Evaluation of Dissolution Behavior of Cefuroxime Axetil as Affected by Polymeric Interaction Using Mixture Design Experiment

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ABSTRACT: The objective of this project was to improve the solubility of poorly water soluble drugs, namely cefuroxime axetil by formulating solid dispersions with hydrophilic polymer. Hydroxypropyl methyl cellulose (HPMC), polyvinyl pyrrolidine (PVP) and polyethylene glycol (PEG) were used as polymeric carriers for the preparation of solid dispersion. Solid dispersions were prepared by the solvent extraction method. Interaction effect of HPMC, PVP and PEG was investigated using a simplex mixture design. A fitted mathematical model was used to express each response as a function of the proportion of the blend components that are able to empirically predict the response to any blend of combination of the components. The synergistic interaction effect of the ternary HPMC: PVP: PEG blend was shown to be strongest among the experimental blends. Nevertheless, an antagonistic interaction effect becomes significant as the HPMC proportion increases in the blends. The study revealed that a mixture design could be a valuable tool in better elucidating and predicting the effects on dissolution beyond the conventional one component blend.

Key words: Solid Dispersion, Cefuroxime Axetil, Simplex Mixture Design, Polymeric Interaction.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects.[1] The oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations.[2] Due to the greater stability, convenience and ease of ingestion, smaller bulk, accurate dosage and easy production solid oral dosage forms have many advantages over other types of oral dosage forms. Most of the new chemical units under development are anticipated to be used as a solid dosage form that initiates an effective and reproducible *in vivo* plasma concentration after oral administration.[3]

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With the recent introduction of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery presents one of the most frequent and greatest challenges to formulation scientists.[4] A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it takes time to be absorbed in the gastrointestinal tract. Thus, a greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products.

Solid dispersion (SD) technique has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs.[5,6] Chiou and Riegelman (1971) defined the term SD as

a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures.[7] SD refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.[1] SD has attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of drugs.[8]

Cefuroxime axetil is an oral cephalosporin which is rapidly hydrolyzed to the active parent compound, cefuroxime which has a broad spectrum of *in vitro* antibacterial activity which encompasses methicillin-sensitive staphylococci and the common respiratory pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella (Branhamella) catarrhalis* and group A beta-hemolytic streptococcus.[9] Chemically cefuroxime axetil is the 1-acetoxy ethyl ester of cefuroxime. The axetil salt renders the molecule more lipophilic, thus allowing enhanced oral absorption.[10]

The dissolution and stabilization of the cefuroxime axetil in solid solutions are influenced by parameters including drug to polymer ratio, hydrophilicity of polymer, and interactions between the polymer and the drug. Immediate release of cefuroxime axetil can be delivered from solid solutions with water soluble carriers and cross-linked hydrophilic polymers. The objectives of this work are: (1) to evaluate selected polymeric carriers not previously studied for their suitability to form SD with cefuroxime axetil and to examine the applicability of a commercially available hydrophilic polymer, in preparing SD by the equilibrium solvent loading method for immediate release applications and (2) to identify the effect of the polymeric concentration in the dissolution of cefuroxime axetil. Previous studies demonstrate that most of the drugs show an elevated dissolution, when the polymeric ratio is high. The high amount of polymer not only affects the cost of the formulation but also other physicochemical properties of the formulation. In this study we developed a novel approach by investigating the effect of polymeric interaction on the dissolution of cefuroxime axetil by mixture experimental design.

MATERIALS AND METHODS

Materials. The active ingredient cefuroxime axetil was collected from Incepta Pharmaceuticals Ltd. as kind gift sample. The hydrophilic polymers used in the study were hydroxypropyl methyl cellulose (HPMC), povidone (PVP K30) and polyethylene glycol (PEG 6000) which were purchased from Loba Chemicals (India).

Preparation of solid dispersion. Solvent evaporation technique was used to prepare SD. Dispersion tube was used to avoid the very low yield percentage of SD after the evaporation of solvent. In our previous studies a stick film of HPMC or PVP was found after evaporation of solvent on the beakers or petri-dishes which were used as container for preparation of SD and it was very difficult to collect the dried SD from there. So, an inert PVC dispersion tube having two openings was used to overcome this problem. Polyethylene was used at one opening of the tube to ease the collection of SD after drying.

