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Research Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF DRUG CEFPODOXIME PROXETIL

C. Senthilkumar*, G. Rameshkumar, S. Subathra, T. Suresh Kumar, S. Arun Kumar
Research Center, Arvind Remedies Ltd, SIDCO Industrial estate, Kakkalur-602003, Tamilnadu, India

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*Email: research@arvindremedies.com

ABSTRACT
The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Aqueous solubility of any therapeutically active substance is a key property, as it governs dissolution, absorption and thus the *in vivo* efficacy. The solubility behavior of drug remains one of the most challenging aspects in formulation development. Once if we are able to increase the aqueous solubility of a drug, the disintegration and dissolution properties can be easily altered, as a result, an increase in bioavailability can be easily achieved. This study deals with enhancing the dissolution of poorly soluble Class IV drug Cefpodoxime Proxetil, using different excipients. In order to achieve maximum dissolution, eight different formulations were developed. Optimization has proven as an effective tool in product development. The formulation ARL 8 was found to be optimized product. The different physical properties and *in vitro* release profile showed better and stable results when compared with marketed product.
KEY WORDS: Cefpodoxime Proxetil (CP), Class IV drug, Compatibility, Optimization, Improvement of dissolution, ICH stability studies.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness, and ease in manufacturing. In pharmaceutical industries, manufacturers of generic tablets are usually focused on the optimization of the excipient mixture composition to obtain a product that meet established standard[1,2].

There are many methods used in the pharmaceutical industry to produce granules. However the most common is wet granulation technique. The wet granulation process offers several advantages. For example, high dose drugs that experience poor flow and/or poor compressibility can be granulated to obtain suitable flow and cohesion for compaction. Drug With low dose, content uniformity in the tablets can be increased[3].

Cefpodoxime Proxetil (1-[(isopropoxycarbonyl) oxy] ethyl ester of (Z)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3- cephem-4-carboxylic acid) is the orally active ester prodrug of third generation Cephalosporin. CP is used orally for the treatment of mild to moderate respiratory tract infections, uncomplicated gonorrhea and urinary tract infections. One of the major problems with this drug is its very poor aqueous solubility that results in poor bioavailability after oral administration. It shows erratic dissolution in gastric and intestinal fluid due to its poor aqueous solubility. Rate of absorption and/or extent of bioavailability for such drugs are controlled by rate of dissolution in gastrointestinal fluids. The peak plasma concentration (Cmax) and the time taken to reach Cmax (Tmax) depend upon extent and rate of dissolution of drug respectively. The efforts to improve the dissolution and solubility of a poorly water- soluble drug remains one of the most challenging tasks in drug development[4,5,6].

In this present research study, from the literature, patent search and the compatibility studies of the excipients the most favorable excipients were short-listed. All the excipients choosen are well known for their suitability and fitness of purpose. Each excipient is controlled by pharmacopoeial specification and are the same or similar to those used in the marketed product.

MATERIALS AND METHODS

Cefpodoxim proxetil was purchased from Nectar lifesciences ltd and Low substituted Hydroxy propyl cellulose was purchased from Shinetsu. Excipients such as Calcium carboxy methyl cellulose, Lactose, croscarmellose sodium, Sodium lauryl sulphate, Starch, Crospovidone, Colloidal silicon dioxide was randomly selected for the study and the tablets were procured from the local market.

Shimadzu UV-1800 spectrophotometer loaded with UVPC software was used for spectral measurements. Waters HPLC – 2695 separation module loaded with empower software for measurements.

PREFORMULATION STUDIES

Physical observation

Active ingredient was mixed well with all excipients in binary ratio and small portion of this mixed powder was placed in a cleaned and dried vial. This vial was kept for observation in stability chamber at **40°C ± 2°C / 75 ± 5%** RH and RT. Mixtures were also placed at **50°C ± 2°C** and **2°C - 8°C**. Physical observation has been carried out visually at the initial stage and after 3 months and one month of exposure to the stated conditions respectively. The results were tabulated in Table 2.

