Disintegrants combination: Development and optimization of a cefadroxil fast disintegrating tablet

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Abstract: Fast Disintegrating Tablets (FDTs) is a rapidly growing dosage form preferred for special population (pediatric, geriatric and psychotic patients). It is also developed with the aim of improving bioavailability and patient compliance. During the present study, cefadroxil fast disintegrating tablets formulations (n=9) were designed and optimized by central composite design with two independent variables (croscarmellose and crospovidone) using design expert® software. The effects of independent variables on formulation properties such as friability, hardness, *in vitro* dispersion and disintegration were assessed by drawing response surface graphs with design expert® software. Tablets were assessed for pharmacopeial and non-pharmacopeial parameters to ensure the quality of compressed tablets. Among all formulations, F3, F8 and F9 have shown better results. The formulation F9 containing 15mg croscarmellose and 33.075mg crospovidone showed good pharmacotechnical attributes as well as shelf life. F 9 showed improved dissolution with $t_{90\%}$ of> 2 min and will lead to better bioavailability.

Keywords: Fast Disintegrating tablet; Croscarmellose; Crospovidone; Optimization.

INTRODUCTION

In recent years, major focus of pharmaceutical research is pointing towards the development of innovative dosage forms for oral administration. Mostly the efforts are made to increase the patient compliance by formulating novel drug delivery systems. Scientists preferred fast disintegrating systems among the dosage forms developed with the aim of improving bioavailability, convenience and patient compliance(Hirani *et al.*, 2009; Nagar *et al.*, 2011; Shyamala and Narmada, 2002;Valleri *et al.*, 2004). Furthermore, the demand for fast disintegrating tablets has been tremendously increased during the last decade owing to its ease of administration for patients who experience difficulty in swallowing conventional tablets and capsules. Fast disintegrating tablets (FDT) are a better option for geriatric and pediatric patients and those who are mentally retarded, disobliging, nauseated, or on reduced liquid-intake/diets (Hay, 1991). Fast disintegrating tablets have become a rapidly growing area in the pharmaceutical industry and attempts are now being made by researchers focusing on the development of FDT for existing drugs/APIs that revealed improved safety and efficacy. The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an FDT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" (FDA, 2007). The breakup or disintegration of such tablet into smaller particles is mediated by the use of superdisintegrants in a drug formulation (Caraballo *et al.*, 1997).The fast disintegrating solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free from risk of choking (Bogner and Wilkosz, 2002; Fu *et al.*, 2004). Therefore, drug bioavailability as well as onset of clinical effect may be significantly better than those observed from conventional dosage forms (Bradoo *et al.*, 2001; Fu *et al.*, 2004; Seager, 1998;Sreenivas *et al.*, 2005).

Various techniques can be adopted for preparing FDTs including direct compression, spray drying, sublimation, lyophilization and addition of disintegrants. Among the other disintegrants including crospovidone, sodium starch glycolate, the croscarmellose sodium is superior with respect to disintegration and dissolution characteristics (Bhagawati *et al.*, 2005; Setty *et al.*, 2008).Many scientist used crospovidone along with croscarmellose to observe the effect of the disintegrants blend on *in vitro* dispersion time, disintegration time and dissolution in FDTs (Basu *et al.*, 2011; Shirsand *et al.*, 2010). Crospovidone was selected because of its solubility in water and physiologically compatible nature. It also proved to be non-toxic, chemically inert, temperature-resistant, pH stable as well as better disintegrant and dissolution enhancer. Therefore, it is extensively used in pharmaceutical dosage forms (Folttmann and Quadir, 2008; Rowe *et al.*, 2009; Sammour *et al.*, 2006; Shah *et al.*, 2011). Direct compression is considered as a better technique and proves as an attractive alternate to traditional granulation technologies because of its simplicity, cost effectiveness and appropriateness for moisture and heat susceptible APIs (Chang *et al.*, 2000).

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Scientists have tremendously adopted experimental design studies for formulation development and optimization on different pharmaceutical dosage forms specially utilizing statistical design of experiments (Madgulkar *et al.*, 2009).Tablet formulation development also accomplished by altering the levels of each variable (factor) at a time, keeping all other variables constant to observe the influence of that particular variable on the formulation. Central composite design (CCD) has many advantages over partial and full factorial design, due to maximum number of formulations, use of central point and response surface methodology graph. Many Researchers have applied CCD professionally for optimization of FDT or immediate release formulations(Di Martino *et al.*, 2005; Goel *et al.*, 2008; Schiermeier and Schmidt, 2002).

