Stability and *in vitro* release kinetic studies of cinitapride (1mg) mouth dissolving tablets

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Abstract: Cinitapride has been widely given in gastro-esophageal reflux disease (GERD) and dysphagia due to irregularities of GI motilities. Mouth dissolving tablets were prepared for rapid availability and action of drug. Multi-point dissolution studies were conducted in 0.1 N HCl solution of pH 1.2 and phosphate buffer of pH 4.5 and 6.8. Drug release profile showed higher liberation of cinitapride at lower pH then basic medium (<80%). Formulation containing crospovidone (10%) was found to be optimized trial having excellent quality pharmaceutical attributes. The lowest AIC, highest MSC and regression (> 0.9) values were observed for Weibull kinetics in all dissolution medium reflecting the excellent model fitting for the present study. Accelerated stability testing data showed excellent results of drug assay (>99%) along with physical characteristics indicating the absence of drug degradation as well excipient interaction. The estimated shelf life period of various optimized trial formulations was found in between 33 to 41 months.

Keywords: Cinitapride, tablets, mouth dissolving tablets, biowaiver, *in vitro* kinetics, stability testing.

INTRODUCTION

Orally formulated pharmaceutical drug products have still sustained their popularity and preference by consumers over other dosage forms available commercially. Beyond technical benefits these products deliver precise dose, ease in ingestion and enhanced drug stability resulting in higher patient satisfaction. Despite of the mentioned advantages, mouth dissolving compacts further facilitate the children and elderly age patient facing problems in swallowing and/or having complain of dysphagia (Hannan *et al.,* 2016; Chowdary *et al,* 2014). Bioequivalence studies are found to be an essential requirement for approval of generic drug products from regulatory view point (Andrade, 2015). However, *in vitro* testing approaches could be serve as a valuable tool that demonstrates a reliable substitute for such *in vivo* procedures. The concept of biowaiver investigations have emerged from Biopharmaceutics Classification System (BCS) that has led to the categorization of the chemicals on the basis of intestinal permeability, solubility and rate of dissolution (Benet, 2013). *In vitro* drug dissolution testing is believed to be highly valuable as it reduces the time frame many folds against the lengthy in-vivo drug testing procedures. Furthermore, such *in vitro* methods are a significant part need to be developed for IVIVC (*in vitro-in vivo*) correlation of any medicinal moiety (Tajani *et al.,* 2017). In this regard, different drug governing bodies like FDA and EMEA put additional restrictions to follow the dissolution time profile testing to maintain especially the quality of oral solid pharmaceuticals (FDA, 2000; EMEA, 2000).

Cinitapride is a model drug structurally categorized in benzamide class. It serves as an effective prokinetic agent with remarkable anti-ulcer healing properties. It works by stimulating the mesenteric nerve plexus originating from gastro-intestinal part and hence facilitates the uptake of acetylcholine leading to the propulsive movement of the gastro intestinal tract (Du *et al.,* 2014; Baqai *et al.,* 2013). Cinitapride is therapeutically prescribed to manage clinical conditions including gastro-esophageal reflux disease, irritable bowel syndrome, dyspepsia and problem of abdominal discomfort (Du *et al.,* 2014; Marcelín-Jiménez *et al.,* 2017).

In the present study *in vitro* release pattern of the mouth dissolving tablets (MDT) cinitapride that were prepared through utilizing various concentrations of common superdisintegrants is explored. Drug liberation behavior was observed in variety of dissolution media of 0.1 N hydrochloric acid solution (pH 1.2), phosphate buffer (pH 4.5 and 6.8). The analysis of formulations was done using model dependent and independent based approaches.

MATERIALS AND METHODS

Chemicals

Cinitapride hydrogen tartarate pure and working standard was provided by Morgan Chemicals (Pakistan). Hydrochloric acid, sodium hydroxide pellets, potassium chloride, potassium dihydrogen phosphate were purchased from the local vendors and were of Merck KGaA Darmstadt 6427 Germany. These chemicals were utilized to prepare buffer solution of pH 1.2, 4.5 and 6.8.

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Instruments

USP dissolution paddle apparatus (Rays Pharma Germany), portable pH meter (Thermo Scientific) and UV-visible spectrophotometer model UV 1800 (Shimadzu, Japan) were used for *in vitro* release kinetic testing. Storage chamber was used for keeping of samples drawn periodically for stability testing

Softwares

Software DD-Solver® Adds-In to Microsoft Excel was used to determine the *in vitro* kinetic model constants with regression values of trial cinitapride MDT formulations. Software R-Gui® version 3.1.2 (Stab Package) was utilized to calculate the shelf life duration of optimized cinitapride (1mg) tablets.

