Formulation design, characterization and optimization of cinitapride (1mg) immediate release tablets using direct compression technology

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Abstract: Cinitapride hydrogen tartarate is relatively a new prokinetic agent that widely prescribed for GERD and epigastric pain. Present study was aimed to develop and optimize cinitapride (1 mg) immediate release (IR) tablet formulation(s) by direct compression using central composite rotatable technique. Overall nine formulations (FC1-FC9) were generated by varying the composition of binder avicel PH 102 (X1) and superdisintegrant crospovidone (X2). The effect of interaction of excipients on hardness (Y1), friability (Y2), disintegration (Y3) and dissolution at 15 min (Y4) were analyzed by RSM plotting. On the basis of physico-chemical evaluation FC3, FC4 and FC6 were found to be the optimized formulations however; FC3 was selected to be the best trial owing to excellent drug release (100.17%) with least friability (0.14%). These IR tablets showed the release pattern similar to the Weibull model with r^2 value of 0.978-0.998. The dissimilarity (f_1) and similarity indexes (f_2) of FC3, FC4, FC6 with the marketed product were estimated to be 2.57 and 76.51, 4.51 and 64.46, 4.32 and 66.78 respectively. Trial optimized formulations were highly stable with the shelf lives of 58-64 months. So, keeping in view the results of present investigation, it is concluded that the technique of manufacturing and optimization is found to be excellent for developing immediate release cinitapride tablets.

Keywords: Cinitapride, immediate release tablets, direct compression, tablet optimization, quality attributes.

INTRODUCTION

Among various means of drug administration, oral drug delivery is found to be the most frequent route due to patient convenience and safety. Tablets are popular solid dosage form being utilized for API delivery worldwide. Tablet formulations can ranged from simple delivery systems to the complex controlled release products (Nagashree, 2015). The label 'immediate release' dosage form is used where the rate of drug release and/or the absorption of drug product, is neither significantly, nor deliberately, retarded by formulation manipulations (Gabrielsson *et al*., 2002). Pharmaceutical industries are now transferring the technology from dry and/or wet granulation to the direct compression (DC) method for tablet manufacturing as DC offers many advantages over other tabletting techniques (Behera *et al*., 2012; Ruiz *et al*., 2012). It overall boost the rapid de-aggregation followed by the fast drug dissolution so making the medicament quickly available for therapeutic effect and thus enhance the patient compliance (de Figueiredo *et al*., 2010; Prabu *et al*., 2010). However; besides the benefits of direct compression technique, it presents many technical issues from manufacturing view point. The selection of excipients and their level/amount play a significant role to make these compacts free from defects like cracks, discoloration, chips and mechanical brittleness during preparation, packaging and transportation (Chatsiricharoenkul *et al*., 2011). Optimization of formulations was through hit and trial in past (Bushra *et al*., 2008) but nowadays is carried out using various mathematical or statistical models comprising of logical runs of excipients and API. Central composite rotatable design is one of the statistical software that based on response surface methodology (RSM) to express the interaction of formulation ingredients (Bushra *et al*., 2014).

Cinitapride is a prokinetic molecule derived from benzamide (4-amino-N-[1-(3-cyclohexen-1-ylmethyl)-4-piperidinyl]-2-ethoxy-5-nitrobenzamide). It is only slightly soluble in water (0.0141 mg/ml), basic (pka = 9.7) and extremely hydrophobic in nature. The salt form of cinitapride (hydrogen tartrate) is highly soluble and bio-available hence successfully utilized in oral formulations. It is a 5-HT4 serotonin receptor agonist with antagonist effects on 5-HT2 and dopaminergic D2 receptors. Clinically it accelerates the tone of the lower esophageal sphincter concurrently with a potent gastrokinetic upshot, and facilitates bowel emptying (Portincasa *et al*., 2009). Officially, cinitapridehas been used in Spain and Latin America since 1990 and lately, in Asia for the treatment of GERD (gastro esophageal reflux), IBS (irritable bowel syndrome) and functional dyspepsia (Du *et al*., 2014; Baqai *et al*., 2013).

