ORIGINAL ARTICLE

Design and statistical optimisation of praziquantel tablets by using solid dispersion approach

Bagade Om, Shete Amruta, Dhole Shashikant, Pujari Rohini, Raskar Vinita[1], Kharat Priyanka

Department of Pharmaceutics, PES, Modern College of Pharmacy (Ladies), Moshi, [1]Emcure Pharmaceutical Ltd., Emcure House, M.I.D.C., Bhosari, Pune, Maharashtra, India

Aim: The present investigation was carried out with an aim to formulate and evaluate praziquantel (PZQ) tablets using solid dispersion approach. **Methodology:** The solid dispersion was prepared by solvent evaporation method using carriers such as mannitol, urea and PEG 6000 with drug: Carrier ratio of 1:1, 1:2 and 1:3. The solid dispersion was evaluated for physical parameters such as angle of repose, bulk density, Carr's index, Hausner ratio, drug content and *in vitro* drug release studies. PZQ tablets (100 mg drug) were prepared further from solid dispersions using direct compression technique. **Results:** The results of individual assays of solid dispersions with different ratios revealed that the 1:2 ratio of PZQ with PEG 6000 showed higher dissolution rates when compared to others. Tablets compressed were evaluated for their physical parameters such as weight variation, thickness, hardness, friability, dissolution, and disintegration tests and compared with plain drug and marketed formulation (Biltricide 600 mg Bayer HealthCare Pharmaceuticals). *In vitro* dissolution profile of optimized batch (F8) showed better release. The highest solubility was shown by tablet prepared from solid dispersion with 1:2 ratio of PZQ: PEG 6000, which was found to be more than plain drug. Infrared spectra showed that the functional groups of PZQ and PEG 6000 were preserved. Results of 2^3 factorial designs affect the dependent variables such as hardness, disintegration time and % friability. **Conclusion:** It was concluded that by adopting a systematic formulation approach one can reach to an optimum level. Hence, solid dispersion formulation using PEG 6000 carriers was found to be a good alternative approach for increasing the dissolution rate of PZQ tablets in distilled water.

Key words: *Carriers, dissolution, optimization, praziquantel, solid dispersion*

INTRODUCTION

Solid dispersion is the group of solid products consisting of at least two different component hydrophilic matrixes and hydrophobic drug. The drug can be dispersed in amorphous particles (clusters) or in crystalline particles.[1] Solid dispersions can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers Solid dispersion is a unique approach which was introduced by Sekiguchi and Obi. Formulation of solid dispersion used to enhance bioavailability of poorly water soluble drug. It represents a useful pharmaceutical technique for increasing dissolution of drug yield eutectic (non-molecular level mixing) or solid solution (molecular level mixing product).[2] They increase aqueous solubility of the drug using carriers such as PEG 6000, Mannitol, Urea, Sorbitol, PVP, Cyclodextrine, etc., Poorly water soluble drug BCS Class II depends on its absorption by the gastrointestinal tract. In the present research study, praziquantel (PZQ) solid dispersion have been developed by solvent evaporation method thereby formulating the tablet. By improving the dissolution profile of these drugs, it is possible to enhance their bioavailability and reduce side effects.[3] The solubility study of drug is important because it provide an opportunity to choose proper manufacturing method, appropriate carriers and solvents selection for formulation purpose, better route of administration and dosage form to achieve bioavailability. PZQ is an anthelmintic drug with

Address for correspondence:
Prof. Bagade Om,
Department of Pharmaceutics, PES, Modern College of Pharmacy (Ladies), Moshi, Pune - 412 105, Maharashtra, India.
E-mail: ombagadescop@gmail.com

Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.154689

poor oral bioavailability (relatively small) due to first-pass metabolism and poor water solubility.

