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FORMULATION DEVELOPMENT AND OPTIMIZATION OF CEFDITOREN PIVOXIL DISPERSIBLE TABLET

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ABSTRACT

The goal of this project is to formulate dispersible tablet of Cefditoren Pivoxil (CP) that is intended to disintegrate rapidly into the water and form a stabilized dispersion. A direct compression method was failed to formulate dispersible tablet of CP so wet granulation method was used. In preliminary study different superdisintegrant croscarmellose sodium (CCS), sodium starch glycolate (SSG) and crospovidone were evaluated for weight variation, content uniformity, hardness, disintegration time, and friability of tablets. Microcrystalline cellulose:low-substituted hydroxypropyl cellulose ratio was optimized 8:2 in whole experiment as it gives minimum disintegration time. Full factorial designs 3^2 was used to optimize concentration of superdisintegrant (X_1) and SLS (X_2) which were selected as independent variables, and friability, disintegration time and % CDR was selected as dependent variable. From response surface plot of disintegration time, % drug release after 15 minis (Q_{15}) and friability it was found that lower disintegration time of tablets could be obtained when X_1 and X_2 are kept at optimum level. Stability study of final batch showed no significant changes in tablet properties.

Key words: Cefditoren Pivoxil, dispersible tablet, disintegration time, drug release

INTRODUCTION

Developing a solid oral dosage form in today's market can be challenging. There are many pressures to discover new entities and maximize the lifecycle of products while maintaining safety, cost-effectiveness, and speed to market. Tablets are almost certainly the most cost-effective and efficient form of dispensing medicines. Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance [1].

While the suspension dosage forms show the best bioavailability and can be easily administered to patients who have problems in swallowing, they have other drawbacks. They have to be reconstituted prior to administration and then stored under refrigerated conditions to prevent them from deterioration[2]. Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. The tablet is the most widely utilized oral dose format [1, 2]. A novel tablet concept which offers ease of oral administration and benefits of increased patient compliance is the fast dissolving/disintegrating tablet (FDDT).

Dispersible tablets disintegrate either rapidly in water, to form a stabilized suspension, so, it's preferred for patients who cannot swallow a solid dosage form and the API is unstable if formulated in liquid formulation. It is also helpful for patients having prolonged illness who are prone to nauseatic sensations if they have to swallow a tablet. The added advantage of this formulation is faster onset of action as compared to standard compressed tablet[3]. The properties of the water dispersible tablet, such as porosity, hardness, disintegration time and increase in viscosity after dispersion are necessary to investigate during manufacturing which decides the product performance[4].

In present research work, dispersible tablet of CP is formulated using granulation technique. Cefditoren is an advanced-generation; broad-spectrum cephalosporin antibiotic approved for the treatment of acute bacterial exacerbation of chronic bronchitis (AECB), group-A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections in adult and adolescent patients. CP has slightly bitter test and has half life of 1.6 hrs and has poor water solubility. So in case of acute bacterial exacerbation of chronic bronchitis (AECB) group-A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections it require immediate release of drug from the dosage form, which make CP suitable candidate for dispersible tablets.

MATERIALS AND METHODS

Materials

Cefditoren Pivoxil was obtained as a gift sample from Cadila Pharmaceuticals Limited (Dholka, Ahmedabad). D-Mannitol, Micro Crystaline Cellulose, L-HPC, Sodium Lauryl Sulphate, Aerosil, Magnesium Stearate and Aspartame were purchased from S.D. Fine chemicals. Croscarmellose sodium, Sodium starch glycolate and crospovidone also were obtained as a gift sample from

Cadila Pharmaceuticals Limited (Dholka, Ahmedabad). All other chemicals were of analytical grade.

Preparation of dispersible dissolving tablet

Dispersible tablet of CP were prepared by granulation according to the formula given in Table 1. All the ingredients were passed through # 60 mesh separately. Then the granules were prepared with intragranular ingredients using water as a binder passing lumps through # 8 mesh. Then extragranular ingredients were weighed and mixed in geometrical order with prepared granules and compressed into tablet of 500 mg using 8 mm round punches on multipunch tablet compression machine, (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India). A batch of 50 tablets was prepared for each of the designed formulations.

Evaluation of Tablet Characteristics

Tablets were evaluated for weight variation, drug content uniformity, friability, disintegration time. Drug content was analyzed using U.V spectrophotometer (Systronics 2201 UV/Visible double beam Spectrophotometer, Japan) at 272 nm. Tablet friability was measured using Roche friabilator (Camp-bell Electronics Mumbai, India) for 4 mins at 25 RPM[5, 6]. Five tablets were selected randomly from each batch and tested for hardness using Pfizer hardness taster, and disintegration time was determined using USP disintegration test apparatus model (ED-2L, Electrolab, Mumbai, India) at 24 ± 2^0 C [7].