PREPARATION OF CEFPODOXIME PROXETIL TABLETS

Conventional tablet of Cefpodoxime Proxetil were prepared by wet granulation technique using different hydrophilic and hydrophobic excipients. Accurately weighed quantity of pre-sieved drug and intra-granular materials (Starch, Carboxy methyl cellulose calcium, hydroxy propyl cellulose - low substituted) were mixed thoroughly and granulated using sodium lauryl sulphate, Croscarmelose sodium dissolved in water. The wet granules were sieved through 30# sieves and dried in tray dryer at 55° C till LOD reaches to 2% W/W. The granules were blended with extra-granular materials (Hydroxy propyl cellulose low substituted, Crospovidone) and finally lubricated using magnesium stearate, colloidal silicon dioxide followed by the granules were compressed using Karnavathi 10 station compression machine. The tablet was then film coated to withstand its stability.

The granules obtained was subjected to precompression parameters such as flow property, which includes angle of repose, Hausners ratio etc. Results were tabulated in table 3.

Eight different trials of tablet was taken and studied. Composition for formulation and coating of Cefpodoxime Proxetil tablet was given in table 1

EVALUATION OF TABLET PROPERTIES

The formulated tablets were evaluated for uniformity of weight and thickness (Campbell electronics), hardness (Campbell electronics), friability (Electrolab India Ltd.) and disintegration time (Electrolab India Ltd.). The controls applied on all of the tablets were the following:

Average weight: It was carried out on 20 tablets using Sartorius weighing balance and average weight was calculated. (Table 4)

Thickness measurement: It was carried out on 20 tablets by measuring thickness using Tablet tester. Mean and standard deviation were determined. (Table 4)

Hardness determination: 20 tablets were taken randomly and hardness was measured using Tablet tester. The mean hardness of 20 tablets of each formulation was determined. (Table 4)

Friability test: Friability was determined on 20 tablets. Tablet samples were weighed accurately and placed in Roche Friabilator (Electrolab India Ltd). After 100 rotations (4 min at 25 rpm) loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand the wear. The percentage friability was determined by using following formula:

% Friability = Initial weight – Final weight / Initial weight X 100

The percentage friability of each formulation was determined. (Table 4)

Disintegration test: Disintegration time was determined to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. The tablets were examined using the USP- XXIV disintegration apparatus (Electrolab India). Six tablets were tested for each batch. The disintegration time of tablets was compared to 15 minutes which is accepted as the general tablet disintegration time. The mean disintegration time of each formulation is shown in table 4.

Drug content studies: Drug content of the manufactured tablets of each batch was determined by Liqiud chromatography.

Solvent mixture: A mixture of 60 volumes of water and 40 volumes of acetonitrile.

Test solution: 20 tablets were weighed and finely grinded from each batch. Aliquot of this powder equivalent to 50 mg of Cefpodoxime was accurately weighed and dispersed in 100.0 ml of the solvent mixture. 5 ml of the solution was then diluted 100.0 ml with the solvent mixture and filter.

Reference solution: A quantity of Cefpodoxime Proxetil RS was dissolved in the solvent mixture to obtain a solution containing about 30µg/ml

Chromatographic system:

Column – Carbon 18

Wavelength – 235 nm

Flow rate – 2 ml/min

Injection Volume – 50 µl

The test solution and the reference solution were injected and the content of Cefpodoxime in the tablets was calculated and given in table 4.

Content of Cefpodoxime Proxetil in each tablet (mg) = Sample area X Std dilution X Purity (an anhydrous basis) X Avg weight / Standard area X Sample dilution X 100

***In Vitro* release studies:** *In vitro* release study of Cefpodoxime Proxetil was carried out using USP Type II dissolution apparatus (Paddle type, model TDT-08L, Electro lab, India) at 37±1°C and 75 RPM using 900 ml of dissolution medium for 30 min . Dissolution medium was prepared by dissolving 3.03 gm of glycine and 3.37 gm of sodium chloride in about 500 ml of water, adding cautiously with swirling 0.8 ml of hydrochloric acid, adjusting the pH to 3.0 and diluting to 1000 ml with water. Aliquots were withdrawn at predetermined time intervals and were replenished immediately with the same volume of fresh dissolution medium. Calculate the content of Cefpodoxime in the medium from the absorbance obtained from a solution of known concentration of Cefpodoxime Proxetil RS in the medium. The results are given in table no 5 with fig 1.