The current research work focused on solubility enhancement by solid dispersion techniques can be used to improve *in vitro* dissolution dependent poorly water soluble drug. The results of 2^3 factorial designs revealed that the amounts of microcrystalline cellulose, magnesium stearate and crospovidone used in tablet formulation significantly affected the dependent variables such as hardness, disintegration time and % friability. It was concluded that by adopting a systematic formulation approach one can reach to an optimum level. Hence, solid dispersion formulation using various carriers was found to be a good alternative approach for increasing the dissolution rate of PZQ.

MATERIALS AND METHODS

Materials

Praziquantel was obtained as a gift sample Microlabs Pvt. Ltd., Goa. Carriers such as Mannitol, Urea and PEG6000 were procured from Lobachemie, Mumbai. Avicel pH 101, magnesium stearate and crospovidone, were procured from Lobachemie, Mumbai. Other reagents and organic solvents used were of analytical grade. Buffer and its dilutions were prepared with double-distilled water.

Methods

Preparation of praziquantel solid dispersion by solvent evaporation method

Accurately weighed drug PZQ (500 mg) and carrier in the ratio of 1:1, 1:2, 1:3. were dissolved in an organic solvent (chloroform). The solution is incorporated into the melt of polyethylene glycol and cooled suddenly and mass is kept in desiccators for complete drying. The solidified mass is crushed, pulverised and passed through 40 mesh sieves. From a practical standpoint, it is only limited to drugs with a low melting point.[4]

Preformulation studies of drug

Solubility studies

Saturation solubility of PZQ in different solvents, that is water, acidic buffer (pH 1.2), phosphate buffer pH 7.4 and phosphate buffer pH 6.8 were determined.

Method

An excess amount of PZQ was added to the conical flask containing 20 ml of solvent and content was stirred for 48 h on a rotary shaker the mixture was then filtered through Whatman filter paper. The solubility of PZQ was determined spectrophotometrically at 210 nm.

Melting point determination

Melting point was measured with the use of Thieles tube apparatus by paraffin oil, thermometer, thread and burner. The sufficient drug powdered was filled in a glass capillary tube, whose one end was sealed previously. The capillary tube was placed in melting point apparatus and the range of temperature when drug just starts melting and till it completely melts was noted.[5]

Infrared spectrophotometric study

Infrared (IR) spectroscopy was conducted and the spectrum was recorded in the wavelength region of 4000–400/cm^{-1}. The procedure consisted of dispersing a sample (drug alone, polymers alone and the mixture of drug and polymers in KBr and compressing into discs by applying a pressure of 7 tons for 5 min in a KBr press. The pellet was placed in the light path, and the spectrum was obtained.

Stability study of drug

Standard stock solution of PZQ (100 mcg/ml) was prepared by dissolving 10 mg of drug in Methanol then volume was made up to 100 ml with distilled water. A volume of 0.6 ml solution from stock was withdrawn and diluted up to 10 ml with distilled water to get the concentration of 6 mcg/ml. Then, resultant solution was scanned from 200 to 400 nm for particular time interval, i.e. 0 min, 30 min, 1 h, 3 h, 12 h and 24 h respectively and the spectrum was recorded to obtained the value of $\lambda_{max.}$

UV/visible spectrophotometric study of praziquantel

Standard stock solution of PZQ (100 mcg/ml) was prepared by dissolving 10 mg of drug in Methanol then volume was made up to 100 ml with distilled water. 0.1 ml solution from stock was withdrawn and diluted up to 10 ml with water to get the concentration of 1 μg/ml. Similarly 0.2 ml, 0.3 ml, up to 0.6 ml solution was withdrawn to get 2 mcg/ml, 3 mcg/ml up to 6 mcg/ml, respectively. Then resultant solution was scanned from 400 to 200 nm and the spectrum was recorded to obtain the value of $\lambda_{max.}$

Preparation of the standard curve of praziquantel

Calibration curve was performing on UV-spectrophotometer (UV shimadzu). Instrument with both the medium of pH 1.2, pH 7.4 and Distilled water with 210 nm wavelength.