Formulation development of cinitapride mouth dissolving tablets

Three batches of cinitapride (1 mg) MDT were developed using different superdisintegrants namely crospovidone (batch I; FC1-FC3), croscarmellose sodium (batch II; FM1-FM3) and sodium starch glycolate (batch III; FS1-FS3). Three formulations were prepared in each batch using the amount of superdisintegrant at 2%, 6% and 10% (Rehman *et al.,* 2018). Characterization of these trial batches was performed according to official procedures (USP, 2012).

Optimization of cinitapride mouth dissolving tablets

On the basis of physico-chemical analysis, formulations (FC2, FC3) containing the crospovidone (6 and 10%) and croscarmellose sodium FM3 (10%) were tagged to be optimized trials of cinitaride MD tablets owing to appropriate percent drug content, rapid disintegration, fast dissolution, and acceptable wetting time

In- vitro release kinetics

Multi point dissolution testing was carried out on six units of formulation trials of optimized cintapride MDT batches (FC2, FC3 and FM3) using eight station paddle apparatus. Dissolution medium including 0.1 N hydrochloric acid (pH 1.2), acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) were prepared as per USP recommendations (USP, 2012). Tablets dissolution was conducted in 500 mL of various medium operated at 50 rpm. Aliquots were drawn at 2, 4, 6 and 10 minutes, filtered and drug release was analyzed by UV spectrophotometer at 266 nm wavelength.

Model dependent analysis

The periodic percent drug release was assessed and fitted to various dissolution models proposed for pharmaceutical oral solid dosages. These models include first order kinetics, Hixon-Crowell model, Higuchi dissolution postulate, Korsmeyer-Peppas model and Weibull drug release kinetics (Bushra *et al*., 2017; Higuchi, 1963; Hixson, 1931; Korsmeyer *et al.,* 1983). The mathematical expressions for above drug liberation models are presented respectively in equation 1-5;

$$\text{Log } Q = \text{Log} Q_0 - \frac{kt}{2.303} \quad (1)$$

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t \quad (2)$$

$$Q = kt^{\frac{1}{2}} \quad (3)$$

$$m = 1 - \exp\left[-\frac{(t-Ti)^{\beta}}{\alpha}\right] \quad (4)$$

$$Mt/M\infty = K_{kp}t^{n} \quad (5)$$

Model independent analysis

The dissolution profile (2, 4, 6 & 10 min) of optimized trials were compared with the best cinitapride MD tablet formulation. Similarity and dissimilarity in the drug release pattern was estimated by calculating f_2 (equation 6) and f_2 (equation 7) factors using software DD-Solver® (Moore and Flammer, 1996)**.**

$$f_1 = \left[\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right] \times 100 \quad (6)$$

$$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{N}\right)\sum(Ri - Ti)^2\right]^{-0.5}\right\} \times 100 \quad (7)$$

Stability testing

Stability studies of cinitapride mouth dissolving tablets were performed as per stability protocol of International Conference of Harmonization (ICH, 2003). Trial formulations (FC2, FC3 & FM3) were exposed to accelerated stability conditions of 40˚±2˚C and 75 ±5% humidity. Tablet units were drawn, tested for physical features (color, smell, and surface quality), disintegration time and assay. Shelf lives of batches were determined through incorporating the assay data obtained during storage period by software R-Gui version 3.1.2 (stab package)

RESULTS

On the basis of physico-chemical analysis, formulations (FC2, FC3) containing the crospovidone (6 and 10%) and croscarmellose sodium FM3 (10%) were tagged to be optimized trials of cinitaride MD tablets owing to appropriate disintegration, fast dissolution, acceptable wetting time and higher values of content uniformity.

Computed adjusted linearity r^2, AIC and MSC values of applied models are presented in table 1. Drug release study showed that the optimized cinitaride trials (FC2, FC3 and FM3) followed Weibull and Korsmeyer-Peppas models. The AIC was also estimated for all models as an additional tool to render the model analysis independent of the number of parameters between models. The lowest AIC 3.582 and highest MSC 11.625 values were observed

in Weibull model that confirms the excellent fitting of the model for present dissolution behavior.

