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Study of Influence of Formulation Variables on Drug Release: Optimization of Sustained Release Matrix Tablets of Metoclopramide HCl Using Central Composite Experimental Design

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Abstract

Metoclopramide Hydrochloride (MCP), has a short half-life. In order to maintain therapeutic levels in blood, it administered in dose of 10-15 mg four times a day. Fluctuation in plasma concentration of drug is commonly observed for drugs that are rapidly absorbed and eliminated when used in long term therapy. This attribute makes metoclopramide a suitable candidate for controlled release delivery. In this work HPMC K4M was used as release rate controlling polymer for the development of controlled release tablet formulation. Experimental Design using CCRD was utilized to determine the influence of varying the concentration of different variables such as polymer and diluents on the release behavior of the drug from matrix tablets and optimization of formulation. Different SR formulation prepared were designed and optimized with the help of software Design Expert® version 10.

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Using Central Composite Rotatable Design (CCRD), fifteen formulations were selected and prepared using HPMC K4M, Avicel PH-102 and Lactose DC as variables. All the trial formulations were evaluated using different pharmacotechnical tests including hardness, friability, disintegration, dissolution. Online Dissolution apparatus type II and 900 ml different dissolution media in the pH range 1-6.8 and distilled water for dissolution. The drug release was studied by applying the dissolution models by DDSolver® software. Hixson-Crowell model was best fit to the F13 SR formulation. The CCRD experimental design was successfully used in optimization of sustained release Metoclopramide HCl formulation.

Keywords: Metoclopramide HCl (MCP); Sustained Release; Optimization; CCRD; Model Dependent approaches; Swelling and Erosion; Stability Study.

1. Introduction

Metoclopramide HCl (MCP), a freely water-soluble drug, acts as dopamine receptor antagonist. The relative shorter plasma half-life of about 5-6 hours requires small dose of 15-20mg peroral to be administered 3-4 times a day [23]. This frequent dosing to overcome plasma level fluctuation, results in extrapyramidal effects. The relatively small dose, rapid absorption from intestine, undesirable side effects and shorter half-life forms strong basis to develop sustained release formulation of Metoclopramide. Metoclopramide is affected by hepatic first pass metabolism which discourages its selection as candidate for sustained release formulation [18]. Modified release dosage forms offer an effective means to optimize the bioavailability and plasma drug levels, which other-wise results in various problems. Controlled release drug delivery System is one of such attempts being made to achieve; control over drug release, drug concentration at target site and optimization of therapeutic effects by controlling drug release, dosing frequency and improved patient compliance. Such sustained release behavior of the formulation would obviate the secondary effects of the metoclopramide on the central nervous system normally encountered with the administration of immediate release formulations. It along with decreasing the number of doses improves the patient compliance [32]. Hypromellose or hydroxyl propyl methyl cellulose (HPMC) is an odorless, colorless white, fibrous or powder material which is stable at large pH ranging from 3-11 [1]. HPMC is a multi-purpose material available in various grades and viscosities which are used in different concentrations in formulations for different purposes i.e. coating agent by (Sangalli and his colleagues 2004).Avecil is commercially available in different particle sizes and moisture grade. Due to variable properties Avicel applications ranges from disintegrant and lubricant depending on the case [1]. The aim of this study was to evaluate the effect of both the diluents and polymer on the drug release behavior and optimization of Metoclopramide HCl from matrix SR oral tablets using CCRD optimization technique.

2. Materials and Methods

2.1. Materials

Metoclopramide HCl (standard obtained from Shaigan Parma (Pvt) limited Pakistan), Avicel PH-102 - (FMC Biopolymer, Philadelphia), Magnesium Stearate (Dow Chemical Co., USA), HPMC K4M cps (Dow chemical Co., US). All glass wares like Beakers, Funnels, Volumetric Flasks, Pipettes, Graduated Cylinders (Pyrex, England).

2.2. Design of the formulations by CCRD

To formulate the tablets RCCD (Rotatable Central Composite design) was used. The Design Expert® (Version 10, Stat-Ease Inc., Minneapolis, MN) was used for the performance of statistical analysis. Ranges of three independent factors used were (X1) HPMC K4M (15%-50%), (X2) Avicel PH-1O2 (15%-40%), (X3) Lactose DC (15%-45%). Disintegration time (R_1) hardness (R_2), friability (R_3) and dissolution (R_4) were taken as response variables. Formulations were selected on random basis and the results obtained were evaluated as shown in the table below[2, 3].