Preparation of 100 μg/ml stock solution

Dissolved 10 mg PZQ with sufficient amount of pH 1.2, pH 7.4 and Distilled water in 100 ml volumetric flask, sonicate it for 5 min and finally volume adjusted to 100 ml with above respective solution to get 1000 μg/ml.

Preparation of standard solution of PZQ in dist. water, acidic buffer of pH 1.2and phosphate buffer pH 7.4 Standard stock solution of PZQ (100 mcg/ml) was prepared by dissolving 10 mg of praziquantel in methanol then volume was made up to 100 ml with distilled water. Same procedure was repeated for pH 1.2, pH 7.4.

- Preparation of working solution for distilled water, pH 1.2 and pH 7.4.

From standard solution 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6 ml was withdrawn in 10 ml volumetric flask and diluted to 10 ml with water to produce concentration 1, 2, 3, 4, 5, and 6 mcg/ml, respectively. The solution was analysed by UV spectrophotometer at 210 nm and result was recorded. The calibration graph was plotted as concentration on x-axis and absorbance on y-axis. Same procedure was repeated for pH 1.2, pH 7.4.

Drug-excipient compatibility studies

The successful formulation of a suitable and effective solid dosage form depends upon the careful selection of the excipients. Excipients are added to facilitate administration, promote the consistent release and bioavailability of the drug. It's necessary to study the compatibility of excipients with drug. Here IR spectroscopy was used to investigate and predict any physicochemical interaction between components in the formulation and to the selection of a suitable compatible excipient.[6]

Optimization of drug to carrier ratio

In order to estimate the relative effectiveness of various concentration of drug to polymer, various formulations were prepared to achieve increased dissolution rate. Nine formulations are having different drug to polymer ratio (1:1, 1:2, 1:3) were designed. In that F8th Batch of formulation gives better results [Table 1].

Evaluation of solid dispersion

The prepared solid dispersion were evaluated for angle of repose, bulk density, tapped density, carr's index, Hausner's ratio, as per official procedure.[7-9]

Drug content

Solid dispersion equivalent to 100 mg of PZQ weighed accurately and dissolved in 10 ml of methanol the stock solutions were further diluted with phosphate buffer pH 6.8. And analysed by UV-visible spectophotometry (shimadzu UV-1800, japan) the absorbance of the above solution was measured at 210 nm using appropriate blank solution. The drug content of PZQ was calculated using the calibration curve.[10]

Surface topographic study

The shape and surface characterization of solid dispersion were observed under a Scanning Electron Microscope Model Joel-LV-5600, USA, at suitable magnification at room temperature.

Preparation of praziquantel tablets

To formulate a tablet of PZQ, the SD binary mixture was selected based on its drug content test. Direct compress tablet prepared from solid dispersion of PZQ according to proportions given in following table. Solid dispersion (1:2 ratio of PEG 6000) containing PZQ 100 mg was mixed with other ingredients and directly compressed on a rotary tablet machine [Table 2].

Evaluation of tablets

The compressed tablets were evaluated for appearance, thickness, friability, hardness, disintegration time.[11,12]

Factorial design for praziquantel tablets

A 2^3 randomised full factorial design was used in the present study. In this design three factors are evaluated, each at two levels, and experimental trials are performed in all eight possible combinations. Avicel pH 101 (MCC) (X_1), magnesium stearate (X_2), crospovidone (X_3) were selected as independent variables. The hardness, friability, disintegration time were selected as dependent variables. The design and coded levels are mentioned in actual values as shown in [Tables 3 and 4].

In vitro drug release

The dissolution test was carried out in acidic buffer (pH 1.2). Aliquots were withdrawn at predetermine time intervals and after suitable dilutions absorbance was measured with the help of UV spectrophotometer at 210 nm.[13]

Stability study

Tablet was packed in suitable packaging condition and stored in following conditions for a period according to ICH guidelines. Parameter was observed for Accelerated stability studies, at room temperature and freezer condition.

