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COMPARISON OF *IN VITRO* DISSOLUTION PROFILES OF CEFPODOXIME PROXETIL - PEG SOLID DISPERSIONS WITH CEPODOXIME PROXETIL

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ABSTRACT

The aims of this study were (1) to compare the *in vitro* dissolution profiles of Solid dispersion of Cefpodoxime Proxetil with PEG 6000, with those of pure drug and physical mixture of Cefpodoxime proxetil and PEG 6000. (2) to apply statistical models to evaluate each ratio of Cefpodoxime proxetil and PEG 6000 in solid dispersion in terms of easy application and usefulness, and (3) to identify the most suitable ratio of Cefpodoxime Proxetil and PEG 6000 as solid dispersion.

Solid dispersions of Cefpodoxime Proxetil were prepared with PEG 6000 in different ratios by using kneading method. Dissolution profile of all these solid dispersions were compared with dissolution profile of Cefpodoxime proxetil and physical mixture of Cefpodoxime proxetil and PEG 6000. The results showed that the Solid dispersions containing PEG in different proportions exhibit faster release (about 2.2 – 3 fold faster) than Cefpodoxime proxetil and physical mixture of Cefpodoxime proxetil and PEG. Among the solid dispersions containing different ratios batch A containing Cefpodoxime proxetil and PEG 6000 in 1:1 ratio exhibited about 3 fold improvement in release profile. The release kinetics of Solid dispersions was investigated using several mathematical equations. In Model-independent method similarity factor, *f*2, was used for the comparison of *in vitro* dissolution profiles. The results showed that model-dependent methods were more discriminative than model-independent methods. Model independent methods seemed to be easier to apply and interpret; only one value is obtained to describe the closeness of the two dissolution profiles. The application and evaluation of model-dependent methods were more complicated; these methods present an acceptable model approach to the true relationship between percent dissolved and time variables, including statistical assumptions that could be checked.

KEYWORDS: Dissolution profile, model independent methods, Cefpodoxime proxetil, solid dispersion.

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INTRODUCTION

Cefpodoxime proxetil (CP) is a poorly water-soluble 3rd generation broad spectrum β- Lactam cephalosporin class of *antibiotic*, according to the BCS system (Class IV), and its dissolution is one of the rate-limiting step for absorption[1]. Drug absorption from solid dosage forms after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two steps, *in vitro* dissolution may be relevant to the prediction of in vivo performance. Based on this general consideration, *in vitro* dissolution tests for immediate-release solid oral dosage forms are used: to assess the lot-to-lot quality of a drug product, to assess the stability of the drug product, to ensure continuing product quality and performance after certain changes (e.g., changes in the formulation, manufacturing process, site of manufacture, and scale-up of the manufacturing process), to develop new formulations[2].

In formulation development, dissolution testing can aid in the selection of excipients, the optimization of the manufacturing process, and the formulation of a test product to match the release of the reference product[3,4]. The solubility, permeability, dissolution, and pharmacokinetics of the drug substance are parameters used to set the dissolution method and specification. The

methods for the comparison of *in vitro* dissolution profiles can be classified into three groups, model-dependent methods, and model-independent methods and methods based on analysis of variance (ANOVA)[5-7].

The purpose of the present work was to enhance dissolution rate, by preparing solid dispersions of CP using PEG 6000 as carrier and by using kneading method[8-10]. The release profile of solid dispersions was compared with CP and physical mixture (PM) of CP and PEG 6000 and among themselves using model-dependent and model-independent methods. The most suitable ratio of CP and PEG 6000 to get solid dispersion of better dissolution profile was determined.

MATERIALS AND METHODS

Cefpodoxime Proxetil (CP) was obtained as a gift sample from Maxim Pharmaceutical Pvt. Ltd. (Pune, India). Polyethylene Glycol (PEG6000) was supplied by Colorcon Asia Ltd. (Goa, India), All solvents used were of analytical grades and were used as obtained.

Solid dispersions of CP with PEG 6000 were prepared in the ratios of 1:1, 1:0.75, 1:0.5, 0.75:1 and 0.5:1 (Batch No A,B,C,D,E respt) of CP to PEG 6000 by using a kneading method. A mixture of CP and PEG 6000 (ratios of 1:1, 1:0.75 and 1:0.5, 0.75:1, 0.5:1 w/w) was wetted with methanol and kneaded thoroughly. The blend was dried and finally passed through # 60. The formulation and batch codes of all Solid dispersions are described in **Table 1**.