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The aim of the present work is to formulate and optimize immediate release cinitapride (1 mg) tablets by direct compression method. Currently, cinitapride immediate release (IR) formulations manufactured by local pharmaceutical companies are insignificant in numbers and majorly imported from international pharmaceuticals that eventually, escalate the cost of the product. In consideration with the above aspects, cinitapride IR trial formulations are aimed to be designed to fulfill the local market needs by cost-effective means.

MATERIALS AND METHODS

Instrumentation

Digital analytical balance (Sartorius, Japan), Ultrasonic cleaner (Elma; America), Tablet testing system PTB 311E version 01,07E (Rays Pharma Germany), Friability tester (Curio FB 2020, Pakistan), Distillation assembly (PLT, Genristo Ltd.), Magnetic stir, USP dissolution apparatus II (Rays Pharma Germany), Portable pH meter (Thermo Scientific) and UV-visible spectrophotometer model UV 1800 (Shimadzu, Japan) using 1cm quartz cells.

Chemicals/reagents

Formulation ingredients cinitapride hydrogen tartrate (API) and the working standard was a gift by the vendor Morgan Chemicals (Pakistan). Excipients including lactose DC (Tabletose, Colorcon Pacific Asia), microcrystalline cellulose (avicel PH102, Mingtia, China), crospovidone (Merck, Germany), colloidal silicon dioxide (Aerosil-200,Evonik), magnesium stearate (Merck, Germany) were procured from the local market. Hydrochloric acid (Merck KGaA Darmstadt 6427 Germany) of analytical grade was procured from the commercial market for formulation testing.

Softwares

In this study, Design Expert ® version 7.0.0, State-Ease, Inc., Minneapolis for formulation development and optimization, DD-Solver® Adds In to Microsoft Excel to assess the drug release patterns, R-Gui® version 3.1.2 (Stab Package) to estimate the shelf life of cinitapride (1mg) immediate release optimized formulation (s), Microsoft Excel and SPSS version 20 (SPSS Inc) were used.

Methodology

Formulation design and optimization of cinitapride immediate release tablets

Various formulation runs were generated by Design Expert software using central composite rotatable design (CCRD) with 2^K factorial design by varying the amount of two formulation variables: X1 avicel PH 102 (filler/binder) and X2 crospovidone (disintegrant). Overall nine formulation combinations (FC1-FC9) with four factorial, three axial and one centre point were produced by making the amount changes at five different levels -1, -α, 0, +1, +α (where α = 1.414). Binder and disintegrant were varied in a concentration of 20-90% (mean 55%) and 2-5% (3.5%) respectively. Lactose DC was also incorporated in the formulation to adjust and compensate the total weight of the tablet to 125mg of all cinitapride IR trial runs. API and the anti adherent/lubricant (colloidal silicon dioxide/ magnesium stearate) were kept constant (table 2). The formulation optimization was performed by evaluating the four response variables: Y1 hardness, Y2 friability, Y3 disintegration time and the Y4 drug release at 15min. Response surface methodology (RSM) was used to explore the interaction of the excipients on the physico-chemical properties of FC1-FC9 tablet batches. Quadratic model was applied to all formulation and response variables and F-value was estimated using the software Design Expert® version 7.0 (Stat-Ease Inc.).

Preparation of immediate release tablets

All powder ingredients were sieved through mesh 20 and then mixed in an empty jar (1kg capacity) manually by tumbling action. Powder blends were compressed through single punch machine having spherical punches of 7mm diameter.

Pre-formulation testi ing

All powder blends were evaluated for the micrometric properties. Powder flow was determined by angle of repose. Hausner's ratio and compressibility index were assessed through tapped and bulk densities of various powder mixtures. The expressions (equation 1 to 3) of above mentioned parameters are:

$$\theta = tan^{-1} = \text{h/r} \quad (1)$$

$$Carr's Index = 100 \times \left(\frac{Tappedbulkdensity - Pouredbulkdensity}{Tappedbulkdensity}\right) \quad (2)$$

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad (3)$$

Quality attribute analysis of immediate release cinitapride (1mg) Tablets

All powder blends with acceptable micromeritic properties were subjected to direct compression. Post compression physical and chemical analysis was carried out as per compendial procedures. Non-pharmacopieal evaluation was also performed including weight variation, thickness and diameter measurement. Friability testing was considered to be one of the major physical attribute of the experimental formulations. Tablet hardness and disintegration time were determined to ensure the breaking and de-aggregation ability of compacts. Dissolution and assay are the significant chemical tests that were carried out by adopting the latest method reported by Rehman and co-workers (Rehman *et al.*, 2017).