At first 5 ml acetone was taken in a 50 ml beaker and appropriate amount of drug-polymer mixture was added and dissolved in acetone by moderate stirring until a clear solution was formed. The solution was then taken in the dispersion tubes and heated on a thermostatic water bath for 24 hrs maintaining the temperature at 65°C. Dispersion tubes were then collected from the water bath and allowed for drying for next 30 min in a dryer at 40°C. Dried samples were taken in a mortar from the dispersion tube. Powder SDs were obtained after grinding and preserved in air-tight screw cap vials and the vials were kept in desiccators until further use.

***In vitro* dissolution study of cefuroxime axetil solid dispersion.** *In vitro* release of cefuroxime axetil SDs was performed by using apparatus I (Paddle) on 900 ml dissolution media. 0.1 N HCl solution was used as dissolution media in the dissolution

study. The dissolution tests were performed for 1 h. 5 ml of sample was withdrawn at 5, 15, 30, 45 and 60 min interval and fresh media was replaced immediately to maintain the sink condition. The samples were filtered through Whatman filter paper. The absorbance of the solutions was measured at 278 nm for the drug by using a double beam UV/VIS spectrophotometer (Shimadzu-1650PC, Japan).

Mixture experimental design. Mixture experiments are a special class of response surface experiments in which the product under investigation is made up of several components or ingredients. Designs for these experiments are useful because many products design and development activities in industrial situations involve formulations or mixtures. In these situations, the response is a function of the proportions of the different ingredients in the mixture. For example, a pancake mix or an insecticide may be developed that blends four or more chemical ingredients.

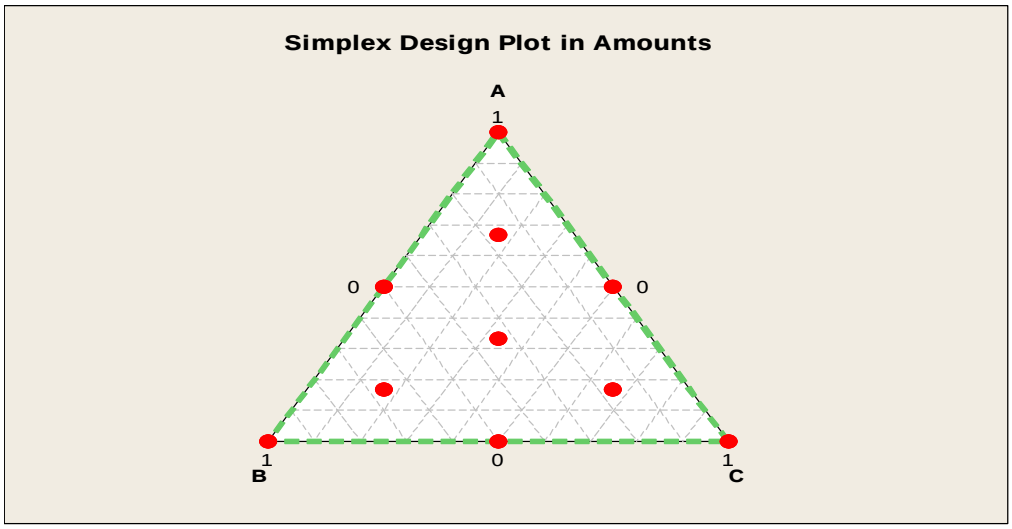

Figure 1. Simplex design plot.

Blends of HPMC, PVP K30 and PEG 6000 containing pure HPMC, PVP K30, PEG 6000 and blends thereof were prepared according to the augmented simplex-centroid mixture design with 10 points (Figure 1). The experimental domain consisted of different proportions of components of X1 (HPMC), X2 (PVP K30), and X3 (PEG 6000) between zero and one ($0 \leq Xi \leq 1$; $\sum Xi = 1$). The experimental domain was within an equilateral triangle (regular simplex). The vertexes of the simplex represented the pure components, the edges of the triangle represented the two-component blends, and points within the triangle represented the three-component blends. To allow error estimation, all blends were prepared in three independent replications, providing a total of 7 blends (Table 1).

Table 1. Formulation of mixture design.