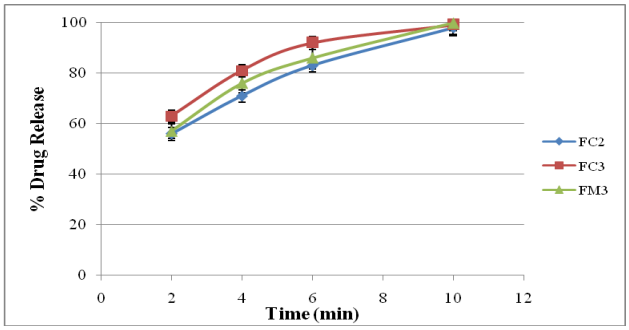

Fig. **1**: Dissolution profile of optimized cinitapride MDT at pH 1.2

The dissimilarity (f_1) and similarity index (f_2) indexes of FC2 on comparison with the best formulation run (FC3) in 0.1 N HCl pH1.2, phosphate buffer pH 4.5 and phosphate buffer 6.8 was respectively appeared to be 8.114, 55.754; 11.045, 50.700 and 10.937, 56.996. $f_1$and f_2 values of FM3 against FC3 was 5.250, 64.904 at pH 1.2, 5.483, 66.075 at pH 4.5 and 7.421, 64.316 at 6.8 correspondingly (table 2).

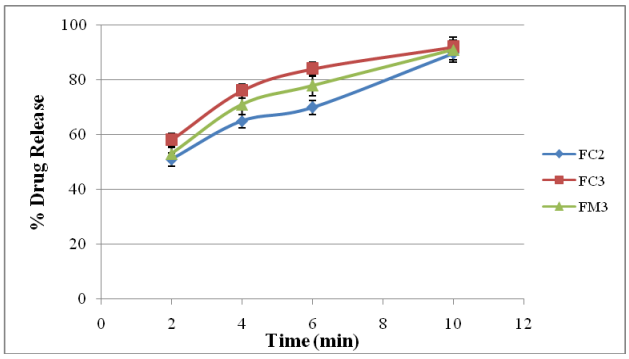

Fig. **2**: Dissolution profile of optimized cinitapride MDT at pH 4.5

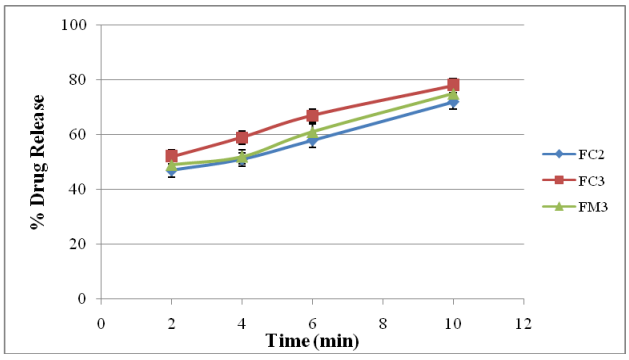

Fig. 3: Dissolution profile of optimized cinitapride MDT at pH 6.8.

From the results of stability testing, it was observed that the selected formulations were highly stable and shelf period of 34 months, 41 months and 33 months were computed for FC2, FC3 and FM3 batches respectively. No change in color, physical appearance, drug dissolution and assay was observed.

DISCUSSION

Cinitapride mouth dissolving tablets were formulated by direct compression using three types of superdintegrants and were optimized. Total nine formulations were designed in such a way that each batch set were comprised of three formulation trials containing crosspovidone (FC1-FC3), crosscarmellose sodium (FM1-FM3) and sodium starch glycolate (FS1-FS3) in concentration of 2%, 6% and 10%. All compressed tablets were subjected to various quality tests. Among all, FC2, FC3 and FM3 formulations exhibited acceptable physico-chemical profile hence labeled to be optimized formulations. The superdisintegrant was a key element responsible for rapid disintegration of drug unit within the oral cavity. This quick disintegration is considered to be a prime requirement of orally disintegrating tablets leading to fast absorption and consequently improved/higher bioavailability.

Dissolution testing is the most vital component in the development and optimization of pharmaceutical products (Zafar *et al*., 2017; Bushra *et al*., 2016). It is also a significant component of various regulatory guidelines establishing IVIVC (*in vitro in vivo* correlation) (Hanif *et al*., 2018). In this study, in-vitro evaluation of cinitapride tablets was carried out for 10 minutes in different dissolution medium. At pH 1.2 (0.1 N hydrochloric acid solution) excellent quantity of cinitapride was released and as well dissolved. However, drug-release profile was declined gradually in phosphate pH 4.5 buffer and found to be minimum in phosphate pH 6.8 buffer (fig.1-3).