Drug release kinetics

Optimized trial formulations (FC3, FC4 and FC6) of immediate release cinitapride (1 mg) tablets were exposed to multi point dissolution testing at physiological pH 1.2. Release pattern of tablet batches were determined at 5, 10, 15, 20 and 30 time interval. Small portion of 5mL sample was drawn, filtered and analyzed by UV spectrophotometer at wavelength of 266 nm. The results were fitted to various dissolution models to observe the drug kinetics. The models (equations 4 to 7) are presented in table 1 (Zafar *et al*., 2018; Bushra *et al*., 2016).

Marketed brand comparison

Directly compressible optimized tablet formulations was compared with the marketed brand using *pair wise analysis* through calculating difference (f_1) and similarity (f_2) factors. These estimations were made by software DD-Solver®**.** The expressions (equation 8 and 9) are as follows (Moore and Flanner, 1996);

$$f_1 = \left[\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right] \times 100 \quad (8)$$

$$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{N}\right)\sum(Ri - Ti)^2\right]^{-0.5}\right\} \times 100 \quad (9)$$

Stability testing

Optimized trial cinitapride immediate release formulations FC3, FC4 and FC6 were subjected to stability testing. Short term stability was carried out by keeping the samples at accelerated conditions as 40˚±2˚C and 75 ±5% humidity (ICH, 2013). Samples were exposed to testing of physical appearance (color, odor, surface quality) assay and dissolution after 1, 2 and 3 and 6 months using the same procedures as mentioned above.

Estimation of shelf life

The assay results obtained during accelerated stability testing period were utilized to estimate the shelf life of optimized trial directly compressible FC3, FC4 and FC6 formulations. R-Gui software version 3.1.2 (stab package) was used for calculation.

RESULTS

The powder blend properties of the trial formulations are given in table 3. The angle of repose, Hausner's ratio and Car's index was found be appropriate for powder blends of various combinations. All cinitapride formulation runs were subjected to compression and were evaluated for quality attributes. Formulations FC1, FC5 FC7 and FC2, FC8, FC9 were rejected due to poor dissolution and higher friability respectively. The detail of quality attributes of the formulations are given in table 4. On the basis of physical and chemical evaluation FC3, FC4, and FC6 were stood to be the optimized formulations. The ANOVA summary of the formulation and response variables is given in table 5 and RSM plots are shown in fig. 1. Drug release kinetic study showed that cinitapride (1 mg) formulations followed the Weibull model (r^2=0.998). However; the square of regression (r^2) values of other kinetic models were given in table 6. The dissimilarity (f_1) index of FC3, FC4 and FC6 when compared with the marketed product was estimated to be 2.57, 4.51 and 4.32 respectively. The similarity index (f_2) of was found to be 76.51, 64.46 and 66.78 correspondingly for formulation trial 3, 4 and 6. Stability studies of selected formulations showed higher shelf life that was estimated to be the 64 months, 58 months and 56 months for FC3, FC4, and FC6 reflecting a very minute decline in the drug content. No change in color, physical appearance, drug dissolution and assay was observed.