Dissolution Testing

In vitro dissolution studies of prepared solid dispersions were carried out in 900 mL of 0.1 N HCl as a medium using USP Apparatus 2 (paddle method) with three replicates. The paddle rotation speed was 75 rpm, and a temperature of 37 ± 1 °C was used in the test. In all experiments, 5 mL of dissolution sample was withdrawn at 15, 30, 45 and 60 min interval, filtered using a 0.45-mm Whatman filter, and replaced with an equal volume of fresh medium to maintain a constant total volume. Samples were analysed by UV spectrophotometry at 263 nm (JASCO, V-550, Japan). Cumulative percentages of drug dissolved from the solid dispersions were calculated by using pcp disso software[11].

Methods To Compare Dissolution Profiles

Model-Independent Methods

For the determination of dissolution data equivalence, FDA guidance documents recommend approaches such as the model-independent approach based on the calculation of difference (f1) and similarity (f2) factors. The main advantage of the f1 and f2 equations is that they provide a simple way to compare the data. Nevertheless, both equations do not account for the variability or correlation structure of the data, and they are sensitive to the number of points used. From a statistical point of view, this method seems to be less discriminating than other methods, such as ANOVA and model-dependent methods. According to the FDA guidance, f1 values of 0–15 and f2 values of 50–100 ensure sameness or equivalence of the two dissolution profiles. In both equations, R and T represent the dissolution measurements at P time points of the reference and test, respectively. Formulas for f1 and f2 value determinations are given as per equations 1 and 2 respectively[2,5,7,11].

$$f_1 = \left\{ \left[\sum_{i=1}^{P} |R - T| \right] / \left[\sum_{i=1}^{P} R \right] \right\} \times 100. \quad \text{.....(1)}$$

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{P} \right) \sum_{i=1}^{P} (R - T)^2 \right]^{-1/2} \times 100 \right\} \quad \text{.....(2)}$$

Model-Dependent Methods

Release kinetics of CP and its solid dispersions was analyzed by various mathematical models, which were applied considering the amounts of drug released from 0 to 60 mins. **Table 2** presents the various models tested. Depending on these estimations, suitable mathematical models to describe the dissolution profiles were determined[2,11].

The following plots were made: cumulative % drug release versus time (zero-order kinetic model); log cumulative % drug remaining versus time (first-order kinetic model); cumulative % drug release versus square root of time (Higuchi model); cube root of drug % remaining in matrix versus time (Hixson–Crowell cube root law); Log cumulative percent drug released Vs log time (Korsmeyer- peppas)[2,5,7].

RESULTS AND DISCUSSION

The *in vitro* dissolution profiles of various solid dispersions are shown in **Figure1**. Each data point represents a mean of three measurements for each solid dispersion. All prepared solid dispersions showed more than 80% release in 60 min. CP and its Physical Mixture (PM) with PEG 6000 showed less than 80 % release in 60 min. All Solid dispersions showed rise in % release at the end of 60 minutes as compared to CP and PM. This indicates that solid dispersions have better dissolution rate than CP and PM. Solid dispersion A showed about 99.15% release at the end of 60 min which was highest among the solid dispersions A-E. Hence dissolution rate of solid dispersion A is higher than all other solid dispersions.

Model-Independent Methods

The dissolution profile of pure drug CP is dissimilar to profiles of PM and solid dispersions A - E. The cumulative % drug release of solid dispersion A was 3 times faster, of Solid dispersion B and C was 2.5 times faster, and of solid dispersions D, E are about 2.2 times faster than CP. It indicates that when drug and PEG 6000 are present as 1:1 ratio in solid dispersion (as in solid dispersion A), maximum rise in dissolution rate is observed. When proportion of PEG 6000 is more than the drug in a solid dispersion (as in D and E) rise in dissolution rate is less than when proportion of PEG 6000 is less than CP. As proportion of PEG 6000 increases from 0.5 to 1 part, (for 1 part of CP) cumulative % drug release was increased from 98% – 99.15%. But as proportion of PEG 6000 increased beyond 1 part, for 1 part of CP, cumulative % drug release decreased to about 94%. The highest dissolution rate is observed when both CP and PEG are present in the same proportion.