Table 1: Drug: Carrier formulation ratio of solid dispersion

Formulation code	Drug (mg)	Mannitol (mg)	Urea (mg)	PEG 6000 (mg)	Drug and carrier ratio
F1	500	500	-	-	1:1
F2	500	1000	-	-	1:2
F3	500	1500	-	-	1:3
F4	500	-	500	-	1:1
F5	500	-	1000	-	1:2
F6	500	-	1500	-	1:3
F7	500	-	-	500	1:1
F8	500	-	-	1000	1:2
F9	500	-	-	1500	1:3

PEG: Polyethylene glycol

Table 2: Formula for PZQ tablets

Ingredient	Quantity given (mg)
SD containing 100 mg PZQ	263.58 mg
Avicel pH 101	150
Magnesium stearate (lubricant)	05
Crospovidone (superdisintegrant)	10
Total weight of tablets	428.58 mg

PZQ: Praziquantel, SD: Solid dispersion

Table 3: Coded levels

Coded levels	Actual values (mg)		
	X_1	X_2	X_3
−1 (low)	150	2.5	2.5
1 (high)	200	10	7.5

RESULTS AND DISCUSSION

Solubility study

Praziquantel was found to be practically insoluble in distilled water, the solubility in different solvent system having different pH was carried out and results are shown in Table 5.

Melting point of drug

The melting point of PZQ was found to be in the range of 134–138°C, which was similar to the standard melting point (136°C).

Infrared spectrophotometer

Infrared spectra's were recorded for pure PZQ drug and physical mixture [Figure 1]. All the above characteristic peaks of drug appear in the spectra of physical mixture at the same wave number, indicating no modification or interaction between the drug and the polymer [Figure 2].

Stability study of drug

From the following data of drug stability, it was found that the drug showed stability even after exposed for the different time interval by analysing the absorbance through UV-visible spectrophotometer at fixed wavelength, i.e. 210 nm [Table 6].

UV spectroscopy of praziquantel

The UV spectrum of PZQ showed λmax at 210 nm, in following curve complies with the reported value.

Standard calibration curve of praziquantel

- Calibration curve in distilled water, acidic buffer of pH 1.2 and phosphate buffer pH 7.4:

Praziquantel in distilled water showed absorption at 210 nm and this wavelength was chosen as the analytical wavelength [Figure 3]. Beer's law was obeyed between 1 and 6 mcg/ml. Regression analysis was performed on the experimental data. Regression equation for the standard curve was y = 0.157x. Correlation coefficient for developed method was found to be 0.999 signifying that the linear relationship existed between absorbance and concentration of the drug. The interference studies with formulation excipients studies were carried, and no difference in absorbance was observed at 210 nm. Same procedure was carried out for acidic buffer of pH 1.2 and phosphate buffer pH 7.4 [Figures 4 and 5].

EVALUATION OF SOLID DISPERSION

Micromeritic study

The values of angle of repose of all samples indicated that solid dispersion was free flowing. These properties are suitable for conversion into solid dosage form [Table 7].

Drug content

The drug content analysis of all the prepared nine formulation in range between 87.5% and 98.5% among all formulation F8th formulation contained the maximum amount of drug [Figure 6 and Table 8].

Surface topographic study

The photographs were observed, and it was found that no obvious aggregation of the solid dispersion was found. The photographs of the formulation as depicted in [Figure 7] showed that discrete, irregular shaped solid dispersion