DISCUSSION

CCRD is widely used by researchers for formulation and optimization (Ngan *et al*., 2014; Emami *et al*., 2014). CCRD was applied to formulate various trials of cinitapride immediate release tablets by Design Expert software. The rotatability of this design provides lesser runs of all likely formulation variable combinations hence found to be highly helpful for formulation optimization. Presently the formulation trials were generated by varying the quantity of microcrystalline cellulose and crospovidone at five levels of +1, -1, 0, +α, - α. Lactose DC was incorporated to make all tablet formulations to the uniform total weight of 125 mg. As without the addition of lactose DC compression of compacts was not possible owing to very minimum contents of API and additives. Hence avicel PH 102 and lactose DC were used in the range of 6.87-130.65 mg and 00-109.87 mg respectively. Whereas fixed amounts of colloidal silicon dioxide/ magnesium stearate (0.625/1.875 mg) and cinitapride (1 mg) were used to design nine different formulations. The influence of binder and disintegrant were observed on tablet characterization including friability hardness, disintegration and dissolution of drug. Response surface plots are efficient in demonstrating the relation between independent variables and responses. The summary of ANOVA showed that the F values were found to be less than 0.05 for all response variables reflecting the appropriateness of the polynomial quadratic models with regression value (r^2) greater than 0.94. Moreover the terms (excipient) interaction was significant with adequate precision (greater than 4) that measures the signal to noise ratio. If A is binder and B is the disintegrant, the final equation in terms of coded factors for hardness, friability, disintegration and dissolution are presented as; (equation10 to13). More or less similar pattern of interaction and quadratic model values were seen in a study deals with formulation optimization of aceclofenac immediate release (Bushra *et al*., 2014) and intermediate release diclofenac potassium tablets by direct compression (Ali *et al*., 2016)

Table 1: Release kinetic models applied to optimized cinitapride (1 mg) IR formulations

S. No.	Models	Expressions
1	First Order model	$\text{Log } Q = \text{Log} Q_0 - \frac{kt}{2.303}$ (4)
2	Hixon-Crowell Kinetics	$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t$ (5)
3	Higuchi release model	$Q = kt^{\frac{1}{2}}$ (6)
4	Weibull drug release kinetics	$m = 1 - \exp\left[-\frac{(t-Ti)^{\beta}}{\alpha}\right]$ (7)

Table 2: Formulation Combinations of Cinitapride (1 mg) Immediate Release Tablets

Batch Codes	Ingredients per Tablet (mg)		Total weight=125mg		*Total weight=138.875mg	
	Cinitapride Hydrogen Tartrate	Microcrystalline cellulose PH 102	Lactose DC	Crospovidone	Colloidal Silicon dioxide/ Magnesium Stearate	Type of Design
FC-1	1.375	112.5	6.125	2.5	0.625/1.875	Factorial
FC-2		6.875	109.87	4.375		Axial
FC-3		68.75	48.0	4.375		Central
FC-4		68.75	50.649	1.725		Axial
FC-5		112.0	2.375	6.25		Factorial
FC-6		68.75	45.35	7.025		Axial
FC-7*		130.65	0	4.375		Axial
FC-8		25.0	93.625	2.5		Factorial
FC-9		25.0	89.875	6.25		Factorial

Table 3: Powder blend properties of cinitapride (1 mg) trial immediate release formulations

Formulation Batches	Bulk Density g/mL	Tapped Density g/mL	Angle of Repose (θ)	Compressibility Index (%)	Hausner's Ratio
Batch FC-1	0.330	0.390	39	17.50	1.18
Batch FC-2	0.375	0.477	41.5	15.95	1.27
Batch FC-3	0.330	0.390	31.4	9.34	1.18
Batch FC-4	0.319	0.390	35.9	12.26	1.22
Batch FC-5	0.326	0.395	35.9	7.58	1.21
Batch FC-6	0.313	0.40	41.4	13.10	1.28
Batch FC-7	0.326	0.385	32.6	12.34	1.18
Batch FC-8	0.341	0.429	41.5	19.35	1.26
Batch FC-9	0.341	0.417	35.9	6.45	1.22

Table 4: Physico-chemical properties of cinitapride (1 mg) trial immediate release formulations

Formulation Batches	Weight variation (mg)	Thickness (mm)	Friability (%age)	Hardness (Kp)	Disintegrating Time (Sec)	Assay (%age)	Dissolution (%age)
Batch FC-1	124.88 ±1.11	3.65±0.02	0.100	8.0±0.3	115	99.980	80.5
Batch FC-2	125.11±1.52	3.21±0.01	0.950	0.8±0.7	63	99.880	100.55
Batch FC-3	126.46±1.33	3.47±0.02	0.143	6.3±0.2	42	101.330	101.275
Batch FC-4	125.14±0.55	3.52±0.04	0.525	7.2±0.3	60	99.510	95.2
Batch FC-5	125.2±0.85	3.50±0.01	0.330	7.0±0.4	55	99.980	83.86
Batch FC-6	124.87±0.52	3.48±0.02	0.480	4.5±0.2	32	100.250	88.5
Batch FC-7	138.8±0.32	3.95±0.03	0.050	10.1±0.4	120	99.920	75.22
Batch FC-8	126.42±0.24	3.38±0.05	0.850	1.8±0.2	35	100.610	98.5
Batch FC-9	125.22±0.88	3.40±0.02	0.800	1.4±0.5	28	99.780	100.22