In-vitro dissolution

Dissolution studies of all tablets were performed using automated programmable dissolution tester (Paddle type, TDL-08L, Electrolab, India). Tablets were added to the 900 ml of 0.1 N HCl at 37°C ± 0.5°C, which was stirred with a rotating paddle at 75 rpm. At time intervals of 2 minutes, 10ml samples were withdrawn and equal volume of fresh medium prewarmed at the same temperature was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test [8, 9]. Assay carried out using U.V. spectrophotometer (Systronics 2201 UV/Visible double beam Spectrophotometer, Japan) at 272nm.

Stability Study

The stability of samples was monitored up to 3-month at ambient temperature and relative humidity (30 °C / 65% RH). Periodically samples were removed and characterized for disintegration time, hardness, drug content and dispersion time [8].

Full Factorial Design

Full factorial design 3^2 was used in the present study. In this design 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations [10]. The amount of intragranular superdisintegrant, CCS (X_1), and the amount of surfactant, SSG (X_2) were selected as independent variables. The disintegration time and percentage friability were selected as dependent variables.

RESULT & DISCUSSION

Hardness of preliminary batches prepared using three different superdisintigrants were found 3 to 5 kg/cm^2. Drug contents were in acceptance limits. It was found that friability of tablets were affected by SLS, in absence of SLS friability was increased. Without the SLS, the binder was not able to form the proper bridges between the drug particles to form strong granules. Among the three superdisintigrants used for formulations, intragranular addition of CCS gave minimum disintegration time as well as superior dissolution profile compare to crospovidone and SSG. While addition of 10% CCS as extragranular agents have shown improve in disintegration of tablets. As a result of data obtained from preliminary trials, various concentrations of CCS and SLS were decided to evaluate using 3^2 full factorial design to get comprehensive plan for their effect on disintigration and dissolution behavior of tablet [11, 12].

Concerning disintegration time, the result of multiple linear regression analysis showed that the coefficient b_1 bear negative and b_2 bear positive sign. Therefore, increasing the intragranular concentration of Croscarmellose sodium is expected to decrease the disintegration time while increasing the concentration of SLS is expected to increase the drug release. SLS 8mg was selected as the optimum concentration that showed disintegration time 51 sec with maximum drug release is 85% in 15 minute. In case of dependent variable disintegration time and Drug release X_1 and X_2 factors showed significant effect on formulation ($P<0.05$).

Disintegration Time: $y1= 53.22 - 3.5\ X_1 + 1.16\ X_2 + 0.167\ X_1X_2 + 0.166\ X_1^2$

($R^2=0.9987$) [1]

Drug release: $y2 = 71.89 + 4.5\ X_1 + 9.66\ X_2 + 0.166\ X_1X_2 - 0.133\ X_1^2 + 0.25\ X_2^2$

($R^2=0.9931$) [2]

Table 1: Formulations of preliminary trials by wet granulation

Formulation Code	CCS1	CCS2	CCS3	CP1	CP2	CP3	SSG1	SSG2	SSG3
INTRAGRANULAR									
CP	255	255	255	255	255	255	255	255	255
D-Mannitol	147	170	113	147	170	113	147	170	113
CCS	-	6	10						
Crospovidone				-	6	10			
SSG							-	6	10
SLS	-	2	2	-	2	2	-	2	2
MCC	48	-	48	48	-	48	48	-	48
L-HPC	-	12	12	-	12	12	-	12	12
EXTRAGRANULAR									
CCS	-	5	10	-	5	10	-	5	10
Aerosil	5	5	5	5	5	5	5	5	5
Magn. Stearate	5	5	5	5	5	5	5	5	5
Aspartame	40	40	40	40	40	40	40	40	40

*All ingredients are given in mg

(CP:Cefditoren Pivoxil, CCS: Croscarmelose sodium, SLS: Sodium lauryl sulphate, SSG: Sodium starch glycolate, MCC: Microcrystalline cellulose, L-HPC: low-substituted hydroxypropyl cellulose)

Table 2: Effect on dependent variable on full factorial design layout

Batch No	Independent variable		Dependent variable		
Sr No	X1	X2	DT	%Drug Release (Q15)	friability
FD1	-1	-1	56	65.21	0.36
FD2	-1	0	57	73.02	0.29
FD3	-1	1	58	60.83	0.25
FD4	0	-1	52	63.12	0.27
FD5	0	0	53	65.82	0.21
FD6	0	1	65	53.61	0.17
FD7	1	-1	49	77.70	0.27
FD8	1	0	50	75.73	0.26
FD9	1	1	51	87.29	0.21
				Actual values	
Independent variable		Lower (-1)		Medium (0)	High (1)
CCS (X1)		2		6	10
SLS (X2)		2		5	8

*X_1 = Intragranular Concentration of CCS, X_2 = Concentration of SLS

The fitted equation (full model) relating the response (disintegration time, friability and drug release (Q_{15})) to the transformed factor was shown in table 2. The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries. Positive or negative the high values of correlation coefficient for the dependent variables indicate a good fit. The response surface plot was drawn using Sigma plot software (Jandel Scientific, San Rafael, CA). Figure 1, 2 and 3 shows the response surface plot of disintegration time, %Drug Release after 15 minis (Q_{15}) and friability versus the intragranular concentration of Croscarmellose sodium and concentration of SLS.