A broad range of drugs can be considered as a candidate for this dosage forms including cardiovascular agents, antibiotics, analgesics, antihistamines and narcoleptics. Cefadroxil is a bactericidal agent prescribed for the treatment of mild to moderate infections of soft tissues like skin, upper respiratory tract and urinary tract especially in children (Shetty *et al.*, 1999). It has pronounced oral absorption and 85% bioavailability. It remains as free drug in plasma (<20% protein binding) and 90% excreted unchanged in urine. The objective of the present study was to formulate FDT of cefadroxil with sufficient mechanical reliability, content uniformity and good enough palatability to provide ease of taking medication in patients of any age group. It was selected as a model drug for the preparation of FDTs because of its compromised water solubility and moisture sensitiveness.

MATERIALS AND METHODS

Formulation Ingredients & Reagents

Cefadroxil (obtained from Biopharm Pvt. Ltd., Pakistan), Croscarmellose, Crospovidone, Micro-crystalline Cellulose, Aerosil®, Aspartame, Talc, Acetonitrile, Potassium dihydrogen phosphate and sodium hydroxide all were of FMC Corporation, USA or Merck, Darmstadt, Germany.

Experimental design

The central composite design (CCD) includes 2^k factorial with its origin at center was applied using design expert®7.0.0software. The independent variables selected were croscarmellose i.e. X_1 (in the range of 0.59-3.41% w/w) and crospovidone i.e. X_2, (in the range of 1.59-4.41% w/w). Other excipients i.e. aerosil, talc and aspartame were kept constant for all formulations in the percentage of 1.5%, 1% and 2%, respectively (table 1). The response variables studied were friability, hardness, in vitro dispersion and disintegration time. Response surface methodology (Stern *et al.*, 1990) was adopted to study relationship between dependent and independent variables. Composition of all the nine formulations as designed by design expert® software with their coded and actual quantities are summarized in table 2.

Table 1: Composition of cefadroxil fast disintegrating tablets

Ingredients	Amount per tablet (mg)
Cefadroxil	500 mg
Croscarmellose	4.42- 25.57mg
Crospovidone	11.92- 33.07mg
Microcrystalline Cellulose	q.s 750 mg
Aerosil	11.25 mg
Aspartame	15 mg
Talc	7.5

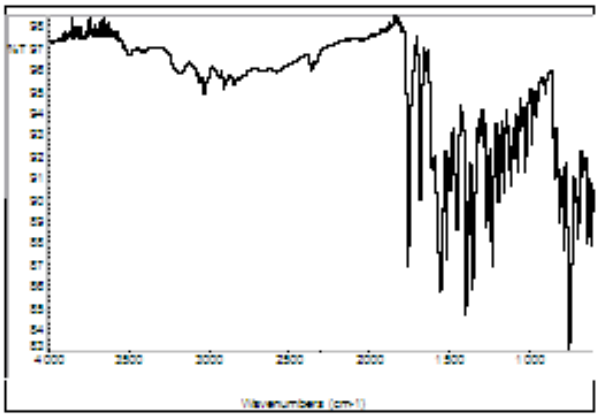

Fig. 1(a): IR spectrum of pure cefadroxil drug.

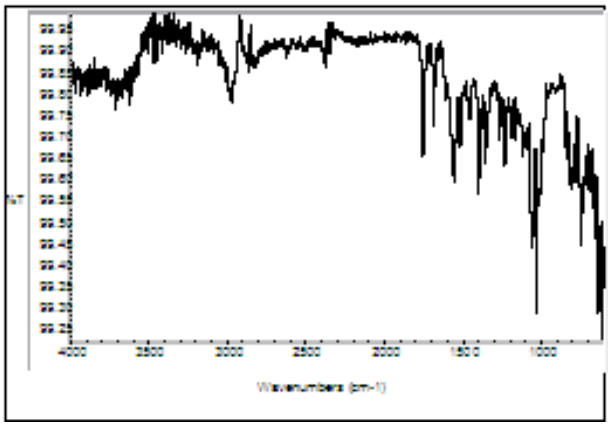

Fig. 1(b): IR spectrum of cefadroxil FDT formulation.