The dissimilarity in dissolution profile of CP and that of PM as well as solid dispersions A-E was indicated by f2 value [less than 50] as shown in **Table 3**. When dissolution profile of A – E was compared among themselves it was observed that dissolution profiles of A,B,C,D and E were comparable as indicated by f2 value [between 50 – 100] as shown in **Table 3.** Dissolution profile of solid Dispersions A, B and C were very similar as shown by f2 value > 70 **(Table 3)**

Model-Dependent Methods

Linearization of the CP dissolution profiles using the equations in **Table 2** would better characterize the differences found among all solid dispersions. Plots for various kinetic models are shown in **Figures 2–6**.

Zero order rate describes the systems where the drug release rate is independent of its concentration. **Figure 2** shows cumulative amount of drug release vs time for zero order kinetics. The first order, which describes the release from the systems where the release rate is concentration dependent, is illustrated by **Figure 3**, which shows log cumulative percent drug remaining vs time. **Figure 4** illustrates Hixson crowell's cube root kinetics showing cube root of % Drug remaining vs time. Higuchi's model shown in the **Figure 5** describes release of the drug as a square root of time dependent process based on fickian diffusion. **Figure 6** shows plot for the Korsmeyer-Peppas equation showing Log Cumulative % Drug Release vs log time.

The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined (Table 4). It was found that *in vitro* release of all five solid dispersions A-E was best explained by Korsemeyer peppas equation as the plots showed the highest linearity ($r^2 \geq 0.98$ for all solid dispersions), followed by First order and Higuchi's model ($r^2 \geq 0.95$ for all solid dispersions). Solid dispersion A showing highest dissolution rate showed highest value of linearity for Korsemeyer Peppas model, followed by first order model followed by Higuchi's model as compared with remaining four solid dispersions (B, C, D, E).

CONCLUSION

Hence based on dissolution data, Model independent studies and model dependent studies, it can be concluded that Solid dispersion A containing 1:1 ratio of CP to PEG 6000 showed highest dissolution rate. Dissolution profile of Solid dispersion A is comparable to B,C, D and E as indicated by similarity factors (between 50 - 100). Highest linearity for dissolution profile was observed for Korsemeyer Peppas model, followed by first order model followed by Higuchi's model for all solid dispersions with values very close to 1 for solid dispersion A.

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Table 1: Solid dispersions of CP and PEG 6000

Batch Code	PD	PM	A	B	C	D	E
CP: PEG	1:0	1:1	1:1	1:0.75	1:0.5	0.75:1	0.5:1

CP : Cefpodoxime Proxetil

Table 2: Applied Dissolution Models

Models	Equations	Graph
Zero order	Qt = Q0 + K0t	Cumulative % drug release Vs. Time
First order	In Qt = In Q0 + K1t	Log cumulative % drug remaining Vs. Time
Higuchi	Qt = KHt1/2	Cumulative % drug release Vs. square root of time.
Hixson- Crowell	W01/3 - Wt1/3 = Kst	Cube root of % drug remaining Vs. Time.
Korsmeyer-peppas	M0/Mt = atn	Log cumulative percent drug released Vs log time.

Qt: amount of drug released in time t, Q0: initial amount of drug in the tablet, k0, k1, kH, Ks: release rate constants, n: release exponent (indicative of drug release mechanism), m: accumulated fraction of the drug, a: scale parameter, Ti: location parameter

Table 3: f2 Values for Each Comparison

Comparison	f2	Dissolution Profile	Comparison	f2	Dissolution Profile
PD × A	13.81	Dissimilar	A × B	70.31	Similar
PD × B	13.36	Dissimilar	A × C	76.05	Similar
PD × C	13.81	Dissimilar	A × D	50.16	Similar
PD × D	13.55	Dissimilar	A × E	69.73	Similar
PD × E	14.54	Dissimilar	B × C	83.90	Similar
PM × A	15.88	Dissimilar	B × D	48.38	Dissimilar
PM × B	15.38	Dissimilar	B × E	73.60	Similar
PM × C	15.59	Dissimilar	C × D	49.33	Dissimilar
PM × D	15.59	Dissimilar	C × E	77.87	Similar
PM × E	16.69	Dissimilar	D × E	55.18	Similar