Code	Component proportion		
	HPMC (X1)	PVP K30 (X2)	PEG 6000 (X3)
MSD1	0.00000	1.00000	0.00000
MSD2	0.50000	0.50000	0.00000
MSD3	0.33333	0.33333	0.33333
MSD4	0.00000	0.50000	0.50000
MSD5	1.00000	0.00000	0.00000
MSD6	0.50000	0.00000	0.50000
MSD7	0.00000	0.00000	1.00000

A one-way analysis of variance (ANOVA) with Tukey's Multiple Comparisons was applied on the data (n=3) to determine a significant ($p<0.05$) difference among the SDs. Mixture regression analysis was performed to determine estimated coefficients and significance of the model terms, the

f-test and coefficient of determinations (R^2). The results were initially fitted to all available mixture regression models of increasing complexity, from linear to full quartic. Model significance, significance of lack-of-fit and adjusted R^2 value were used to judge the adequacy of model fitness. The adjusted R^2 value describes the proportion of variation in the responses that is explained by the model and the value has been adjusted for the number of terms. The influence on the response of each component singly or in combination with the other components can be obtained by expressing the blending properties of the mixture components with Scheffe-type polynomial model[11] as equations:

Linear: $$response = \sum_{i=1}^{q} \beta_i x_i \quad (1a)$$

Quartic: $$response = \sum_{i=1}^{q} \beta_i x_i + \sum_{i<j} \sum^{q} \beta_{ij} x_i x_j \quad (1b)$$

If the linear or quartic formula is deemed inadequate for graduating the response, the remedy would be progressing up to special forms or even higher orders of polynomial models as following:

Special cubic:

$$response = \sum_{i=1}^{q} \beta_i x + \sum_{i<j} \sum^{q} \beta_{ij} x_i x_j + \sum_{i<j<k} \sum \sum^{q} \beta_{ijk} x_i x_j x_k \quad (1C)$$

Special quartic:

$$response = \sum_{i=1}^{q} \beta_i x + \sum_{i<j} \sum^{q} \beta_{ij} x_i x_j + \sum_{m=1} \sum \sum_{i<j<k} \sum^{q} \beta_{ijk} x_i x_j x_k x_m \quad (1d)$$

where β values are the fitted regression coefficient for each term and X values are the proportions of the formulation components in the mixture, and they should all account for the compositional restrains (equation 2)

$$\sum_{i=1}^{q} x_i = 1 \quad and \quad 0 \leq x_i \leq 1, \qquad i = 1,2, \ldots\ldots\ldots\ldots\ldots, q \quad (2)$$

On the other hand, the effect of liner and blending on the response of interest for the independent covariates are expressed by a standard polynomial for that consist of *n* covariates as the equation,

$$response = \alpha_0 + \sum_{l=1}^{n} \alpha_l Z_l + \sum_{l<m} \sum^{n} \alpha_{lm} Z_l Z_m + \cdots \ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

Mixture regression analysis was performed to determine the estimated coefficients and significance of the model was determined by graphical method. The dissolution response was found to be best fitted (graphical analysis) with quartic model.

RESULTS AND DISCUSSION

Effect of primary blend. There were three primary blends containing a single polymer, PVP K30, HPMC and PEG 6000, the formulation codes of which were MSD1, MSD5 and MSD7, respectively. The responses of primary blends are shown in the Table 2. The best tool to identify the effect of primary blend is to analyze the Cox response trace plot. The trace plot shows how each component affects the response relative to the reference blend. In this study, the reference blend is the centroid of the design vertices. This trace plot provides the following information about the component effects.

Table 2. A simplex centroid design with PVP K30, HPMC and PEG and *in vitro* dissolution data of solid dispersion.