Compatibility analysis

Compatibility analysis on cefadroxil powder and excipients i.e. aspartame, aerosil, avicel, croscarmellose, crospovidone and talc was conducted to see any interaction among these chemicals. For this purpose, FTIR spectra were attained using Nicolet™iS™5 FT-IR spectrometer, Thermo Scientific™ USA, with OMINIC software. The scanning range and resolution were 400-4000 cm^{-1} and 1 cm^{-1}, respectively. The IR spectra attained were matched with the standard IR spectra indicated in literature and pharmacopeia.

Table 2: Central composite design with two factors, nine runs with one center point as designed by design expert®.

Formulation code	Coded factor (amount)		Factors amount (mg)	
	X_1	X_2	X_1	X_2
F 1	0	- α	15	11.925
F 2	1	1	22.5	30
F 3	0	0	15	22.5
F 4	-1	-1	7.5	15
F 5	-α	0	4.425	22.5
F 6	-1	1	7.5	30
F 7	1	-1	22.5	15
F 8	+α	0	25.575	22.5
F 9	0	+α	15	33.075

Where X_1 = croscarmellose, X_2= crospovidone and α = 1.414.

Table 3: Preformulation evaluation of powder blend.

Formulation code	Angle of repose (°)	Carr's index (%)	Tapped density (mg/ml)	Bulk density (mg/ml)	Hausner's ratio
F 1	22.13	18.70	0.54	0.43	1.23
F 2	18.15	15.76	0.59	0.49	1.18
F 3	14.30	16.52	0.57	0.48	1.19
F 4	28.90	24.02	0.61	0.46	1.32
F 5	23.40	18.27	0.50	0.41	1.22
F 6	21.70	17.30	0.59	0.48	1.20
F 7	15.99	17.60	0.51	0.42	1.21
F 8	16.34	14.17	0.60	0.52	1.17
F 9	14.50	14.40	0.55	0.47	1.16

Keep the decimals constant, 1 or 2, depending on your precision

Table 4: Post compressional evaluation of cefadroxil FDT formulations. N=12?

Formulation code	Weight variation (mg±SD)	Thickness (mm±SD)	Hardness (kg±SD)	Friability (%)	Disintegration (sec)	Drug dissolution in 20 min (%)	Drug contents (%)
F 1	747.93±7.40	6.826±0.07	58.59±3.07	0.62	76	82	98.56
F 2	746.15±9.49	6.595±0.04	63.07±3.63	0.54	19	99	98.82
F 3	746.99±5.517	7.029±0.05	49.49±1.86	0.66	26	101	96.93
F 4	748±10.88	7.372±0.06	46.72±3.34	0.76	85	81	98.90
F 5	749.99±12.60	7.172±0.05	37.59±3.36	0.72	63	85	101.22
F 6	750.12±8.10	7.299±0.04	40.59±4.99	0.68	41	82	95.19
F 7	747.19±8.13	7.287±0.078	58.09±3.94	0.51	55	76	97.93
F 8	750.63±9.26	7.256 ±0.061	60.59±2.98	0.47	37	101	102.03
F 9	748.59±7.9	7.145±0.034	40.96±2.45	0.59	25	105	99.56

All data ±SD

Table 5: Additional evaluation performed for FDT formulations

Formulation code	Wetting time	Water absorption	*In vitro* dispersion time
	Sec	%	sec
F 1	97	78.32	83
F 2	40	85.94	28
F 3	45	123.97	31
F 4	106	85.71	97
F 5	84	82.59	75
F 6	71	91.36	48
F 7	69	70.54	62
F 8	51	126.64	39
F 9	48	118.67	36
F Control	100	73.28	95

Table 6: Model dependent *in vitro* drug release kinetics of selected cefadroxil FDT sinphosphate buffer of pH 6.8 (simulated salivary fluid)

Formulation code	Zero order		First order		Hixson-Crowell Model		Weibull Model			
	K_0	R^2adj	K_1	R^2adj	K_{HC}	R^2adj	α	B	T_i	R^2adj
F 2	14.425	0.5016	0.736	0.9708	0.154	0.9595	1.734	1.254	0.007	0.9515
F 3	14.744	0.2851	1.132	0.9610	0.159	0.9307	1.046	1.226	0.001	0.9353
F 8	14.388	0.2438	1.003	0.9849	0.155	0.9400	1.007	1.273	0.290	0.9755
F 9	14.730	0.2718	1.161	0.9635	0.160	0.9325	0.909	1.037	0.000	0.9386

Table 7: Stability testing results of optimized formulation according to ICH guidelines.