Table 4: Parameters of various dissolution models applied

Dissolution Model	PD	PM	A	B	C	D	E
Zero-order K_0	0.6847	0.8011	2.0319	2.0315	2.0310	1.7721	1.9608
R^2	0.9444	0.9483	0.8138	0.7376	0.7687	0.7728	0.7485
First-order K_0	-0.0083	-0.0101	-0.0758	-0.0657	-0.0695	-0.0373	-0.0519
R^2	0.9683	0.9975	0.9821	0.9878	0.9823	0.9521	0.9793
Hixson–Crowell K_0	-0.0026	-0.0031	-0.0142	-0.0134	-0.0137	-0.0094	-0.0118
R^2	0.9615	0.9693	0.9814	0.9484	0.9701	0.9036	0.9231
Higuchi K_0	4.6453	5.4395	14.102	14.2044	14.1638	12.3474	13.7002
R^2	0.9895	0.9969	0.9799	0.9578	0.9686	0.9676	0.9625
Korsmeyer peppas K_0	4.7155	4.9099	29.1634	41.67	36.102	32.4566	37.5511
R^2	0.9562	0.9919	0.9842	0.9830	0.9993	0.9737	0.9988

$R^{2=}$ Determination Coefficient, K0 = Release rate constant

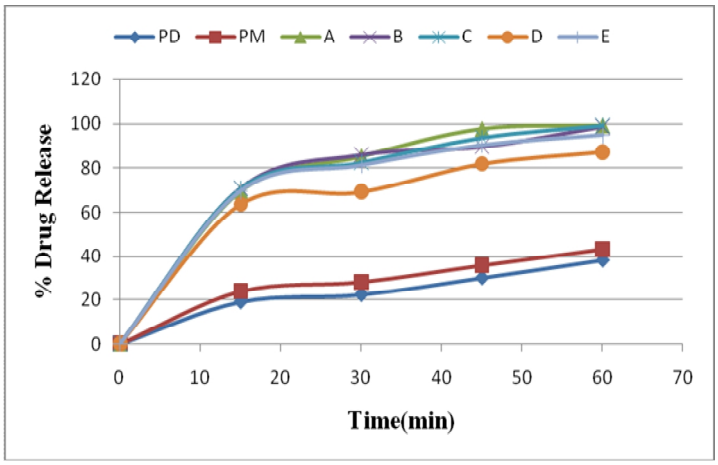

Figure 1: Mean (n = 3) *in vitro* dissolution profiles of solid dispersions of CP

