e- ISSN 0976 - 1047
Print ISSN 2229 - 7499

International Journal of Biopharmaceutics

IJB

Journal homepage: www.ijbonline.com

MIXTURE DESIGN EXPERIMENT ON DISSOLUTION OF PIOGLITAZONE HCL SOLID DISPERSION AS AFFECTED BY HYDROPHILIC POLYMERS INTERACTION

Harun Ar Rashid[1], Khandokar Sadique Faisal[1], Md. Habib Ullah Bhyian[2], Md. Jahangir Alam[2], Md.Mehdi Hasan[1*]

[*1]Department of Pharmacy, Faculty of Health science, Northern University Bangladesh, Dhaka -1205, Bangladesh.
[2]Department of Pharmacy, Faculty of Health science, University Of Asia Pacific, Dhaka- 1207, Bangladesh.

ABSTRACT

Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water soluble drugs overcame the limitations of those previous approaches. No studies, to date, have systematically examined the effect of different hydrophilic polymer on the dissolution of poorly water soluble drug. In this study, interaction effect of hydroxy propyl methyl cellulose cp15 (HPMC cp15), polyethylene glycol 6000 (PEG 6000), povidone 30 (PVP K30), eudragit EPO, polaxamer 407 on dissolution of pioglitazone HCl solid dispersion were investigated by a mixture design experiment. Blends of HPMC, PEG 6000, PVP K30, eudragit and polaxamer 407 were prepared according to an augmented simplex-centroid mixture design (10 points) and the drug polymer ratio was 1:3 in the solid dispersion formulation. An appropriate mathematical model was fitted to express the response. The synergistic effect of HPMC : PG : POLOXMER, had shown to be much stronger in quaternary blends. In addition, Eudragit showed antagonistic effect ($p<.05$). The contour plot reveled the effects of the tertiary bends on the dissolution of pioglitazone. Tertiary blend of HPMC, PVP and PEG demonstrated a synergistic effect on the dissolution, at higher proportion of PEG. This study suggested that a mixture design approach could serve as a valuable tool in better elucidating and predicting the interaction effects beyond the conventional polymers blends.

Key words: HPMC cp15, PEG 6000, Eudragit EPO, PVP K30, Contour plot, Regression analysis.

INTRODUCTION

Most of the recently discovered chemical entities, in spite of high therapeutic activity, have low aqueous solubility and poor bioavailability, leading to poor absorption in the gastrointestinal tract. For absorption of the drug from the gastrointestinal tract (GIT), it should be present in solution state in GI fluid. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption (Lipinski CA *et al.*, 1997). Lot of efforts has been made to increase the dissolution of drug. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water soluble drugs overcame the limitations of those previous approaches (Mooter GVD *et al.*, 1998). This technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs

Corresponding Author

Md. Mehdi Hasan
E-mail: mehdinub@yahoo.com

because it is simple, economic, and advantageous (Goldberg AH *et al.,* 1966).

Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion (Leunner C *et al.,* 2000). When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs (Chiou LW *et al.,* 1971).

Pioglitazone hydrochloride [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]-2, 4-thiazolidinedione monohydrochloride] is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. It is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that Pioglitazone hydrochloride (PGH) improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. It improves glycemic control while reducing circulating insulin levels. PGH has a very poor dissolution in aqueous fluids (Howlader SI *et al.,* 2012).

In spite of highly therapeutic value, Pioglitazone hydrochloride is practically insoluble in water and has a very poor dissolution in aqueous fluid; which prompted us to investigate the possibility of improving the solubility of Pioglitazone by solid dispersion technique.
In our previous paper, the dissolution enhancement of Pioglitazone HCl was studied preparing solid dispersion with water soluble, PEG 6000, PVP K30, Poloxamer 407, Eudragit EPO and HPMC cp15. The result illustrated that Solid dispersions of Pioglitazone HCl with PVP K30, HPMC, PEG 6000, Eudragit EPO and Poloxamer 407 showed 75%, 74%, 100%, 50% and 62% release respectively after 30 minutes where as pure Pioglitazone HCl showed only 12.05% . Based on the result solid dispersion technique can be applied for improving the dissolution profile of poorly aqueous soluble drug (Faisal KS., 2013).