Table 1: Independent variables and levels

Independent variables (Factors)	Levels		
	-α	0	+α
A; Amount of HPMC K4M (%)	15	32.5	50
B; Amount of AvecilPH102 (%)	15	27.5	40
C; Amount of Lactose DC	15	30	45

2.3. Preparation of SR Metoclopramide HCl tablets

Direct compression method was used after mixing the powder for about 10min in ERWEKA® motor drive type AR 403 which is a main drive for ERWEKA® world-wide known all-purpose equipment, to compress the target weight with punches having round shape.

2.4. Evaluation of SR Metoclopramide HCl tablets

All the tablets formulations compressed were subjected to assess for different pharmacopoeial characteristics including hardness [4] , friability [4], disintegration time, disintegration [5]. The drug release of Metoclopramide HCl tablet formulations was evaluated by using USP [5] official method. All the measurements were made automatically by software Disso.net at λ = 309 nm.

2.5. Model dependent approaches

To compare different formulations model dependent approaches are frequently employed and also used in optimization process due to differences in release mechanism. The model dependent approaches applied are reported in literature [6, 7]. Hixson-Crowell cube root model [7-9]Korsmeyer-peppas model [7, 10].

3. Results

Among fifteen possible combinations the blended mixtures of each runs were selected randomly on the basis of

target tablet weight i.e. 200mg given in the table below.

Table 2: Trial Metoclopramide Formulations Derived from DE using Central Composite Model

Run	HPMC K4M (%)	Avicel PH102 (%)	Lactose DC (%)	HPMC K4M (mg)	Avicel PH102 (mg)	Lactose DC (mg)	Mg. Stearate (mg)	MCP (mg/tablet)	Total weight (mg/tablet)
10	50	15	45	100	30	90	5	30	255
13	15	27.5	30	30	55	60	5	30	180
14	15	15	45	30	30	90	5	30	185

Compressed formulations were subjected to physicochemical evaluations represented in table 3.

Table 3: Physicochemical Tests of Metoclopramide Formulations

		Hardness (Kg±SD)	Friability (%)	Disinteg. Time	Shelf Life
Limits [5]		7-9 Kg	<1%	(min)	(months)
SR	F10	7.62±0.215	0.57	236	60
	F13	8.60±0.113	0.20	258	66
	F14	7.95±0.223	0.33	225	57

Response surface methodology graphs are sown in figure. 1(a, b, c, d).

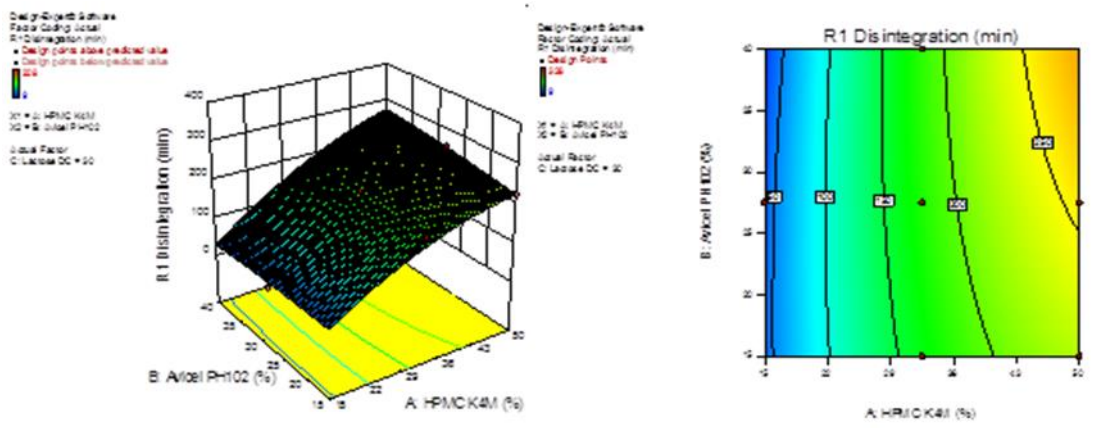

Figure 1a: Response surface plot for disintegration time A: 3D surface plot, B: contour plot