The in vitro dissolution rate of all prepared tablets shown in figure 4, indicate that formulation FD9 contain CCS 20% and SLS 8% gave superior dissolution profile compare to other formulations [13]. It was found that for FD9 87.29% drug was released at 30 mins while conventional formulation of CP gave 54.37% drug release after 30 mins (data not shown). Results shows that concentration of CCS greatly affect the dissolution rate, by increasing concentration of CCS disintegration time decrease that may improve dissolution rate [14, 15]. Addition of SLS also affect the disintegration time, it slightly decrease the disintegration time as increasing the concentration of SLS but meanwhile it increase the % cumulative drug release within the same formulation.

Three months stability study at ambient temperature and relative humidity (30 °C / 65% RH) of formulation FD9 revealed that the formulation was stable and

there were no significant changes observed for hardness, drug content and disintegration time. Hence, the results of stability studies reveal that the developed formulation has good stability.

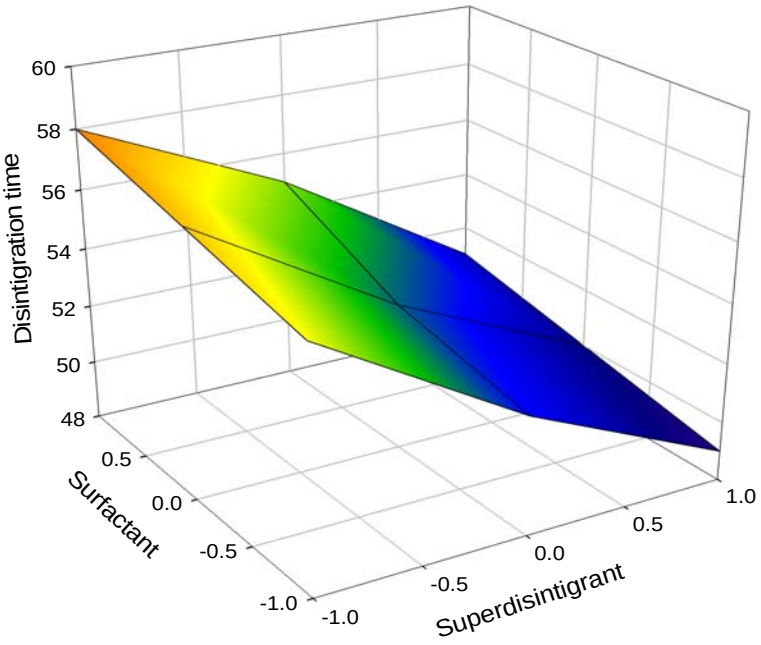

Fig. 1: Surface plot of disintegration time

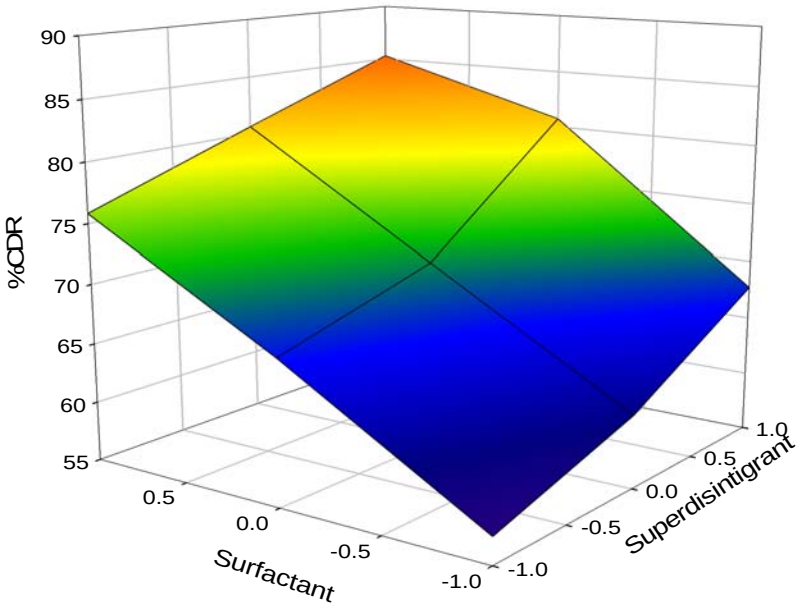

Fig. 2: Surface plot of % drug release at 15 min (Q_{15})