Code	Component proportion			Response (% drug release)
	HPMC (X1)	PVP K30 (X2)	PEG 6000 (X3)	
MSD1	0.00000	1.00000	0.00000	90.9100
MSD2	0.50000	0.50000	0.00000	32.2658
MSD3	0.33333	0.33333	0.33333	90.9894
MSD4	0.00000	0.50000	0.50000	67.6306
MSD5	1.00000	0.00000	0.00000	16.7500
MSD6	0.50000	0.00000	0.50000	65.0328
MSD7	0.00000	0.00000	1.00000	80.3600

The plot indicates that as the proportion of HPMC (solid black curve of Figure 2) in the mixture increases (and the other mixture components decrease), the dissolution of the drug decreases. The correlation co-efficient HPMC is -0.812 (p=0.027). This indicates that HPMC has a negative impact in the mixture design. Increased HPMC amount in the mixture decreases the dissolution of cefuroxime axetil and *vice versa*. As the concentration of polymer molecules increases, they begin to interact with each other hydro dynamically, leading to a concentration dependence of the diffusion coefficient. The interaction of polymer molecules is characterized by the overlapping of the polymer chains and intermolecular entanglement leading to a dynamic network structure.[12]

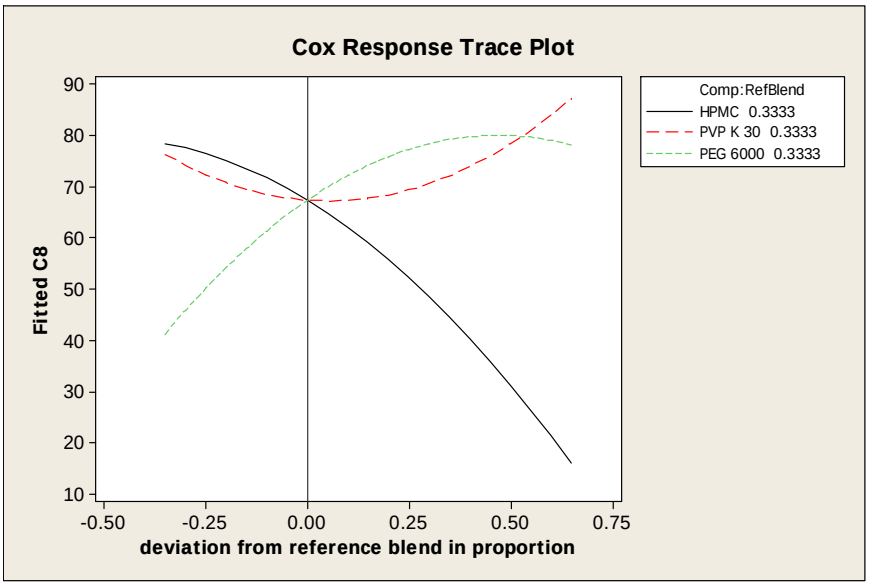

Figure 2. Cox response trace plot showing the effect of HPMC, PVP K30 and PEG 6000 blend.

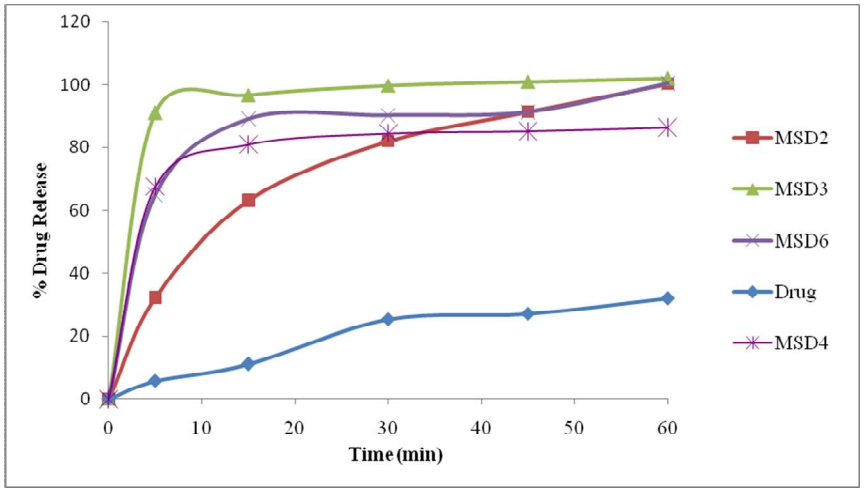

Figure 3. Drug release from mix polymeric solid dispersion.

It is clear that with the increase of PVP K30 proportion the dissolution rate of the drug increases. The correlation co-efficient of PVP K30 is 0.361 (p=0.427) which indicates that PVP K30 has a positive impact in the mixture design. The p-value (p>0.005) indicates there is no evidence to reject the

null hypothesis. On the other hand, as the proportion of PEG 6000 (short-dashed curve of Figure 2) in the mixture increases (and the other mixture components decrease), the dissolution also increases and vice versa.