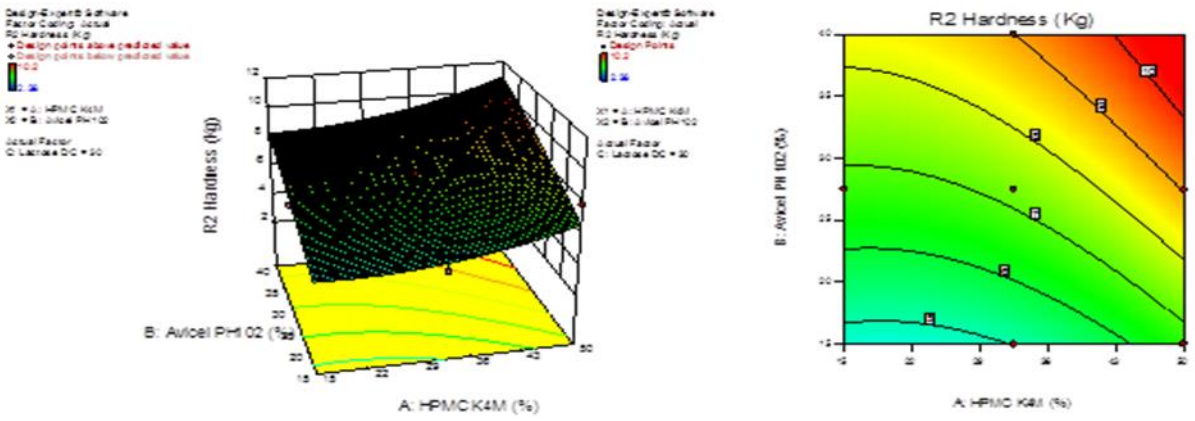

Figure 1b: Response surface plot for hardness A: 3D surface plot, B: contour plot

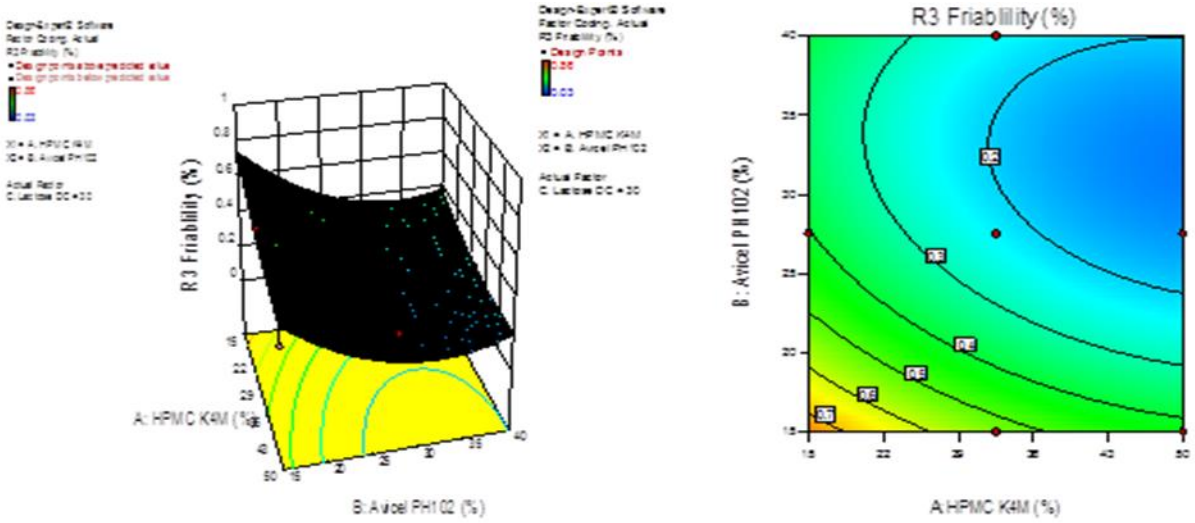

Figure 1c: Response surface plot for friability A: 3D surface plot, B: contour plot