Dissolution data was incorporated into various mathematical models including first order, Hixson-Crowell, Higuchi, Korsmeyer-Peppas and Weibull model to determine release pattern. Various researchers had also utilized the similar models to determine the release kinetics in past (Zafar *et al*., 2014; Bushra *et al*., 2017; Khan *et al*., 2011). These dissolution mechanisms are considered to be time series models, explaining the relation of total drug release at different time points. DD-solver software was used to determine the coefficient of regression (r^2) of applied models (Costa and Lobo, 2001). It was observed that optimized trial cinitapride formulations (FC2, FC3 and FM3) were best fitted to Korsmeyer-Peppas and Weibull models at pH 1.2, 4.5 and 6.8. At pH 1.2, the value of r^2 for Korsmeyer-Peppas model were found to be 0.99, 0.94 and 0.98; at pH 4.5 (0.96, 0.94 and 0.97) and at pH 6.8 (0.89, 0.97, and 0.87) for FC2, FC3 and FM3 formulations respectively.

Table1: Application of various In Vitro Dissolution Models

Code	First order			Higuchi			Hixon Crowell			Weibull				Korsmeyer-Peppas			
	K_1 (h−1)	r^2	AIC	MSC	K (h1/2)	r^2	AIC	MSC	KHC (h-1)	r^2	AIC	MSC	A	β	r^2	AIC	MSC	Kkp(h-n)	N	r^2	AIC	MSC
pH 1.2																						
FC2	0.342	0.923	19.167	2.068	33.382	0.838	22.146	1.324	0.090	0.802	22.945	1.124	10089.479	3.346	0.993	8.606	4.709	44.013	0.348	0.998	3.678	6.066
FC3	0.457	0.972	14.101	3.087	35.915	0.387	26.489	0.009	0.119	0.854	20.729	1.430	101.521	2.247	0.999	20.050	11.625	54.332	0.272	0.942	17.391	2.265
FM3	0.379	0.961	16.451	2.767	34.493	0.789	23.293	1.056	0.099	0.865	21.494	1.506	1006.670	2.837	0.981	13.134	3.596	46.544	0.336	0.986	12.647	3.718
pH 4.5																						
FC2	0.258	0.743	23.152	0.860	29.883	0.823	21.663	1.233	0.069	0.500	25.816	0.194	10342.146	3.051	0.936	17.156	2.359	39.321	0.350	0.964	15.587	2.751
FC3	0.368	0.856	20.045	1.442	33.214	0.385	25.865	0.012	0.099	0.612	24.026	0.446	1.401	0.561	0.999	6.215	8.007	50.273	0.272	0.944	16.614	2.300
FM3	0.307	0.857	20.712	1.445	31.626	0.721	23.387	0.776	0.083	0.625	24.562	0.483	2.831	0.797	0.979	12.483	3.502	43.896	0.320	0.979	13.390	3.276
pH 6.8																						
FC2	0.169	0.279	26.550	0.746	24.464	0.473	23.000	0.141	0.046	0.858	28.045	1.119	7019.533	2.587	0.953	12.876	2.672	36.208	0.284	0.891	17.065	1.625
FC3	0.219	0.144	26.237	0.635	27.377	0.283	24.363	0.166	0.058	0.878	28.218	1.130	148.354	1.724	0.995	3.582	5.028	42.241	0.261	0.976	10.986	3.177
FM3	0.182	0.098	26.427	0.593	25.449	0.505	23.238	0.203	0.0497	0.634	28.017	0.991	7690.589	2.658	0.924	15.303	2.187	37.319	0.289	0.876	18.075	1.494

Korsmeyer's explains the relation between log % cumulative drug release and log time. The "*n*" value for optimized trial batches were observed to be 0.261 to 0.350, confirming the Fickian mode of transport (n< 0.45). Drug release has occurred via molecular diffusion due to the chemical potential difference during Fickian transportation. Additionally the regression values of Weibull model were also computed to be higher. These values were 0.993, 0.936, 0.953 for FC2, 0.999, 0.999, 0.995 for FC3 and 0.981, 0.979, 0.924 for FM3 at pH 1.2, 4.5 and 6.8 correspondingly. The details of the above applied models are presented in table 1.