Acceptance criteria: Not less than 75% of the stated amount of Cefpodoxime.

STABILITY STUDIES

The result of stability studies at 40°C was carried out according to ICH guidelines. The result has been given in table 6 and Fig 2.

RESULTS

PREFORMULATION STUDIES

Physical Observation

CP – Cefpodoxime Proxetil

✓ : No colour change

× : Colour change

Inference: Selected excipients were found to be compatible with CP and also other excipients.

EVALUATION OF PRE COMPRESSION PARAMETERS

Inference: Evaluation properties of granules found to show excellent flow properties.

EVALUATION OF POST COMPRESSION PARAMETERS

Inference: The values were found to be in limits.

DISSOLUTION STUDIES OF CP TABLETS

Inference: *In vitro* drug release was performed and release of ARL 8 was found to better when compared with marketed reference sample.

STABILITY PARAMETERS EVALUATION OF CP TABLETS

Inference: The study report indicated that tablets did not show any physical changes during the study period, and the drug content was found to be more than 85% at the end of 6 months in accelerated conditions. The results indicated that the formulations were quite stable at accelerated storage conditions. Results are shown in table no 6 with fig no 2.

Table 1: Formulae used in the preparation of tablets

Ingredients	Formulation Code (mg)							
	ARL 1	ARL 2	ARL 3	ARL 4	ARL 5	ARL 6	ARL 7	ARL 8
Intragranular materials								
Cefpodoxime Proxetil	139.74	139.74	139.74	139.74	139.74	139.74	139.74	139.74
Starch	15.00	10.00	10.00	10.00	41.26	16.99	15.26	2.26
Lactose	64.26	48.76	31.26	31.26	.....	.....	.....	.....
Calcium CMC	.....	.....	.....	.....	.....	.....	10.00	11.50
Binding materials								
Sodium lauryl sulphate	5.00	10.00	10.00	10.00	10.00	10.00	10.00	11.50
Croscarmellose sodium	12.00	12.00	12.00	12.00	12.00	12.00	12.00	14.00
Extragranular materials								
Crosspovidone	9.00	12.00	12.00	12.00	12.00	12.00	12.00	13.00
Magnesium stearate	5.00	5.00	5.00	5.00	5.00	5.00	5.00	6.00
L-HPC	.....	12.50	30.00	30.00	30.00	54.27	44.00	50.00
Colloidal silicon dioxide	.....	.....	.....	.....	.....	.....	2.00	2.00
Average Weight (mg)	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**
Coating materials								
Opadry white 21 K	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Polysorbate 80	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Iso propyl alcohol (ml)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Methylene dichloride(ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total weight (mg)	**255.0**	**255.0**	**255.0**	**255.0**	**255.0**	**255.0**	**255.0**	**255.0**

Table 2: Compatibility studies of Cefpodoxime Proxetil with excipient

S.No	Drug+Excipient	Parameter	Initial Value of Parameter	Condition				Comments
				1st MONTH		3rd MONTH		
				50°C	2-8°C	RT	40°C	
1	CP + CCS	Change in Colour	No color change	✓	✓	✓	✓	Compatible
2	CP + Lactose	Change in Colour	No color change	✓	✓	✓	✓	Compatible
3	CP + Starch	Change in Colour	No color change	✓	✓	✓	✓	Compatible
4	CP + SLS	Change in Colour	No color change	✓	✓	✓	✓	Compatible
5	CP + Crospovidone	Change in Colour	No color change	✓	✓	✓	✓	Compatible
6	CP + Magnesium stearate	Change in Colour	No color change	✓	✓	✓	✓	Compatible
7	CP + L-HPC	Change in Colour	No color change	✓	✓	✓	✓	Compatible
8	CP+ Calcium CMC	Change in Colour	No color change	✓	✓	✓	✓	Compatible
9	CP + Colloidal silicon dioxide	Change in Colour	No color change	✓	✓	✓	✓	Compatible