Table 5: ANOVA for response surface quadratic model

Parameter	Standard Deviation	R-Squared	% CV	p-value	F-value	Comment
Hardness	1.06	0.960	20.28	0.025	14.69	Significant
Friability	0.053	0.990	11.31	0.0029	12.17	
Disintegration Time	12.15	0.9530	19.80	0.0331	65.03	
Dissolution	3.64	0.946	3.96	0.040	10.62	

Table 6: Regression coefficient values (r^2) of various kinetic models (Optimized formulations)

Code	First order kinetics	Hixon-crowell model	Higuchi model	Weibull model	Best fit model
FC3	0.912	0.945	0.738	0.998	Weibull Kinetics
FC4	0.899	0.925	0.772	0.978	
FC6	0.984	0.979	0.874	0.988	

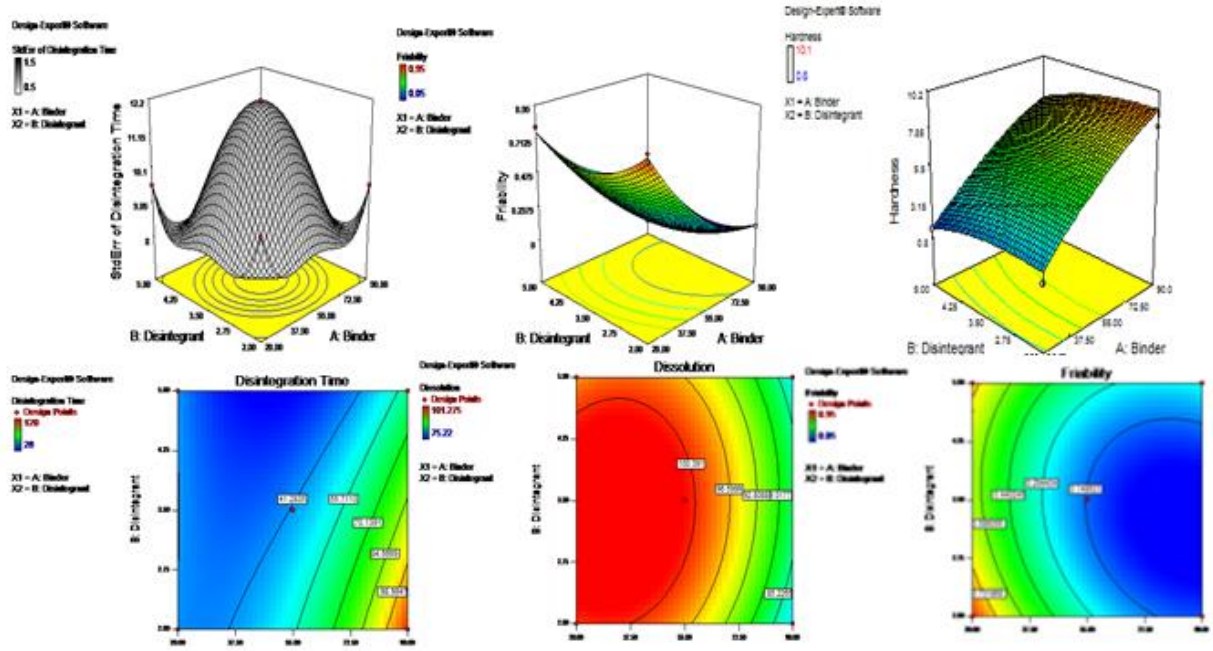

Fig. 1: RSM Plots reflecting the effect of formulation variables on response variables.