Effect of binary blend. This study was purposely designed to investigate the effect of HPMC, PVP K30 and PEG 6000 interactions on the dissolution of cefuroxime axetil. Thus, the discussion focused on the effects of interaction relative to the pure effects of these polymers. In our present study solid dispersion with formulation code MSD2, MSD6 and MSD4 presented the binary blend. The evolution of dissolution rate of binary blends (at 1/2:1/2 ratio) are demonstrated in Figure 3.

All solid dispersions of HPMC, PVP K30 and PEG 6000 have been found to cause an increased dissolution of the drug. In the present study, all solid dispersions prepared with polymeric blends were also expected to exert a positive effect on the dissolution of cefuroxime axetil. As depicted in Figure 3, solid dispersion with binary blends of HPMC:PVP (MSD2) and HPMC:PEG (MSD6) exhibited an increased dissolution of cefuroxime axetil ($p<0.05$). The HPMC:PEG (MSD6) blends was found more effective than the HPMC:PVP (MSD2). This is due to the polymer component of the blend, HPMC having a negative impact on the dissolution when the polymeric content is high. But the hydrophilic nature of the HPMC is high. At a lower content HPMC can increase the dissolution of cefuroxime axetil. In the mixture design we used higher polymeric ratio (1:5), but the dissolution is high compared to pure drug. This is due to the mixing of the polymers, because in formulation MSD2, the second polymer is PVP and in the formulation MSD6, second polymer is PEG. The percent release of MSD6 is greater than that of MSD2 due to the higher hydrophilic character of PEG over PVP. Another secondary blend is MSD4, the component of which is PVP and PEG. The dissolution profile of it is better than the pure drug. The result indicates that mixture blend of polymer is better than the single blend of the polymer.

Effect of tertiary blend. In our present study, we used three polymers and three different blends. The result revealed a quite interesting fact. The behavior of each polymer is discrete from each other and a single polymer also showed different behavior in different blends. Figure 3 showed that the dissolution profile of the tertiary blend (MSD3) is eminent over all the formulation.

From the Figure 3 it was clear that the tertiary mixture blend exhibits higher or same dissolution value compared to the pure blends of polymers where polymers were in highest amount. Consequently, a strong polymer complex might have occurred in the system that led to more flexible network structure, reflecting a high amorphous nature. From these observations and explanations, we proposed the occurrence of a ternary synergism of HPMC, PVP and PEG in addition to binary synergisms in our ternary blends. In a different view, PEG might have formed its own network interpenetrating with the network from PVP and HPMC synergism that finally resulted in more flexible network structure.

Fitted regression models, contour and surface plots. Mixture regression analysis was applied on the experimental data. The design used in this study supports the fitting of the linear model (Cornell, 2002) and initially we intended to fit all responses to this model. However, after the statistical analysis, we found a significant lack-of-fit for the models fitted to some of the responses. On the other hand, those responses were adequately described by a more complex model of quartic. Table III represents the results of fitting model of response (% drug release). In our present study, we used the forward selection technique of MINITAB 16 to identify the term of the fitted regression equation. The estimated regression coefficients of X1, X2, X3, X1*X2, X1*X3, X2*X3, X1*X2*X3 are 16.75, 90.91, 80.36, -86.26, 65.91, -72.02 and 1041.62, respectively. It is clear that, both fittings finally provided high adjusted coefficient of determinations (R^2=0.8034). The R^2 values were found to be essentially high and the variances found in all responses were explained well by the models. The significant interaction terms in the fitted model

of the dissolution generally showed that the dissolution of cefuroxime axetil will be affected by both of the polymers, and the binary interactions between HPMC-PVP, HPMC-PEG, or PEG-PVP as well as ternary interactions among all polymers. The following equation shown the fitted model for the response-

$$Dissolution = 16.75x_1 + 90.91x_2 + 80.36x_3 - 86.26x_1x_2 + 65.91x_1x_3 - 72.02x_2x_3 + 1041.62x_1x_2x_3 \quad (4)$$

Table 3. Analysis of variance of model fits.