The lowest AIC value (3.582) and the highest MSC value (11.625) of FC3 formulation concludes that Weibull model is the best fit model, explaining the dissolution kinetics (table 1). The MSC is the modification of the Akaike Information Criterion (AIC), commonly employed to opt for the best model fitting when those under consideration do not contain the same number of parameters (Akaike, 1973). The model having the highest value of MSC is considered to be the suitable most among other dissolution patterns (Naqvi *et al*., 2018).

Dissolution profile comparison of FC2 and FM3 was made by f_1 and f_2 analysis taking FC3 as reference formulation due to quality attributes including friability, wetting time, higher dissolution and assay of tablets. f_1 and f_2 analysis is commonly used in drug development process, formulation development and comparative profile analysis (Khan *et al.*, 2013; Şayar *et al.*, 2008). f_1 measures the % difference between two dissolution profiles and f_2 is log reciprocal square-root transformation of the sum of squared errors between two products (Popy *et al.*, 2012). The f_1 and f_2 values of FC2 formulation at pH 1.2 was 8.114, 55.754, at pH 4.5 were 11.045, 50.700 and pH 6.8 were 10.937, 56.996 whereas for FM3 it was 5.250, 64.904 at pH 1.2, 5.483, 66.075 were at pH 4.5 and 7.421, 64.316 were at pH 6.8 (table 2).

FDA emphasizes on stability assessment of newly designed formulations at different climatic conditions to ensure their effectiveness and stability throughout their shelf life. Accelerated stability testing is mostly utilized to determine the shelf life of pharmaceutical products. Various studies documented the changes in physical and chemical properties of drug dosage forms upon exposure to humid environment. Delay in drug release was observed in delavirdine mesylate tablets when exposed to moist atmosphere (Rohrs *et al.*, 1999). In the present study, cinitapride tablets were subjected to the accelerated storage conditions (40±2 °C and 75±5% RH). At defined time intervals samples were taken and subjected to stability characterization tests. No physical change (discoloration, damage, softening etc) was observed in any trial formulation. Results of disintegration test, percent content and percent drug release were also within the defined range, confirming the physiochemical stability

Table 2: Model Independent Evaluation of trial cinitapride MDT Formulations

Batch Code	Similarity Factor (f_2)	Dissimilarity Factor (f_1)	Status
pH 1.2			
FC3 Vs. FC2	55.754	8.114	Analogous Profile
FC3 Vs. FM3	64.904	5.250	
pH 4.5			
FC3 Vs. FC2	50.700	11.045	Analogous Profile
FC3 Vs. FM3	66.075	5.483	
pH 6.8			
FC3 Vs. FC2	56.996	10.937	Analogous Profile
FC3 Vs. FM3	64.316	7.421	

Table 3: Quality attributes of optimized cinitapride formulation during storage conditions

Batch Code	Physical Features	Disintegration Time	Drug Dissolution	Percent Assay
Initial				
FC2	Complies	17	99.50 ± 2.10	100.21 ± 0.33
FC3		13	99.78 ± 1.80	100.97 ± 1.39
FM3		21	97.50 ± 1.81	100.31 ± 0.33
One Month				
FC2	Complies	18	98.06 ± 1.12	99.89± 1.12
FC3		14	98.86 ± 1.09	100.71± 1.12
FM3		23	97.06 ± 1.02	99.89± 1.12
Three Months				
FC2	Complies	20	97.81 ± 0.91	99.47± 2.03
FC3		16	98.51 ± 1.47	100.511± 2.03
FM3		25	96.88 ± 0.98	99.56± 1.87
Six Months				
FC2	Complies	23	96.18 ± 1.24	99.30± 1.21
FC3		18	97.48 ± 1.39	99.82± 1.21
FM3		28	95.98 ± 1.32	99.02± 1.02

of optimized formulations and indicative of API compatibility with the other formulation components as well. The results of stability test are summarized in table 3. Test results were added in R-Gui software to determine the shelf lives of optimized formulations. FC2, FC3 and FM3 exhibited a shelf life of 34, 41 and 33 months respectively.

CONCLUSION

Higher drug release was observed in 0.1 N Hydrochloric acid medium of pH 1.2 with gradual decline of drug in phosphate buffer of pH 4.5 and 6.8. Regression, AIC, and MSC values confirmed that the *in vitro* behavior of drug was very similar to the Weibull and the Korsmeyer-Peppas models. Trial optimized cinitapride mouth dissolving tablets were found to be highly stable with shelf life period of 33-41 months.

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