Table 3: Physical properties of granules of different formulations

Parameters	ARL 1	ARL 2	ARL 3	ARL 4	ARL 5	ARL 6	ARL 7	ARL 8
Angle of repose*	26.84±1.2	27.63±1.22	28.02±1.28	26.73±1.26	26.61±1.27	28.54±1.25	26.29±1.26	26.84±1.3
Bulk density*	0.544±0.0	0.537±0.01	0.55±0.018	0.544±0.01	0.545±0.07	0.542±0.07	0.538±0.01	0.57±0.06
Tapped density*	0.587±0.0	0.589±0.01	0.603±0.02	0.594±0.02	0.596±0.02	0.59±0.02	0.586±0.01	0.58±0.01
Compressibility index* (%)	8.900±0.9	8.690±0.25	8.280±0.88	8.310±0.38	8.590±0.37	8.040±0.62	8.500±0.20	9.290±0.6
Hausner's ratio*	1.09±0.01	1.09±0.003	1.09±0.010	1.09±0.004	1.09±0.004	1.08±0.007	1.09±0.002	1.10±0.00

*** Mean ± SD (n=3)**

Table 4: Evaluation parameters of Cefpodoxime Proxetil tablet

PARAMETERS	ARL 1	ARL 2	ARL 3	ARL 4	ARL 5	ARL 6	ARL 7	ARL 8
Average weight (mg)*	255.07 ±0.12	255.97 ±0.15	255.07 ±0.31	255.97 ±0.15	255.97 ±0.06	255.03 ±0.25	255.03 ±0.06	255.97 ±0.06
Thickness (mm)*	3.38 ±0.03	3.37 ±0.01	3.39 ±0.01	3.39 ± 0.02	3.37 ±0.01	3.38 ±0.02	3.40 ±0.01	3.40 ±0.01
Core Hardness (kP)*	8.83 ±0.06	8.83 ±0.06	8.86 ±0.06	8.87 ±0.05	8.86 ±0.05	8.90 ± 0.1	8.90 ±0.05	8.90 ±0.06
Core Friablity (%)*	0.01 ±0.001	0.03 ±0.002	0.018 ±0.002	0.028 ±0.002	0.028 ±0.002	0.017 ±0.002	0.01 ±0.001	0.01 ±0.001
Disintegration time (min)	10 min 12 sec	8 min 24 sec	6 min 04 sec	5 min 42 sec	4 min 12 sec	4 min 31sec	3 min 34 sec	2 min 49 sec
Drug content (%)*	99.39 ±0.7	98.16 ±0.15	99.72 ±0.53	99.88 ±0.33	98.82 ±0.91	99.11 ±0.15	99.28 ±0.96	99.76 ±0.77

*** Mean ± SD (n=20)**

Table 5: In vitro Percentage drug release studies of Cefpodoxime Proxetil tablet

S.No.	Formulation code	Drug release* (%) (30 min)
1.	ARL 1	41.40 ± 0.020
2.	ARL 2	48.56 ± 0.011
3.	ARL 3	56.14 ± 0.015
4.	ARL 4	57.85 ± 0.021
5.	ARL 5	62.96 ± 0.020
6.	ARL 6	66.59 ± 0.014
7.	ARL 7	88.86 ± 0.013
8.	ARL 8	90.78 ± 0.020
9.	Marketed Sample	82.63 ± 0.016