Hardness = +6.30+3.12 *A -0.65 *B -0.15 *A*B -0.70*A^2-0.50 *B^2 (10)

Friability = +0.14 -0.31*A+0.015*B+0.070 *A*B+0.18 *A^2+0.18* B^2 (11)

Disintegration Time = +42.00+23.10 *A-13.32 * B-13.25 *A*B+22.50* A^2-0.7 *B^2 (12)

Dissolution = +101.27-8.52*A-0.30*B+0.91 *A* B-6.34 *A^2-4.36* B^2 (13)

It is very important to establish the micromeritic characters of the blends before subjecting to compaction. For this purpose bulk density, tapped density, angle of repose, Hausner ratio and compressibility index were measured. In this work powder properties of various formulation runs were excellent to fair/acceptable flow characteristic and compressibility. Determination of flow behavior of powders is important as various production problems have been observed due to improper flow especially in case of direct compression formulations. Imprecise filling and non-uniform blending are the commonly encountered problems of tabletting (Smewing, 2002). It is well documented that researchers have evaluated the micromeritic properties of solid dosages compression and flow patterns (Qureshi *et al*., 2017). Post compression physical and chemical analysis was carried out as per compendial and non-procedures. Friability testing was considered to be one of the major physical attribute of the experimental formulations. Tablet hardness and disintegration time were determined to ensure the breaking and de-aggregation ability of compacts. Dissolution and assay are the significant chemical tests that were carried out by adopting the latest method reported by Rehman and co-workers (Rehman *et al*., 2017; Rehman *et al*., 2018). The assay results of the present study were found in the range of 99.51-101.33 % that fulfilled the pharmacopieal requirement. Disintegration time of all compressed tablets was found to

be < 3 min. Crospovidone is responsible for the short disintegration time. Similar findings were observed by Flicker and Betz, 2012 while preparing immediate release carbamazepine tablets containing an appropriate percentage of crospovidone (Flicker and Betz, 2012).

Upon characterization FC1, FC5 and FC7 were rejected due to limited drug release. Moreover; FC2, FC8 and FC9 were also tagged to be sub-standard due to poor and borderline limits of friability. Three formulations FC3, FC4 and FC6 were selected to be optimized cinitapride IR trials and even FC seems to be the best formulation owing to higher quality attributes among them.

To determine drug release kinetics, the dissolution data of cinitapride optimized formulations (FC3, FC4, and FC6) were subjected to different mathematical models and equations. The dissolution data was evaluated by first order, Higuchi, Hixon-Crowell and Weibull models as reported for many trials with diverse release patterns (Zafar *et al*., 2018; Ali *et al*., 2016; Bushra *et al*., 2016). The regression coefficients and release constants were estimated by DD-solver (Zhang *et al*., 2010). After analyzing the data through various kinetic models, optimized formulations were found to follow the pattern of Weibull model possessing the coefficient of correlation of 0.978 to 0.998.

Stability testing is an integral part of formulation development process which confirms the quality of product and ensures the patient safety and optimum therapeutic effects (Bajaj *et al*., 2012). The effects of environmental factors and packing components, different storage conditions can be studied with the help of stability studies (Lusina *et al*., 2005). In this work, optimized cinitapride immediate release formulations were assessed for stability as per the recommendations of International Conference on Harmonization (ICH QIA (R2), 2003). The samples were retained at accelerated conditions (40 ± 2^{o}C temperature and RH 75±5%) in blister packing. tablet characterization of kept formulations was performed including hardness, friability, % drug release and assay over a period six months. Stab pack R-Gui software version 3.2.1, (The R Foundation for Statistical Computing) was used to calculate the shelf life of the selected formulations. It is the most frequently used software by the researchers to simplify the complex shelf life calculations (Bushra *et al*., 2016; Ali *et al*., 2014). No physical alterations in color, shape, odor and thickness were noticed and all the results of physicochemical tests were laid within the limits.

CONCLUSION

Cinitapride (1mg) immediate release tablets were successfully developed using simplest combination of excipients by direct compression method. FC3, FC4 and FC6 were found to be the optimized trials on the basis of physical and chemical tablet attributes. Multi point dissolution established that the selected cinitapride (IR) trials have adopted the Weibul kinetic pattern. All optimized formulations were highly stable with estimated shelf life period of 58 to 64 months. Hence these formulations are recommended to proceed for pilot studies in future.

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