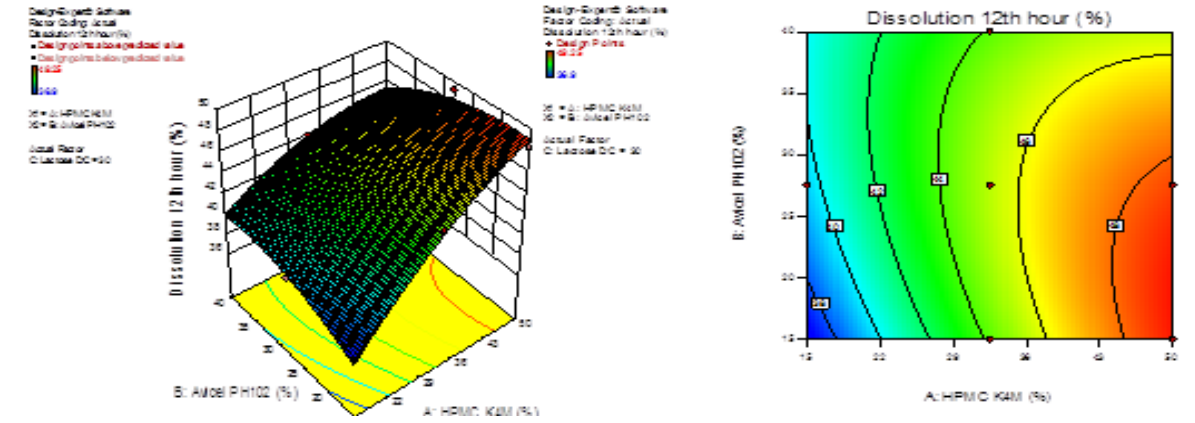

Figure 1d: Response surface plot for Dissolution (%) at 12th hour A: 3D surface plot, B: contour plot

The friability results are shown in table 4.

Table 4: In Vitro Model Dependent Kinetic Studies of Metoclopramide HCl SR Tablets in Different Media

	Zero Order Model		First Orders Model		Higuchi Model		Hixson-Crowell Model		Korsmeyer –Peppas Model		
	R^2	K_0 (h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H ($h^{-1/2}$)	R^2	K_{HC} ($h^{1/3}$)	R^2	n	K_{KP} (h^{-n})
Dissolution Medium 1: SR in 0.1NHCl (pH 1.2)											
F-10	0.8662	4.484	0.8565	0.485	0.9779	27.1123	0.9804	0.0752	0.9186	0.4223	20.5238
F-13	0.8703	4.606	0.8670	0.356	0.9855	18.2124	0.9901	0.0503	0.9208	0.5129	18.2347
F-14	0.8647	3.451	0.8612	0.338	0.9708	22.1358	0.9755	0.0555	0.9004	0.4557	15.7345
Dissolution Medium 2: SR in Phosphate Buffer pH 4.5											
F-10	0.8377	3.600	0.8106	0.421	0.9622	12.3219	0.9752	0.0347	0.9766	0.5003	26.3210
F-13	0.8450	4.652	0.8469	0.451	0.9690	10.5620	0.9887	0.0571	0.9852	0.5195	32.9803
F-14	0.8334	3.603	0.8257	0.413	0.9440	7.8346	0.9788	0.0438	0.9829	0.5125	26.2206
Dissolution Medium 3: SR in Phosphate Buffer pH 6.8											
F-10	0.8671	3.571	0.8456	0.510	0.9122	21.3210	0.9654	0.0605	0.9454	0.4863	40.5096
F-13	0.8809	4.605	0.8673	0.495	0.9156	19.8324	0.9848	0.0506	0.9667	0.5006	48.7022
F-14	0.8725	3.542	0.8605	0.424	0.9053	26.0872	0.9780	0.0414	0.9589	0.4903	43.4434
Dissolution Medium 4:SR in Distilled Water											
F-10	0.8408	3.126	0.8111	0.422	0.9457	15.5679	0.9783	0.0629	0.9403	0.4886	44.3456
F-13	0.8654	4.147	08153	0.466	0.9558	13.6305	0.9925	0.0333	0.9452	0.4958	47.2212
F-14	0.8556	2.128	0.8067	0.453	0.9502	11.7322	0.9804	0.0401	0.9308	0.3787	38.3321

Disintegration time of SR was calculated (table 3). The fig. 1a-1d shows the Response Surface Plots and contour plots. Multiple point dissolution of all the SR formulations was performed in different dissolution medium as represented in figures. 2a-2d.