In reviewing the literature, very few works have been carried out to investigate the effect of hydrophilic polymers interactions (either synergism or antagonism) on dissolution of Pioglitazone HCl. The available studies only concern on the effect of single polymer rather than polymeric mixture. Additionally, information on the hydrophilic polymer interaction other than HPMC and PVP hardly found. The development of a pharmaceutical formulation is usually a trial and error technique including a careful control of the variables one at a time in a series of logical steps. This is generally a time consuming method in which the effect of each experimental variable will be investigated separately, while keeping all others constant. Rather than using trial and error, a mixture design can be applied to determine the individual portion of each component, such that this considered an economic and time saving method. Indeed, mixture designs have been utilized to optimize mixture proportions in many product development areas in the food industry, pharmaceutical industry and engineering (Karam LB *et al.,* 2006). With these in mind mixture experiments along with non-linear modeling were used in the present study to investigate the polymer interactions (synergism or antagonism) in a blend of multiple components. Thus, the objectives of the present study were to investigate interaction effect among the PEG 6000, PVP, Poloxamer 407, Eudragit EPO and HPMC on the dissolution of Pioglitazone HCl solid dispersion as well as to fit an appropriate mathematical model to express 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.

MATERIALS AND METHODS

Pioglitazone HCl was a generous gift form Beximco Pharmaceutical Pvt. Ltd. (Dhaka, Bangladesh). PVP K30 (BASF), HPMC cp15 (BASF), PEG 6000 (Merck Chemicals), Poloxamer 407(BASF), Eudragit EPO (BASF) were used as hydrophilic polymer. All other chemicals and reagents used were of analytical grade and procured from authorized dealer.

Preparation of solid dispersion

The solid dispersion of Pioglitazone HCl was prepared by solvent evaporation method. The method consists of three steps; firstly preparation of a solution containing both the method consists of three steps; firstly preparation of a solution containing both the hydrophilic polymer and The method consists of three steps; firstly preparation of a solution containing both the hydrophobic drug, Secondly, evaporation of the solvent and formation of solid dispersion and finally drying in vacuum oven. To dissolve both drug and hydrophilic polymer a mixed solvent system of acetone and ethanol was used in a ratio of 1:4(v/v). The drug and the polymers showed an effective solubility in this solvent mixture. In this experiment drug polymer was in the ration of 1:3. The solution of polymers had been prepared according to the mixture design as showed in Table 1. The solution was stirred at room temperature for 2 hours, and the solvent was removed under vacuum at 60^0C in a rotary evaporator. Solid residue was dried in a vacuum oven for 18 hours at 50^0 C temperature, pulverized, and sieved using a set of sieves. Powders samples were stored in a closed container away from the light and humidity until use.

Experimental Design

In this study, Blends of HPMC cp15, PEG 6000, PVP K30, Eudragit EPO and Polxamer 407 were prepared according to the augmented simplex-centroid

mixture design with 10 points (Figure 1). The experimental lattices consist of six equally spaced points on the boundary of the triangle and four interior points strategically positioned to provide greater flexibility when modeling the mixture surface.

The experimental domain consisted of different proportions of components of X_1 (HPMC), X_2 (PEG 6000), X_3 (PVP K 30), X_4 (Eudragit EPO) and X_5 (Polaxamer 407) between zero and one ($0 \leq Xi \leq 1$; $\Sigma X_i = 1$). 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 the blends were prepared in three independent replications, providing a total of 18 blends. The experimental design and the mean values of dissolution of the solid dispersion are presented in the Table 1.