Test	F 3			F 8			F 9		
	Month (s)			Month (s)			Month (s)		
	0	3	6	0	3	6	0	3	6
Friability (%)	0.66	0.82	1.02	0.47	0.62	0.79	0.59	0.63	0.74
Hardness (Newtons)	49.50	35.50	27.10	60.50	58.40	45.70	40.90	38.50	33.20
In vitro dispersion time (sec)	31	27	22	28	24	19	36	33	29
Assay (%)	106.6	100.5	97.9	103.7	97.7	95.9	102	99.8	98.4
Shelf Life (Months)	5			4			12		

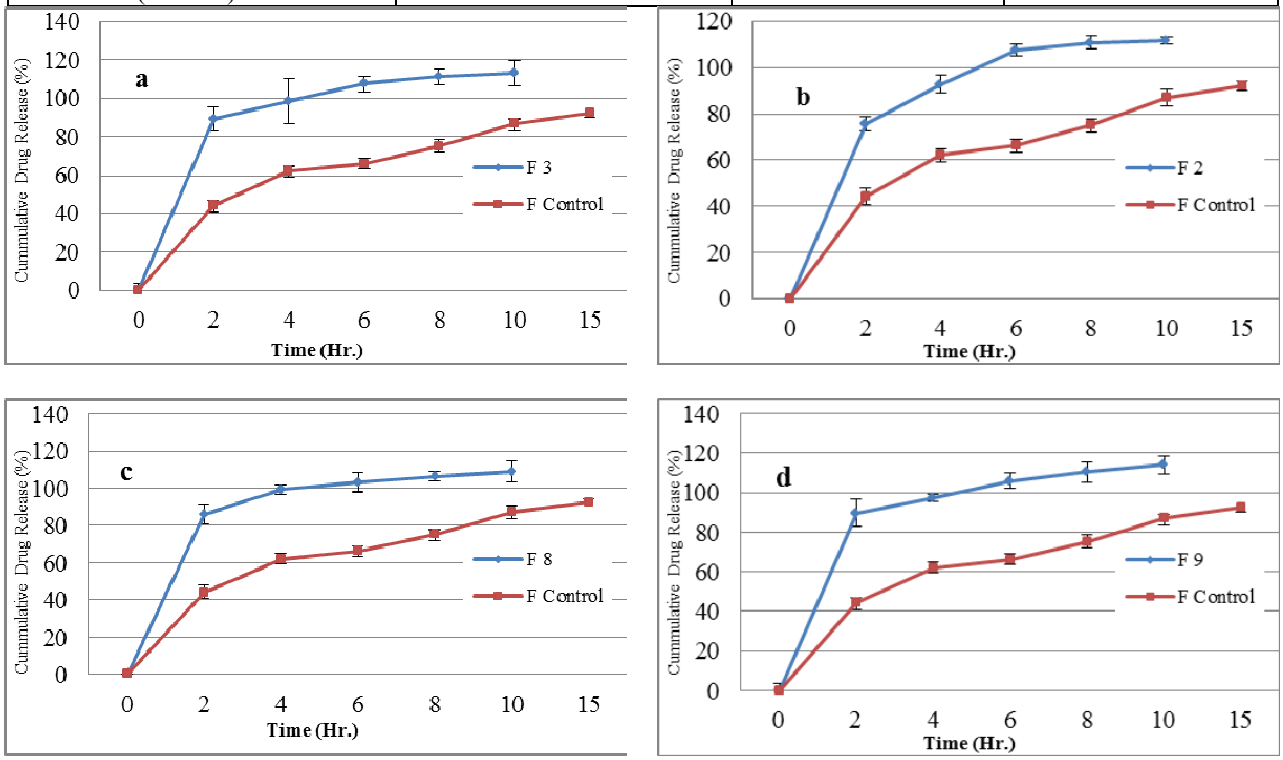

Fig. 2 (a): Dissolution profile of developed FDT formulation (F 2) and F control at pH 6.8 **(b):**Dissolution profile of developed FDT formulation (F3) and F control at pH 6.8 **(c):**Dissolution profile of developed FDT formulation (F 8) and F control at pH 6.8 **(d):**Dissolution profile of developed FDT formulation (F9) and F control at pH 6.8

Preformulation studies

The preformulation studies were performed before compressing the tablets. The powder blend was analyzed for flow characteristics by estimating angle of repose, Carr's compressibility index, bulk density, Hausner ratio and tapped density.