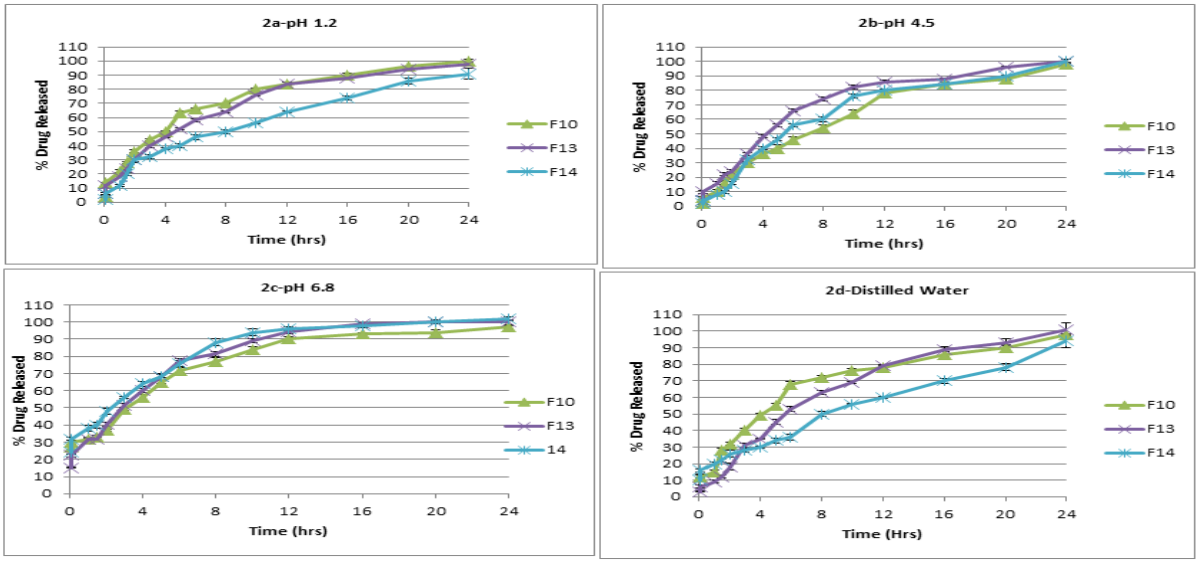

Figure 2: (a-d): Percentage Release of Metoclopramide HCl from SR Tablets at pH 1.2, 4.5, 6.8 and Distilled Water (n=12)

Table 5: Analysis of variance for disintegration

Source	*Sum of Squares*	*df*	*Mean Square*	*F Value*	*p-value Prob> F*	
Model	1.470E+005	9	16330.17	23.29	0.0015	significant
A-HPMC K4M	1.014E+005	1	1.014E+005	144.55	< 0.0001	
B-Avicel PH102	752.34	1	752.34	1.07	0.3477	
C-Lactose DC	6273.72	1	6273.72	8.95	0.0304	
AB	1754.47	1	1754.47	2.50	0.1745	
AC	3439.11	1	3439.11	4.90	0.0776	
BC	183.16	1	183.16	0.26	0.6310	
A^2	2507.90	1	2507.90	3.58	0.1172	
B^2	45.41	1	45.41	0.065	0.8093	
C^2	1355.52	1	1355.52	1.93	0.2231	
Residual	3505.82	5	701.16			
Cor Total	1.505E+005	14				

Table 6: Analysis of variance for Hardness

Source	*Sum of Squares*	*df*	*Mean Square*	*F Value*	*p-value Prob> F*	
Model	70.37217	9	7.81913	7.221798	0.021171	significant
A-HPMC K4M	11.59386	1	11.59386	10.70816	0.022141	
B-Avicel PH102	34.31932	1	34.31932	31.69754	0.00245	
C-Lactose DC	2.834052	1	2.834052	2.617548	0.166612	
AB	0.234173	1	0.234173	0.216284	0.661437	
AC	1.006224	1	1.006224	0.929355	0.379306	
BC	2.076211	1	2.076211	1.917602	0.224729	
A^2	1.078687	1	1.078687	0.996282	0.364036	
B^2	0.154013	1	0.154013	0.142247	0.721535	
C^2	8.778887	1	8.778887	8.108235	0.035929	
Residual	5.413562	5	1.082712			
Cor Total	75.78573	14				

The results of kinetic studies are shown in (table 4). The tables 5-8 show the analysis of variance for

disintegration, hardness, Friability and dissolution respectively.