*** Mean ± SD (n=6)**

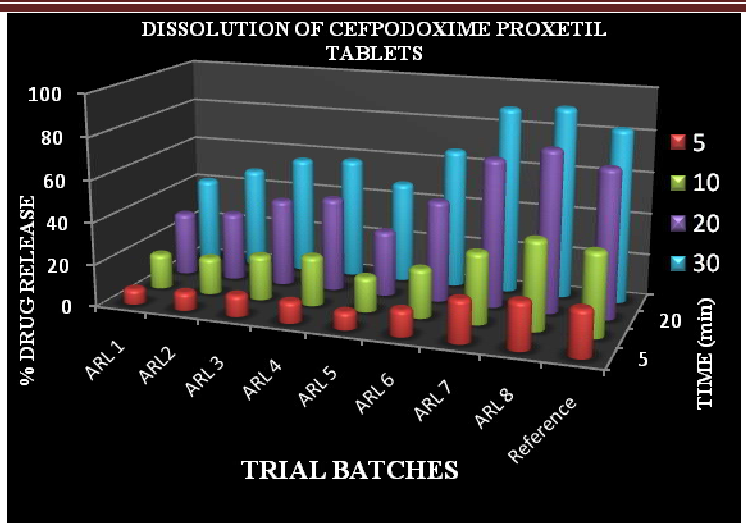

Fig 1: Comparative in vitro dissolution of Cefpodoxime Proxetil tablets trial batches

Table 6: Evaluation of stability parameters of final batch – Accelerated Studies

S.NO	Time interval (ARL 08) (months)	Accelerated studies	
		Dissolution (%)*	Assay (%)#
1	0.0 (Initial)	90.78 ± 0.02	99.76 ± 0.77
2	1.0	89.96 ± 0.02	98.06 ± 0.81
3	2.0	87.37 ± 0.012	97.06 ± 0.62
4	3.0	86.53 ± 0.014	96.94 ± 0.55
5	6.0	85.46 ± 0.02	96.26 ± 0.78

* Mean ± SD (n=6)
# Mean ± SD (n=20)

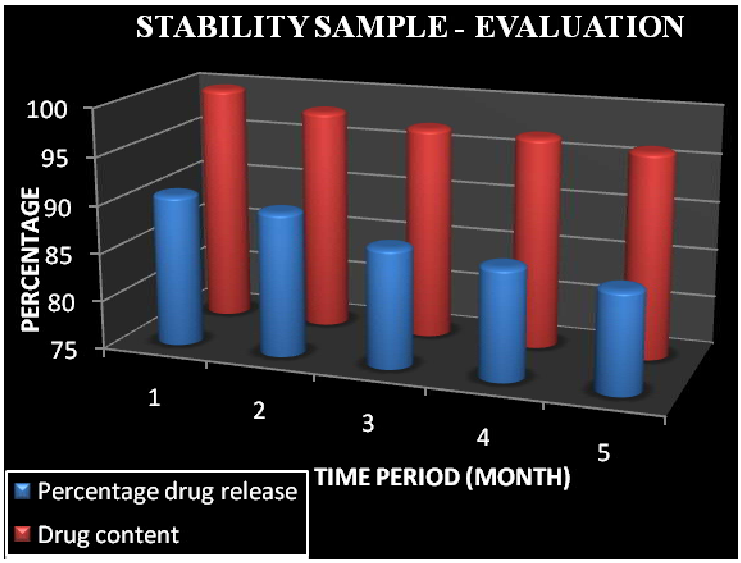

Fig 2: Comparative dissolution and drug content study of CP tablets for stability batches

DISCUSSION

Compatibility studies performed with various excipients, the physical attributes of the tablet were found to be satisfactory. Then the dosage form was formulated using wet granulation method and the granules was made using the selected excipients and its evaluation parameters such as flow properties was found to be within the range of excellence.

Tablet was compressed using 9.5 mm biconvex punches. Results for other physical evaluations were also found to be within an acceptable range. For instance, average weight, hardness of the tablet, thickness was found to be within the limit. Friability of the tablet was well within the acceptable range of 1%. DT was performed which was well within the limit 30 min. Percentage drug release was studied using the drug release was found to around 90.78 %.

Assay for CP: The resolution factor R between the CP S and R epimer peaks was 2.512 (NLT 2.5), and the tailing factor for CP R epimer was 1.07 (NMT 1.5). The assay percentage was 98.32% (90% to 110%), with relative standard deviation (RSD) of 1.06% (NMT 1%).

Stability studies for the formulation batches has been performed according to ICH guidelines at 40°C ± 2°C, 75% RH ± 5% RH. The content of drug and drug release at the end of 6th month was found to be 96.26% and 85.46% respectively. The tablet was found to be stable at the end of 6th month.

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