Process of Cefadroxil* FDT *tablets manufacturing by direct compression

Cefadroxil tablets were prepared by direct compression method. The single punch machine of Erweka (Korsch, Germany) was used. All the ingredients were accurately

weighed using electronic balance (Mettler Toledo B204-S) according to the design. Weighed ingredients were sieved by 30 mesh sieve. These ingredients were then mixed using geometric dilution method in a polybag for 5 minutes excluding lubricant and glidants i.e. aerosil and talc. All the ingredients were again mixed for further 5 minutes. The final blend was compressed directly using round shaped punches with tablet weight ranging from 746.15-750.6 mg.

Evaluation of tablet properties

Each batch of tablets were evaluated for different pharmacopeial and non-pharmacopeial tests such as weight variation, hardness, thickness variation, friability, disintegration time, drug release and assay. Weight variation determination was carried out by weighing twenty tablets individually using electronic balance, calculating the average weight and comparing the individual tablet weights with average weight. Tablets (n=20) were randomly chosen from each formulation using Digital Hardness Tester (OSK Fujiwara, Ogawa Seiki Co. Ltd., Tokyo, Japan.). The thickness of twenty randomly selected tablets was measured by means of digital thickness tester and the data was statistically analyzed. Twenty tablets of each formulation were weighed and subjected to abrasion by employing a Friability Tester (H. Jurgens and Co- GmbH, D2800, Germany). Disintegration test was executed with basket rack assembly (Pharmatest, DISINT 3, Germany), using disks to avoid floating of tablets in 900 ml distilled water maintained at 37±2ºC.

Additional test for FDTs

As the trial formulations were FDT, some additional tests were also performed, like wetting time, water absorption and in vitro dispersion time (Bhagawati *et al.*, 2005; Bi *et al.*, 1996;Shirsand *et al.*, 2010). Wetting time was determined by placing six tissue papers in a petri dish with internal diameter of 6.5 cm. Ten milliliters of water containing few drops of water soluble dye (crystal violet) was poured on these tissue papers. Dye solution helped in identifying complete wetting. Each tablet unit was placed on the top of tissues papers and time for complete wetting was noted down with the help of stop watch. Water absorption property was calculated by weighing tablet before and after complete wetting using the formula given below:

$$\frac{W_{after} - W_{before}}{W_{before}} \times 100$$

In vitro dispersion time was recorded after placing each tablet in a small beaker having 10 ml of water and time was noted for complete dispersion.

Assay of cefadroxil using RP-HPLC

The assay of FDT formulations was carried out using HPLC system 20A series (Shimadzu Corporation, Japan) as mentioned in the official monograph of cefadroxil (USP 31). Mobile phase was prepared using pH 5.0 buffer and acetonitrile in the ratio of 960:40; filtered using 0.5micrometer porosity and pumped at a flow rate of 1.5ml/min. The separation was carried out on a C_{18} column. The column temperature was maintained at 25ºC. The sample of 20µl was injected and analyzed under isocratic conditions. Chromatograms were recorded at λ=230 nm using UV-VIS detector. Standard solution of cefadroxil monohydrate (reference standard) was prepared by dissolving 25mg of reference standard of cefadroxil in 25ml of mobile phase. The resulting concentration was 1 mg/ml or 1000µg/ml. A total of 20 tablets were carefully weighed; triturated with the help of mortar and pestle to get a fine powder and the amount of powder equivalent to 200mg of cefadroxil was transferred to a 200ml volumetric flask. It was dissolved in the mobile phase by shaking for about 15 min. The final concentration of sample solution was kept equivalent to 1 mg/ml or 1000µg/ml.