Table 7: Analysis of variance for Friability

Source	*Sum of Squares*	*df*	*Mean Square*	*F Value*	*p-value Prob> F*	
Model	0.89	9	0.099	9.83	0.0108	significant
A-HPMC K4M	0.14	1	0.14	13.93	0.0135	
B-Avicel PH102	0.19	1	0.19	18.45	0.0077	
C-Lactose DC	0.097	1	0.097	9.64	0.0267	
AB	6.553E-003	1	6.553E-003	0.65	0.4568	
AC	0.089	1	0.089	8.81	0.0312	
BC	0.100	1	0.100	9.89	0.0255	
A^2	6.810E-003	1	6.810E-003	0.68	0.4486	
B^2	0.073	1	0.073	7.26	0.0431	
C^2	5.022E-004	1	5.022E-004	0.050	0.8322	
Residual	0.050	5	0.010			
Cor Total	0.94	14				

Table 8: Analysis of variance for Dissolution % at 12^{th} hour

Source	*Sum of Squares*	*df*	*Mean Square*	*F Value*	*p-value Prob> F*	
Model	221.76	9	24.64	20.82	0.0019	significant
A-HPMC K4M	172.88	1	172.88	146.11	< 0.0001	
B-Avicel PH102	0.020	1	0.020	0.017	0.9019	
C-Lactose DC	0.21	1	0.21	0.17	0.6932	
AB	20.63	1	20.63	17.44	0.0087	
AC	3.24	1	3.24	2.74	0.1590	
BC	2.26	1	2.26	1.91	0.2254	
A^2	5.28	1	5.28	4.46	0.0884	
B^2	3.72	1	3.72	3.15	0.1363	
C^2	0.93	1	0.93	0.79	0.4152	
Residual	5.92	5	1.18			
Cor Total	227.68	14				

4. Discussion

Optimization technique was employed to prepare 15 formulations. Out of fifteen designed formulations one SR formulations (table 2) was selected having three variables. Central Composite Design was also effectively used for the optimization of formulations [11-13]. Rotthauser and his colleagues in 1998 used Central Composite Design for optimization of effervescent tablet formulation to evaluate the effect of lubricants and compressional force on physical characteristics of these tablets [2]. Magnesium Stearate (5%) was kept constant for all formulations. The description of the effect of formulation factors on the responses with the help of empirical models (linear and quadratic) is one of the major advantages of the response surface design [14]. The three-dimensional response surface plots and the contour plots are portrayed in figs. 1 (a, b, c). These plots show that

effect of two factors on a response at the same time, showing increase in the disintegration time with the increase of HPMC and MCC with only a little effect on the overall hardness and friability of the tablets. Different quality attributes of all the compressed trial formulations such as, hardness, disintegration time and dissolution were evaluated according to the USP specifications [15]. The results are shown in table 3. Nyqvist and his colleagues in 1982 also evaluated the physicochemical properties of tablets prepared by using Avicel PH 102, HPMC K4M and magnesium Stearate as excipients showed excellent physicochemical properties [16]. All the SR formulations were compressed with good hardness having the values of 8-10 kg, and friability was also found less than 1% (table 3)[17]. Shah and his colleagues in 2011 prepared fast dissolving Metoclopramide tablets using crospovidone, croscarmellose sodium and sodium starch glycolate by direct compression method and performed pharmacopoeial quality assessment tests. The hardness and % drug contents were in the range of 8-10 Kg/cm² and 98.54% to 101.23% respectively while % friability for all the formulations was found to be within limits (<1) [18]. The disintegration time of trial formulations were also found to be within limits. SR formulation took more than four hours to disintegrate (table 3). In SR formulations, presence of polymer HPMC K4M in the concentration of 22-43.46% increased the disintegration time (table3). During the development of formulations, dissolution testing can help in the selection of excipients as well as optimization of the manufacturing process and enable formulation of the test product to match the release of the reference product [19]. In vitro dissolution test is performed to measure the amount of drug released into the dissolution medium within specified time. [20]. In the present study multiple point dissolution test of Metoclopramide HCl was conducted in four different dissolution media i.e. 0.1 N HCl, phosphate buffer pH 4.5, 6.8 and distilled water (fig. 2-5). SR formulations (F10, F13, F14) containing higher concentrations of HPMC K4M (40-48%) F13 showed further decrease in the overall drug release rate compared to the rest of the two (figs. 2a-2d). Tandya and his colleagues in 2007 reported list of polymers which can be used in controlled release formulations [21].