Source	Degree of freedom	Adjusted sum of square	Adjusted mean square	F	P
Dissolution					
Model	3	3959.23	1329.74	4.06	0.140
Lack of fit	0	0	0	0	0
Pure error	0	0	0		

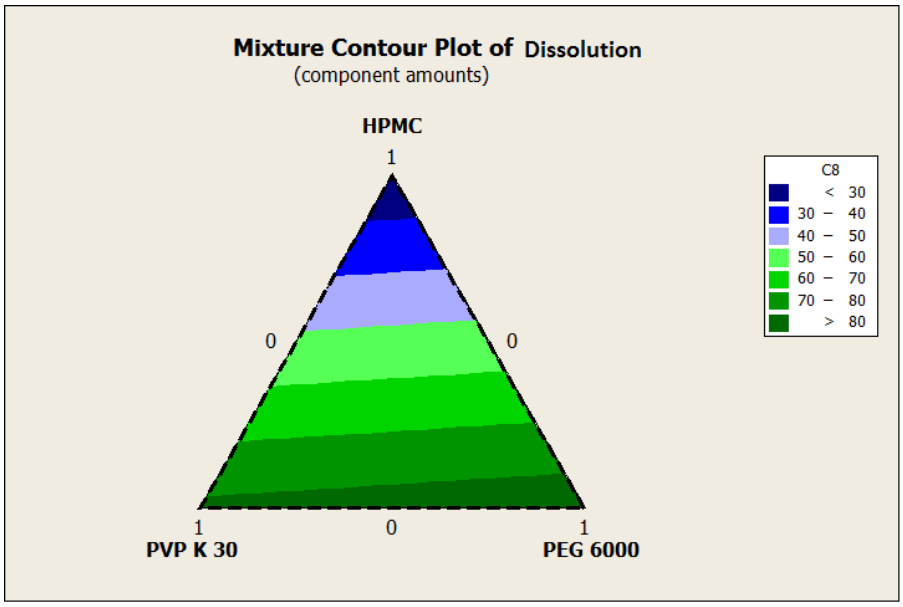

Figure 4. Contour plot

Considering the equation (4), it is clear that the highest co-efficient (1041.62) confirmed that the strongest synergistic effect on dissolution of cefuroxime axetil can be obtained by using a tertiary blend of HPMC: PVP: PEG. On the other hand, the highest negative co-efficient (86.26) indicates that the binary blend of HPMC: PVP exerted highest antagonistic effect. In addition, primary blend term of the equation shows positive co-efficient. It means that all of the three polymers increase the dissolution of pure cefuroxime axetil. These effects can be clearly visualized in the pattern of the respective contour plot. The analysis of the contour plot strengthens the terms of the equation (4). The equation indicates that the highest synergism can be obtained by the tertiary blend of HPMC: PVP: PEG. The contour plot also showed similar result (Figure 4).

For dissolution responses, the contour plot showed synergistic effect of ternary mixtures in a large area that maximized in between the points of ternary mixtures with higher PEG 6000 and similar

polymer proportion (centre of the simplex), which is far away from the HPMC corner. Inversely, antagonistic effect is dominated within the large area in the simplex, near the points of pure HPMC, binary mixture of HPMC: PVP. In future, the synergistic region near PEG corner should be of interest in order to focus on the combinations that could give optimum dissolution and to a certain extent, a high stability. The lower region near the HPMC corner should be a constraint due to undesirable effects like high viscosity and viscous diffusion layer.

CONCLUSION

The results of the current study suggest that solid dispersions of cefuroxime axetil prepared by the solvent evaporation method with various polymers can be used to enhance the apparent solubility and subsequent dissolution rate of this poorly soluble drug. In our study we designed a simplex mixture design to investigate the effect of polymer mixture on dissolution of cefuroxime axetil. The result of mixture polymeric solid dispersion is very promising. All of the formulations showed a higher level of dissolution than its pure polymeric blends. In our present study many aspects of future study are revealed. The mechanism of drug dissolution, in case of mixture polymer, is yet to be confirmed. It can be suggested that polymeric mixture may exert suitable effect not only in dissolution enhancement, but also other technique like prolonged or controlled drug delivery.

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