Dissolution profile study

The drug release profile for cefadroxil tablets were carried out. Dissolution apparatus (PharmatestDT70, Germany), apparatus II (paddle method) was used with dissolution medium at 37±0.5°C and 50 rpm. The medium used was phosphate buffer (pH 6.8) at 37±0.5ºC.The recommended dissolution medium for FDT is buffer pH 6.8 (simulated salivary fluid) (Khan *et al.*, 2007; Masareddy *et al.*, 2008). Approximately 5 ml of sample was withdrawn and filtered from each vessel at 0, 2, 4, 6, 8, 10, 15 and 20 min and substituted with 5ml of fresh medium. Dissolved amount of cefadroxil was determined by UV-VIS spectrometer (Spekol 2000 series, Analytikjena) at 230 nm. For each formulation, dissolution rates of tablets (n=12) was determined and mean±standard deviation values were also calculated.

Comparison of dissolution profiles

Model Dependent Approach

Drug release profiles obtained from *in vitro* dissolution studies were built-in into a variety of kinetic models. These models were zero order; first order; Hixson–Crowell cube root law and Weibull model. This was accomplished with the use of DDSolver® excel based Add in program(Zhang *et al.*, 2010).The selection of the best fit model was based on the goodness of fit. The highest values of correlation coefficient (R^2) proved the best fit model to explain drug release from the formulation.

Model Independent Approach

Model independent approach included pair-wise procedures i.e. similarity factors and ratio tests i.e. mean dissolution time(Costa and Sousa Lobo, 2001). Difference factor (f_1) and similarity factor (f_2) were described by different scientists(Moore and Flanner, 1996). The f_1 and f_2 values were determined for the selected formulation using DDSolver®.

