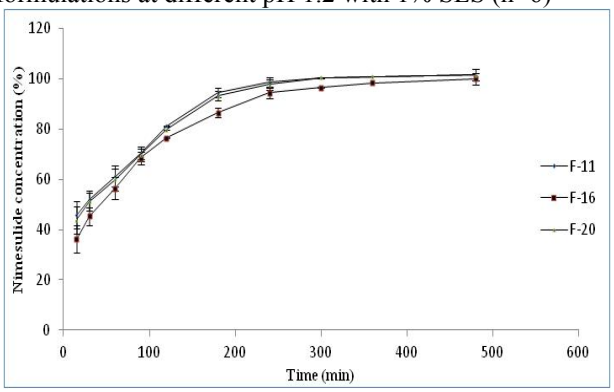

Fig. 3: NM (%) release from intermediate release formulations at different pH 4.5 with 1% SLS (n=6)

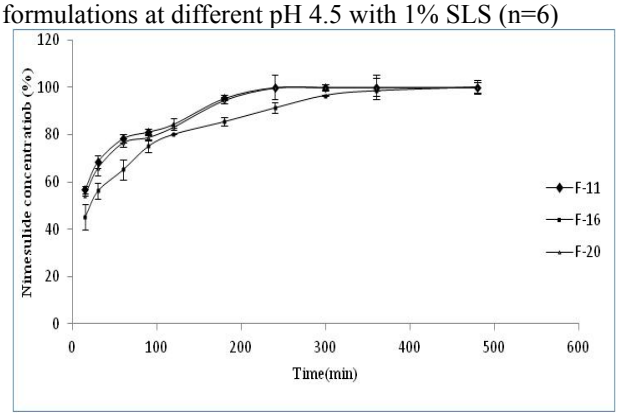

Fig. 4: NM (%) release from intermediate release formulations at different pH 6.8 with 1% SLS (n=6)

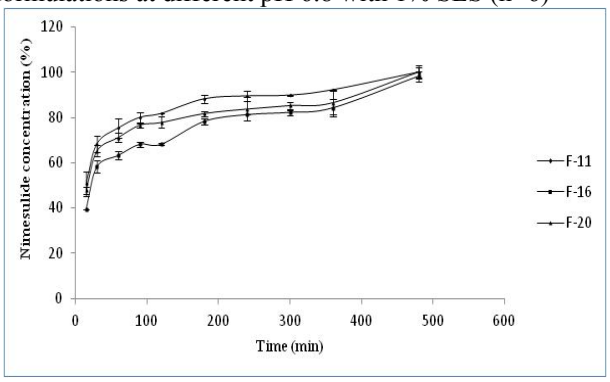

Fig. 5: NM (%) release from intermediate release formulations at different pH 7.4 with 1% SLS (n=6)

Table 7: Model Independent approaches

Similarity	F11	F20
pH 1.2		
f_1 (%)	12.947	10.005
f_2 (%)	55.466	59.672
pH 4.5		
f_1 (%)	6.331	5.167
f_2 (%)	62.965	67.337
pH 6.8		
f_1 (%)	8.999	7.445
f_2 (%)	53.579	57.521
pH 7.4		
f_1 (%)	13.042	7.531
f_2 (%)	50.059	60.188

Intermediate release formulation's (F11, F16 and F20) results of zero order and first order regression values were 0.817 to 0.930 and 0.995 to 0.996 in dissolution medium of pH 1.2, phosphate buffer pH 4.5; r^2 were 0.878 to 0.890 and 0.951 to 0.983, in slightly acidic pH 6.8 the results were 0.912 to 0.941 and 0.899 to 0.957 while 0.914 to 0.923 and 0.915 to 0.936 was calculated in slightly alkaline pH 7.4 respectively (see table 6). Dash *et al.,* in 2010 established relationship between models and geometry of dosage forms after calculating the regression values (Dash *et al.,* 2010).

Higuchi model the r^2 values were 0.971 to 0.979 at acidic pH 1.2, 0.951 to 0.961 with phosphate buffer pH 4.5, 0.932 to 0.967 with alkaline pH 6.8 and 0.928 to 0.956 at pH 7.4. Results revealed that values of zero order, First order and Higuchi regression values are near to 0.951 and Intermediate Nimesulide showed first order release at lower pH but zero order at higher pH like 6.8 and 7.4. Values of n in Korsmeyer and Peppas less than 0.45 and showed Fickian diffusion controlled due to presence of matrix forming hydrophilic polymer HPMC. Values of β in case of Weibull model were greater than 1 and sigmoid shape was observed. Sathe *et al.* in 1996, Polli *et al.* in 1996 and Yuksel *et al.* in 2000 also explained shape factor of drug release with help of Weibull model (Sathe *et al.,* 1996, Polli *et al.,* 1996, Yuksel *et al.,* 2000).

Similarity factor of F11 and F20 after comparing with F16 (which was selected as a reference formulation due to its excellent physicochemical properties) was 55.462 and 59.672 in pH 1.2, 62.695 and 67.337 in pH 4.5, 53.579 and 57.521 in pH 6.8 and 50.059 and 60.188 in pH 7.4. Similarly difference factor of F11 and F20 after comparing with F16 were 12.947 and 10.005 in pH 1.2, 6.331 and 5.167 in pH 4.5, 8.999 and 7.445 in pH 6.8, 13.042 and 7.531in pH 7.4 (see table 7). Liu *et al.,* in 1997 also reported similarity and dissimilarity comparison of dissolution profile (Liu *et al.,* 1997). Similar reports were also described by Harris *et al* discussing the matrix release of HPMC formulation of famotadine which had

the Fickian release pattern due to matrix forming nature of HPMC.

Accelerated stability studies of three selected intermediate release tablets of NM were performed for 24 months. All the physicochemical tests like disintegrating time, friability, hardness, weight variation, dissolution and assay were within the limit. Shelf life of three selected formulations was estimated by R Gui and was found 74 months (Muhammad *et al.,* 2010).

CONCLUSIONS

Intermediate release Nimesulide tablets were successfully optimized after using the central composite rotatable design. Micromeritics studies of planned formulation made easy for selection of those formulations which were compressed by single punch machine. Comparative studies between placebo and drug containing formulations were applied. Physicochemical and quality controlled studies were performed and results were further optimized by model dependent and model independent approaches.

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