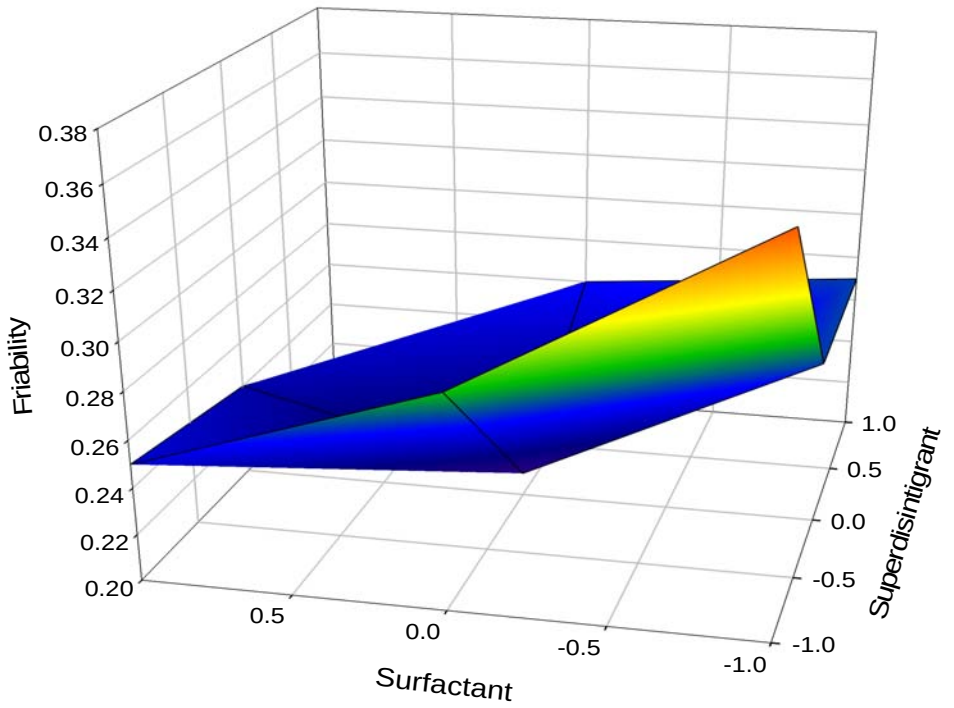

Fig. 3: Surface plot of friability

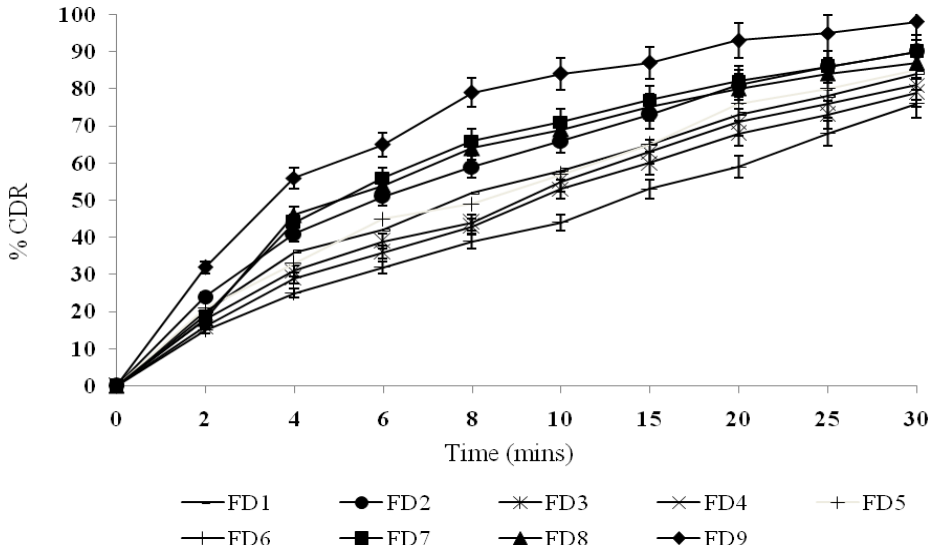

Fig. 4: *In vitro* dissolution profile of factorial batches FD1 to FD9

CONCLUSION

It is clearly predicted that as the concentration of CCS increases it decrease the disintegration time. It not only decreases disintegration time intragranularly, but addition of CCS extragranularly also decrease the time to disintegrate the tablet. It is concluded that 50% intragranular and 50% extragranular concentration of superdisintegrant give minimum disintegration time. Addition of SLS also affect the disintegration time, it slightly decrease the disintegration time as increasing the concentration of SLS but meanwhile it increase the % cumulative drug release within the same formulation. Formulation FD9 was the optimized formulation having least disintegration time as well as other parameters were in acceptable range.

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