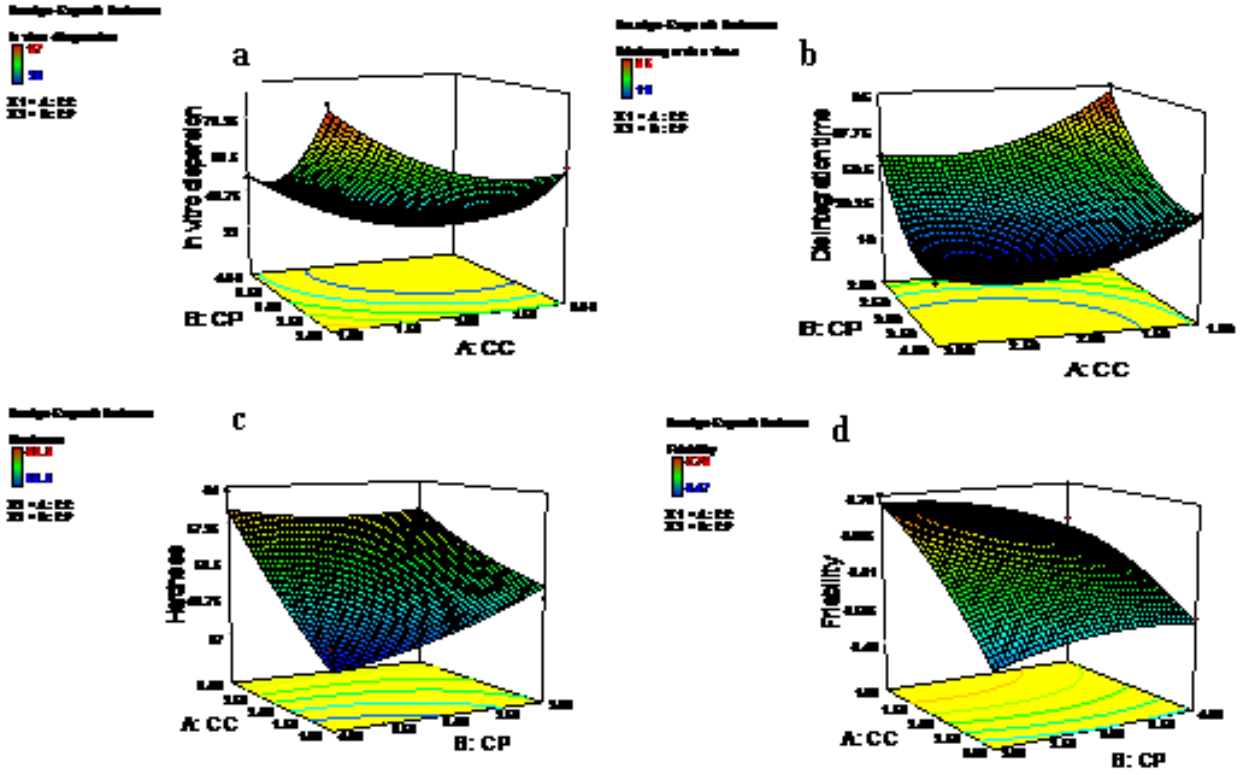

Fig. 3(a): RSM presentation of the effect of croscarmellose and crospovidone on the *in vitro* dispersion time. **(b)**: RSM presentation of the effect of croscarmellose and crospovidone on the disintegration time. **(c)**: RSM presentation of the effect of croscarmellose and crospovidone on hardness. **(d)**: RSM presentation of the effect of croscarmellose and crospovidone on friability

Accelerated stability studies

Accelerated Stability studies of the formulation F3, F8 and F9 was performed as per ICH guidelines 40±2°C/75% RH±5% RH (I.H.T, 2003). Samples withdrawn periodically and analyzed for different pharmaceutical parameters like friability, hardness, in vitro dispersion and assay. Shelf life was calculated using R Gui 3.0.2 package (Copyright© 2013, The R Foundation for Statistical Computing).

RESULTS

During the present study, FDT of cefadroxil was developed and optimized using design expert® software. FTIR spectra of pure drug and formulation of cefadroxil revealed no interaction between drug and all other excipients. The powder blend was analyzed for flow characteristics before compressing tablets. The angle of repose ranged between 14.3º-28.9º, whereas Carr's compressibility index was in the range of 14.14-24.02%. Hausner ratios were less than 1.32. Weight and thickness variation for all the formulations were in the USP limit of ± 5%. All the formulations were disintegrated within 85 sec. Chemical assay of cefadroxil in trial formulations was in the range of 95.19-102.03%. The lowest wetting time and *in vitro* dispersion time was 40 and 28 sec. The formulations were optimized on the basis of preformulation, additional test of FDT and pharmacotechnical attributes. Selected F2, F3, F8 and F9were subjected to drug release profile comparison using DDSolver Add-in program. The best fit models for FDT were first order and Weibull model. F3, F8 and F9 were kept in temperature/humidity controlled chamber in specified conditions according to ICH guidelines for six months. Stable FDT formulation of cefadroxil was F9 with reasonable shelf life.

DISCUSSION

The current study involved the formulation development and optimization of cefadroxil FDT tablets according to FDA guidance (FDA, 1997). Cefadroxil was selected as a model drug for FDT because only few tablet formulations of cefadroxil were available in the local market. Design Expert® software was used to develop cefadroxil FDT using CCD design. The formulations (n=9) was designed by design expert® having two variables croscarmellose (0.59-3.41% w/w) and crospovidone (1.59-4.41% w/w). Other excipients i.e. aerosil, talc and aspartame were kept constant for all formulations in the percentage of 1.5%, 1% and 2%, respectively. Microcrystalline cellulose was

used in quantity sufficient for 750 mg of total tablet weight. Many scientist utilized Croscarmellose and crospovidone as super disintegrants to develop mouth dissolve or FDT(Farhana*et al.*, 2013;Sammour *et al.*, 2006;Shirsand *et al.*, 2010).In order to catch indication on the probable interaction of the drug with the excipients, FTIR studies was performed. IR spectra are displayed in fig. 1 (a and b) of cefadroxil and cefadroxil FDT formulation. These spectra revealed no marked interaction among cefadroxil and excipients.

The flow properties of powder blend significantly affect tablet formulation as compromised flow of powder blend results in weight variation as well as content non-uniformity. Therefore the powder blend was analyzed for flow characteristics by estimating angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner ratio (table 3). During the preformulation studies, it was observed that desired flow properties were achieved by incorporating microcrystalline cellulose, aerosil and talc in the trial formulations. The angle of repose was in the range of 14.3º-28.9º (least value with F3), whereas Carr's compressibility index was in the range of 14.14-24.02% (lowest with F8). Hausner ratio of the powder blends were in between 1.168 and 1.32.Hausner'sratiolower than 1.25 depict better flow properties. Bulk and tapped densities ranged between 0.416-0.497 gm/ml and 0.509-0.612 gm/ml, respectively (table 3). These ingredients (microcrystalline cellulose, aerosil and talc) have ability to be used as excipients in tablet preparation by direct compression rendering good tableting properties (Rojas *et al.*, 2013).