A one-way analysis of variance (ANOVA) was applied on the data (n = 3) to determine a significant ($p < 0.05$) difference among the solid dispersions. 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 as equations

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

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

If the linear or quadric 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

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

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

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

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 that consist of n covariates as in the equation 3 .[8]

$response = \alpha_0 + \sum_{l=1}^{n} \alpha_l Z_l + \sum_{l<m} \sum^{n} \alpha_{lm} Z_l \ Z_m + \cdots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$ Mixture regression analysis was performed to determine estimated coefficients and significance of the model was determined by graphical method. The dissolution response was found to be best fitted (graphical analysis) with quadric model. Once the estimated model equation for response was obtained, contour and surface plot were generated. The plots show how response relates to components based on the model equation.

Data analysis

The experimental design, data analysis, contour and surface plots were developed using a Minitab 16 (Minitab Inc. USA) statistical software package. The level of confidence used was at $\alpha = 0.05$

RESULTS AND DISCUSSION

The suitability of individual polymers for preparing solid dispersion of Pioglitazone HCl was preliminarily studied in our previous paper (Faisal KS *et al.*, 2013). It was found that all the polymers were compatible with drug and showed significant dissolution enhancing effects. This study was purposely designed to investigate the polymeric interactions on the dissolution of Pioglitazone HCl. Thus, the discussion has focused on the interaction effects related to the pure effects of these polymers.

Effect of quaternary blend

The quaternary blend consists of four polymers, formulation coded R11, R12, R13, R14, R15. The dissolution profiles of the quaternary blend solid dispersions are demonstrated in figure 2.

All blends have been found to enhance the dissolution profile of Pioglitazone HCl in contrast to pure one. Of all, quaternary blends containing Poloxamer show a higher dissolution profile than other blends. This may be due to Poloxamer's ability to self-aggregate, forming of micelles and liquid crystalline phases. In addition, hydrophilicity is another advantage for the solubilization of poorly water-soluble drugs. For drug delivery purposes, hydrophobic drugs may be solubilized within the core of the micelle or conjugated to the micelle-forming polymer (Tantishaiyakul V *et al.*, 1999).

The effect of polymeric blend on the dissolution of Pioglitazone HCl depends on the nature of polymer present in the blend. Quaternary blends containing PVP, PEG and Poloxamer have a synergistic effect on the dissolution. It can be shown from the figure 2 that, absence of any of the three polymers is credible for lowering the dissolution profile. Presence of Eudragit in quaternary blends results an antagonistic effect on dissolution rate of Pioglitazone HCl. However, absence of Eudragit in the blend (R15) increases the dissolution profile of the drug. This exerts that Eudragit has a negative effect on the dissolution rate. In a previous study, it was reported that incorporation of hydrophilic Eudragit in solid dispersion of Nifedipine causes a sustain release of the drug. Thus incorporation of Eudragit in the quaternary blends may be the reason for sustain release profile of the drug. onlinecourse. scince.psu.edu/sate503/node/61

Effect of pentameric blend

The polymeric interaction in pentameric blends have been investigated by Cox response plot. In a Cox response plot polymeric blends are evaluated on the basis of a reference blend. Cox response plot revels (figure 3) that increasing the poloxamer proportion in the pentameric blend, yields an immensely increased dissolution comparing to the tertiary blends of solid dispersions. The similar effects have been observed in the pentameric blend with higher proportion of poloxamer. This can be attributed to Poloxamer's self-aggregating property, formation of micelles and liquid crystalline phases, and greater hydrophilicity (Singhare DS *et al.*, 2005).

Polyethylene glycol (PEG) is a popular choice for solid dispersion preparation of poor water soluble drug because of its hydrophilicity. Pentameric blend (R7), with highest amount of PEG, exerted a higher dissolution profile. The Cox response plot has no discrepancy with this. However, slight downward tendency was found in the Cox response plot. This indicates that after crossing a certain amount, PEG decreases the dissolution of Pioglitazone. It might be ascribed to the viscous layer formed around the solid particles in higher PEG concentrations and therefore decreased the diffusion coefficient ultimately lowering drug dissolution.

The individual characteristic of the polymers control the dissolution effect of the pentemeric blends (figure 3). Poloxamer and PEG have surfactant and hydrophilic properties whereas PVP exerts co-solubilizing properties. From these observations and explanations, it may be proposed that the occurrence of a ternary synergism of Ploxamer-PEG-PVP in addition to binary synergisms (PVP-PEG and PEG-Poloxamer) in our pentameric blends (Figure 4).