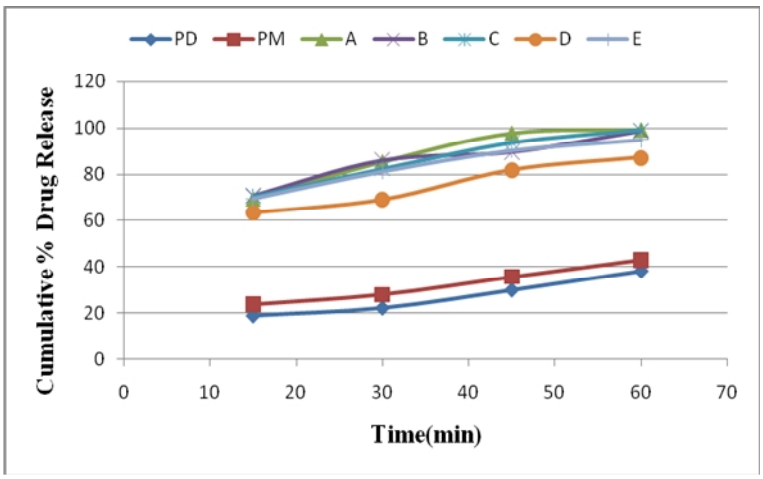

Figure 2: Zero-order plots for CP solid dispersions

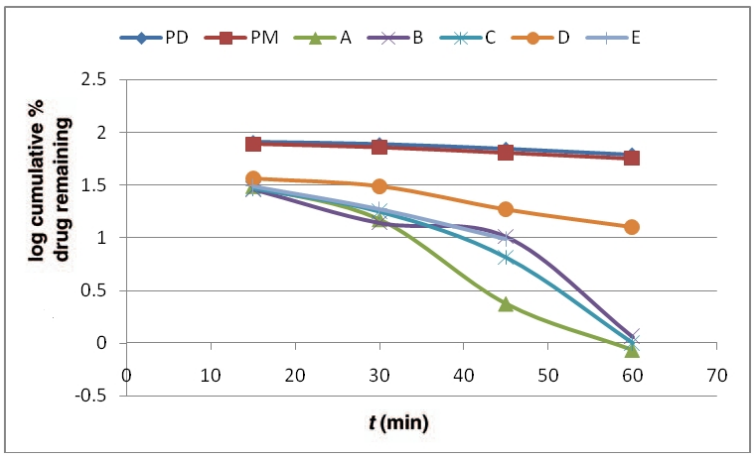

Figure 3: First-order plots for CP solid dispersions

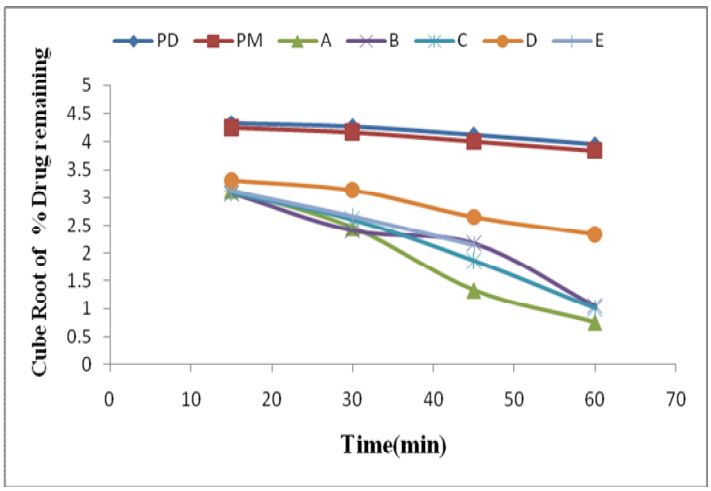

Figure 4: Hixson–Crowell plots CP solid dispersions

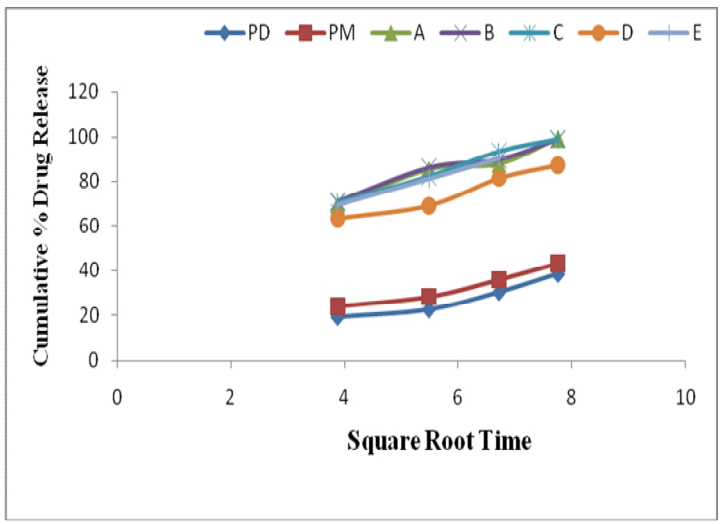

Figure 5: Higuchi plots for CP solid dispersions

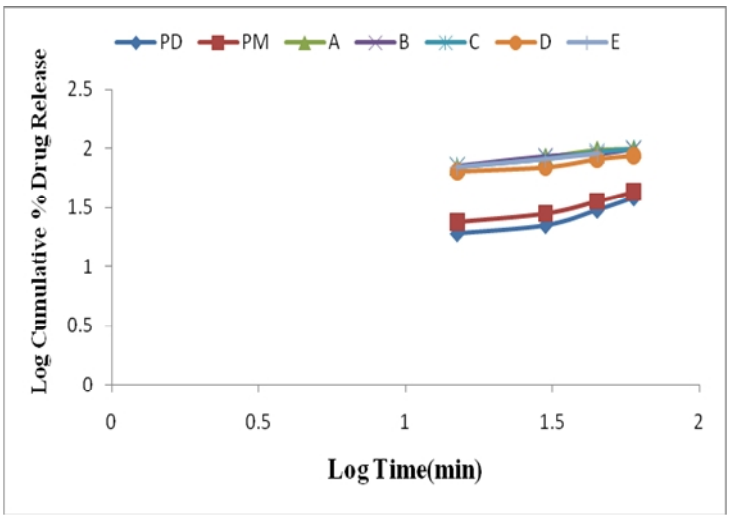

Figure 6: Korsmeyer peppas plots for CP solid dispersions

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