All the developed formulations were subjected to pharmacotechnical attributes including, weight, thickness, hardness, friability, disintegration, dissolution and assay (table 4). All of the formulations have shown the weight and thickness variation within the specified pharmacopeial limits *i.e.,* ±5%. Average tablet weight ranged from 746.15-750.6 mg with thickness ranged between 6.595-7.372 mm. Researchers have mentioned that hardness has to be kept low near to 4 Kg or 40 Newton for FDT (Aurora and Pathak, 2005; Chang *et al.*, 2000; Shah *et al.*, 2011). All the trial formulations showed reasonable mechanical strength showing hardness in the range of 37.59-63.07 Newton. The lowest hardness was observed with F5 (i.e. 37.59±3.36) (table 4). The most important parameter has to be considered during FDT formulation optimization is disintegration time. During the current study, different combinations of croscarmellose and crospovidone were used to get least disintegration time. Other researchers also used a combination of two disintegrants for preparing FDT tablets and observed that the disintegrants blend improved in vitro dispersion time, disintegration time and dissolution (Basu *et al.*, 2011; Shirsand *et al.*, 2010). The lowest disintegration time was observed with F2 i.e. <20 sec. It is suggested that crospovidone and croscarmellose produced a combined effect of improving disintegration and dissolution. The *in vitro* dispersion test revealed that most of the formulation was dispersed in 10 ml of water within 90 sec. The F2 was dispersed in least time i.e. 28 sec. Water absorption property was in between 70.54 and 126.64% w/w (table 5). Damodharan *et al.*(2009) developed dispersible tablet of cefadroxil and reported 20 sec disintegration time and fast drug release i.e. 102.5% in 15 min (Damodharan *et al.*, 2009).Results of the present study were in close agreement with published reports(Farhana*et al.*, 2013; Shirsand *et al.*, 2010). It was observed that the assay results of the developed formulations were inside specified pharmacopeial limits i.e. 90-120% of the label claim. The results of optimization using different kinetic models are summarized in Table 6. As the developed formulation is FDT for which the suggested dissolution medium is buffer pH 6.8, the release profile was studied in the specified buffer (Khan *et al.*, 2007; Masareddy *et al.*, 2008). The release profile was compared with the marketed formulation (F control) also. The best fit models for trial FDT as well as F control were First order and Weibull model.

The f_1 and $f_2$indexes were also determined to compare drug release from the developed trial formulations with that of marketed formulation (F control). The results proved that the trial formulation showed faster dissolution within 15 min as compared to market brand. f_1 values were less than 15 and f_2 values were in the range of 23.17-25.84. Although these values were not in the specified limit (FDA, 1997), the trial FDT were better than marketed formulation as proved by applying model independent approach. Similar results were also mentioned by another researcher (Basu *et al.*, 2011).

RSM plots were constructed using design expert® to study the interaction between independent and dependent variables. fig. 3(a) and (b) depict the combined effect of croscarmellose and crospovidone on in vitro dispersion and disintegration time. Both the disintegrants work through swelling and capillary action(Basu *et al.*, 2011; Folttmann and Quadir, 2008; Sammour *et al.*, 2006; Shah *et al.*, 2011;Shirsand *et al.*, 2010). Fig. 3(c) and (d) summarizes the effect of croscarmellose and crospovidone on responses i.e. friability and hardness. Crospovidone shows no pronounced effect on these responses, however increase in croscarmellose content results in increased hardness and reduced friability.

The accelerated stability studies were accomplished according to ICH guidelines (ICH, 2003) to assess drug and formulation stability. F 9 was the most stable one with less variation in different pharmacotechnical parameters including chemical assay. The shelf life was also estimated and found to be 12, 4 and 5 months for F9,

F8 and F3, respectively (table 7). The shelf life of optimized F9 is reasonable, however can be improved by employing better packaging and stabilizers as the drug is moisture sensitive.

CONCLUSION

In the present study, stable fast disintegrating tablets containing 500mg cefadroxil were successfully prepared applying central composite design with the most appropriate combination of crosscarmellose and crospovidone as super disintegrants. It was observed that among three optimized formulations, F9 was the best selected fast disintegrating tablet containing croscarmellose 15mg and crospovidone 33mg proving good physical and chemical stability.

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