In addition, pentameric blends containing mixture of Eudragit-HPMC have an antagonistic effect on the dissolution of pioglitazone($P<.05$). This is due to the sustain release characteristic of Eudragit. More ever, HPMC formed a viscous diffusion layer around the drug particle. In addition with Eudragit, It may form a more complex diffusion layer, which attributed the antagonistic effect of HPMC-Eudragit mixture.

Fitted Regression Models, Contour Plots

To empirically predict the dissolution as functions of the proportions of the blend components, mixture regression analysis was applied on the experimental data. Initially, we intended to fit all responses to this model but the design used in this study supports the fitting of the quartic model (Cornell JA., 2002). 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 special cubic. The results of fitting quartic model and terms in equation are presented in Table 2 and Table 3 respectively.

As presented in Table 3, significant interaction terms in the quartic model of the dissolution generally indicated that the dissolution will be affected not only by the individual polymers, but also by the binary interactions as well as ternary interactions among all polymers.

The equation for the quartic model for the dissolution are shown following

$$\text{Dissolution}=77.7\,x_1 + 75.8x_2 + 86.8x_3 + 96.9x_4 + 45.3x_5 - 555.8x_1x_5 - 394.4x_1x_3 + 804.3x_1x_4 + 1185.1x_1x_2x_4 \quad (4)$$

Considering the equation (4), it can be asserted that all of the polymers have positive effect on the dissolution of pioglitazone, since positive co-efficient have been found in equation (4). Among the polymers, poloxamer has shown the highest co-efficient, this indicates that the synergestic effect of poloxamer on dissolution. The similar effects can be visualized in the pattern of the respective contour plot (Figure 5).

The binary effects of HPMC and Eudragit exerted an antagonistic effect on the dissolution. This may be attributed to the polymeric interaction resulted a viscous diffusion layer, which ultimately retarded the drug dissolution. The binary effect of HPMC and PVP shows a negative co-efficient, whereas blend of PVP-poloxamer exerts a positive co-efficient in equation 4.

The tertiary effect of HPMC, PVP and Poloxamer exerted highest co-efficient in the equation (4), which confirmed that the strongest synergism could be obtained by using HPMC, PEG and Poloxamer.

The contour plot (figure 5) revel the effects of the tertiary bends on the dissolution of pioglitazone. Tertiary blend of HPMC, PVP and PEG demonstrated a synergistic effect on the dissolution, at higher proportion of PEG. (Figure 5a). This synergistic effect mainly attributed to the higher solubilizing effect of PEG. Similar effects can be observed in contor plot 5 b and 5c. Considering the figure (5c and 5f), this is clear that the presence of the Eudragit in the tertiary blend is responsible for the negative synergistic effect. This negative effect of these blend is due to presence of Eudragit, at a higher amount Eudragit retarded the drug diffusion.

Table 1. Augmented simplex-centroid mixture design and the responses

Code	Component proportion					Response (% Drug release)
	HPMC X1	PEG 6000 X2	PVP K 30 X3	Polaxomer X4	Eudragit X5	
R1	1	0	0	0	0	80.78±0.58
R 2	0	1	0	0	0	80.57±0.5
R 3	0	0	1	0	0	98.73±0.35
R 4	0	0	0	1	0	100.34±0.65
R 5	0	0	0	0	1	49.58±0.65
R 6	0.6	0.1	0.1	0.1	0.1	43.38±0.68
R 7	0.1	0.6	0.1	0.1	0.1	74.61±0.35
R 8	0.1	0.1	0.6	0.1	0.1	55.12±0.45
R 9	0.1	0.1	0.1	0.6	0.1	87.51±0.65
R 10	0.1	0.1	0.1	0.1	0.6	24.39±0.38
R 11	0	0.25	0.25	0.25	0.25	61.78±0.65
R 12	0.25	0	0.25	0.25	0.25	43.033±0.50
R 13	0.25	0.25	0	0.25	0.25	49.17±0.45
R 14	0.25	0.25	0.25	0	0.25	37.25±0.55
R 15	0.25	0.25	0.25	0.25	0	99.5±0.46
R 16	0.2	0.2	0.2	0.2	0.2	74.91±0.45
R 17	0.2	0.2	0.2	0.2	0.2	74.8±0.60
R 18	0.2	0.2	0.2	0.2	0.2	76.51±0.45