4.1. Model dependent approaches

In order to describe the drug release from Metoclopramide HCl to get optimized formulation (SR) various mathematical model like Zero Order, First Order, Higuchi's equation, Hixson-Crowell and Korsmeyer&Peppas were applied to the in vitro release data obtained in various dissolution media (0.1N HCl, phosphate buffer pH 4.5, 6.8 and distilled water). Criterion of selecting the most appropriate model was based on the best goodness of fit. Correlations (R^2) of individual batch with applied equations are given in table 5. The release rates were calculated from the slope of the appropriate plots and regression coefficient was determined (tables 4). When SR formulations were subjected to Zero Order model, the values of R^2 in 0.1N HCl, pH 4.5 and 6.8 and distilled water came out to be very poor (see tables 4).SR formulations are showing higher values for all the test media i.e. 0.1N HCl, pH 4.5 and 6.8 and distilled water and showing better compliance than other formulations with Zero Order model. Reddy and his colleagues (2003) reported that once-daily sustained-release matrix tablets of HPMC K4M based Nicorandil did not follow zero order release pattern [22]. The First order describes that the rate of drug release from systems is concentration dependent. The SR formulations are not following First Order release pattern. Hassan and his colleagues in 2003 reported similar results (0.987) for the Metoclopramide HCl tablets [23]. Mandal and Pal (2008) reported that the formulations of metformin HCl formulated using different grades of HPMC (HPMC K4M, K15M, K100M) did not follow first order release pattern [24]. However, the coefficient of correlation values of F10 and F14 formulations were comparatively lower than that of F13

formulations as presented in tables 5. Similar Higuchi kinetics were reported by Merchant and his colleagues in 2006 in the preparation of once daily tablet formulation of cefpodoxime from HPMC by direct compression [25]. Another study by Shoaib and his colleagues in 2010 reported R^2 values of 0.988 for slow release formulation Famotidine HPMC K4M matrix [26]. Abdel-Rahman and his colleagues in 2009 prepared HPMC based matrix tablets of Metoclopramide HCl and reported the R^2 values 0.998 [27]. Hassan and his colleagues in 2003 reported similar Higuchi findings (R^2 = 0.9929) and found it best fit for the release data of Metoclopramide HCl controlled release tablets [28]. The SR Metoclopramide HCl formulation (F13) was observed to show best linearity and compliance with Hixson-Crowell model. The value of R^2 were found out to be 0.999 (0.1NHCl), 0.995, (phosphate buffer pH 4.5), 0.990 (phosphate buffer pH 6.8) and 0.996 (distilled water). Whereas the value of R^2 for intermediate and immediate formulations in the same media was comparatively lower than that of slow release formulations (tables 5). Similar findings were reported by Shoaib and his colleagues in 2006 prepared Ibuprofen HPMC matrix tablets and obtained R^2 value of 0.996 [29]. In another study, Sankar and his colleagues in 2010 also obtained similar results i.e. R^2 = 0.9999 for zidovudine HPMC matrix tablets [30, 31]. To find the drug release mechanism the in vitro release data were applied to Korsmeyer-Peppas model (KorsmeyerPeppas, 1983). The corresponding plot of log cumulative % drug release vs time for all the trial formulations indicated good linearity as mentioned in table 5. Similar R^2 results (0.9959) were obtained by Radhika and his colleagues 2005 using HPMC as polymer in glipzide tablets formulation development [32]. The value of release exponent (n) for SR formulations was following non-Fickian diffusion or anomalous release pattern (table 4). Venkatesh and his colleagues in 2010 used HPMC as polymer in the preparation of Prochlorperazine Maleate Sustained Release Tablets and found n values less than 0.5 [33]. In another study Korsmeyer–Peppas Model was applied to HPMC polymer based Metoclopramide tablets by Shiyani and his colleagues in 2008, the value of n was 0.266 showing Quasi –Fickian diffusion [34, 35].

5. Conclusion

By applying optimization technique different formulations of Metoclopramide Hydrochloride with varying release rates were developed. Multiple point dissolution studies using different dissolution media such as 0.1 N HCl, phosphate buffer pH 4.5, 6.8, distilled water was performed using USP Dissolution apparatus II (Paddle Method). Models such as Zero Order, First Order, Higuchi Model and Korsmeyer-Peppas Models were used to study the dissolution rate kinetics. The best fit models were Hixson-Crowell for SR formulation F13.

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