Table 2. Analysis of variance of model fits

Source	Degree of freedom	Adjusted sum of square	Adjusted mean square	F	P
Fitted with quartic model					
Dissolution					
Model	5	4046.24	809.25	4.84	0.025
Lack of fit	9	1481.78	164.64	179.73	0.006
Pure error	2	1.83	.92		

Table 3. Estimated regression coefficients (reduced terms) and adjusted coefficient of determination (r^2) of model fits

Terms fitted with quartic model	Dissolution
HPMC cps 15 (x1)	77.7
PEG 6000 (x2)	75.8
PVP K 30 x3	86.8
Polaxomer x4	96.9
Eudragit x5	45.3
HPMC*Eudragit (x1*x5)	-555.8
HPMC*PVP K 30 (x1.x3)	-394.4
HPMC*Polaxomer (x1.x4)	804.3
HPMC*PEG 6000*Polaxomer (x1.x2.x4)	1185.1

Figure 1. Simplex-centroid mixture design

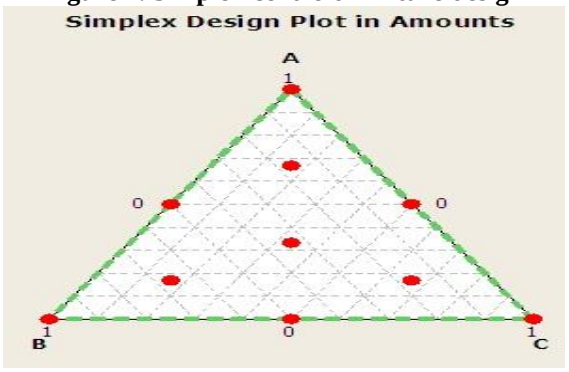


Figure 2. Dissolution effect of quaternary blend

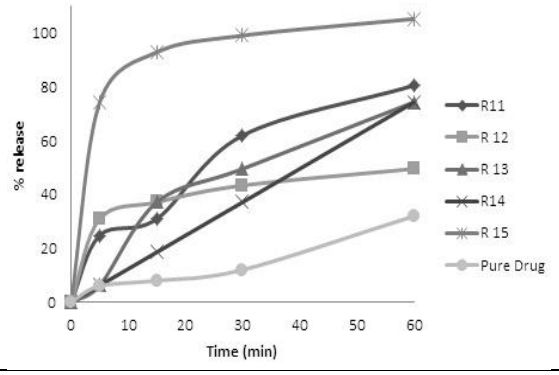


Figure 3. Cox Response Plot

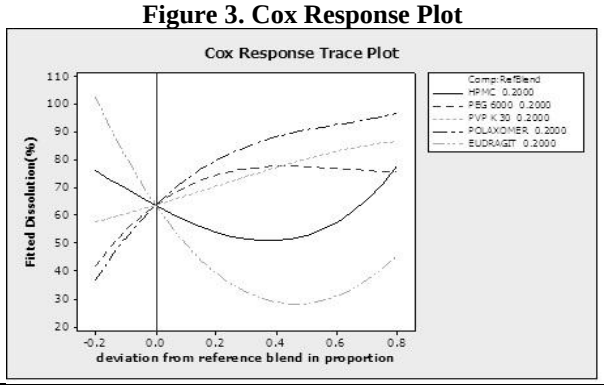


Figure 4. Dissolution effect of pentameric blend

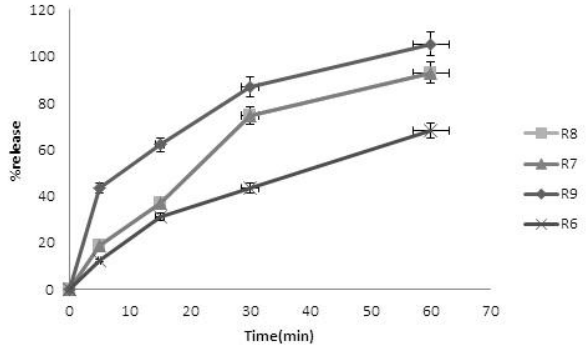
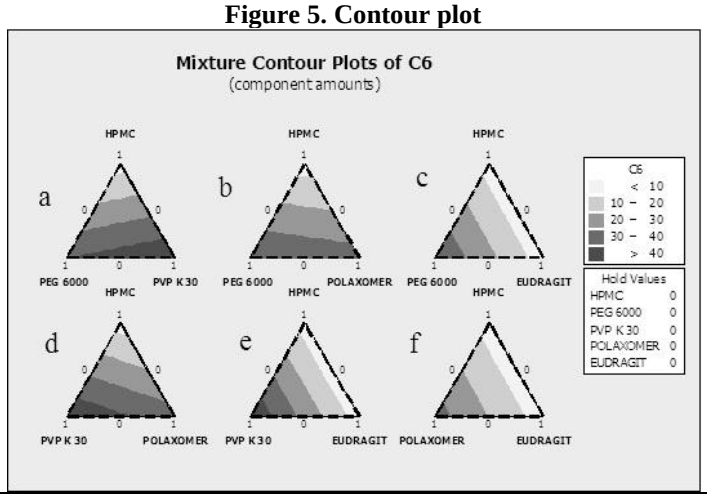


Figure 5. Contour plot



CONCLUSION

In this study simplex mixture design was used to investigate the effect of polymeric interaction on dissolution of Pioglitazone HCl. The result of polymeric mixture is very promising. All the formulation showed a higher dissolution rate compared to the pure form of drug. The co-relation of co-efficient of ternary blend of HPMC, PEG and PVP was highest among the statistically significant terms which attributed, HPMC, PVP, PEG significantly increased the dissolution of the drug. Many aspects of the future study have been reveled in this study. The mechanism of drug dissolution, in case of mixture polymers has yet not been confirmed. In future attention can be given, to revel the mechanism lies behind the dissolution enhancement by the mixture polymer.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

REFERENCES

Chiou LW and Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci*, 1971; 60(9): 1281-1302,

Cornell J. Experiment with Mixtures, Design, Models, and the Analysis of Mixture Data, 3rd edn, John Wiley & Sons, Inc., New York, 2002.

Faisal KS, Giri A, Azam KR. Solid dispersion formulations of Pioglitazone HCl using five different polymers for enhancing dissolution profile. *J Pharma & Life Sic (IJPLS)*, 2013; 4(1): 2269-2275.

Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. II. Experimental evaluation of eutectic mixture: urea-acetaminophen system. *J Pharm Sci*, 1966; 55: 482-487.

Howlader SI, Chakrabarty JK, Faisal KS. Enhancing dissolution profile of diazepam polymers by solid dispersion technique. *International Current Pharmaceutical Journal*, 2012; 1(12): 423-430.

Karam LB, Ferrero C, Martino MN, Zaritzky NE and Grossman MV. Thermal, microstructural and textural characterization of gelatinized corn, cassava and yam starch blends. *Int. J. Food Sci. Tech*, 2006; 41: 805 – 812.

Leunner C and Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm*, 2000; 50(1): 47-60.

Lipinski CA, Lombardo F, Dominyl BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*, 1997; 23: 3–25.

Mooter GVD, Augustijns P, Blaton N, Kinget R. Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. *Int J Pharm*, 1998; 164: 67–80.

Singhare DS, Khan S, Yeole PG. Poloxamers: Promosing block co-polymers in drug delivery. *Indian Journal of Pharmaceutical Education & Research*, 2005; 67: 523 – 531.

Tantishaiyakul V, Kaewnopparatv N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone. *International Journal of Pharmaceutics*, 1999; 181: 143–151