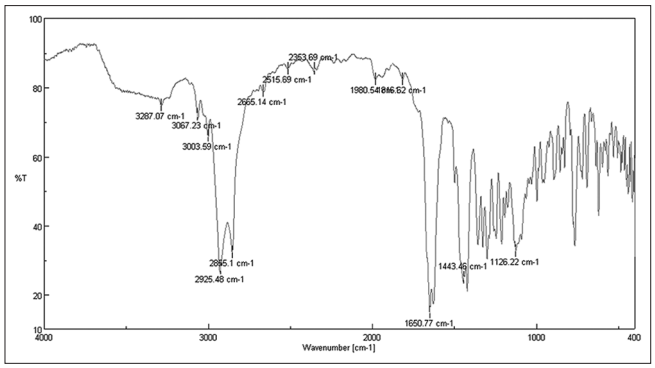

Figure 1: Infrared spectra of pure praziquantel drug

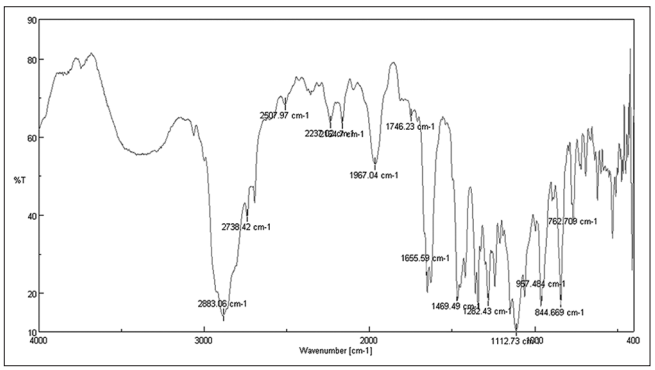

Figure 2: Infrared spectra of bland mixture (Praziquantel, Mannitol and Urea)

Table 4: Stability data of optimised batch (F8) at temperature 40±2°C and RH 75%±5%

Evaluation parameters	Storage time (60 days)						
	0	7	15	21	30	45	60
Hardness (kg/cm^2)	4.05	4.02	4.02	4.01	4.03	4.00	4.00
Drug content (%)	97.5	97.4	97.4	97.3	97.3	97.2	97.2
Friability (mg)	428.58	428.57	428.57	428.56	428.55	428.55	428.52

RH: Relative humidity

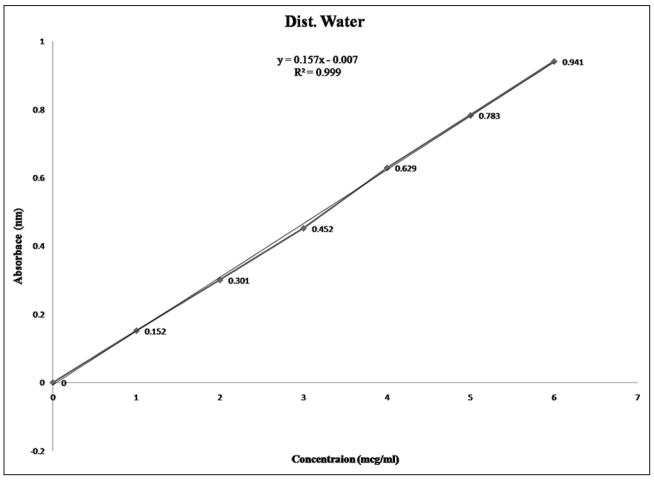

Figure 3: Calibration curve of praziquantel in distilled water

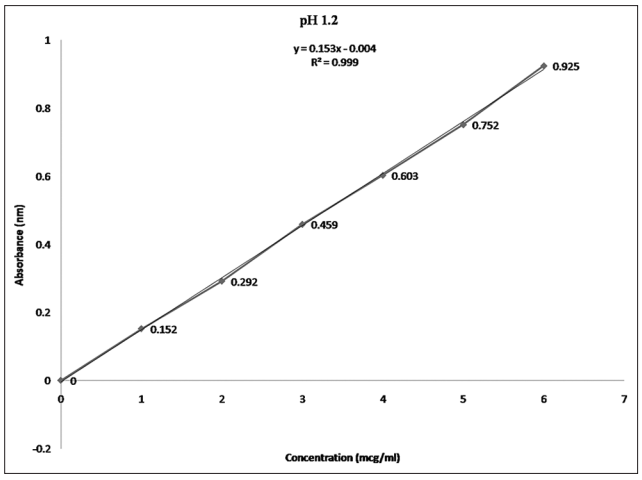

Figure 4: Calibration curve of praziquantel in acidic buffer of pH 1.2

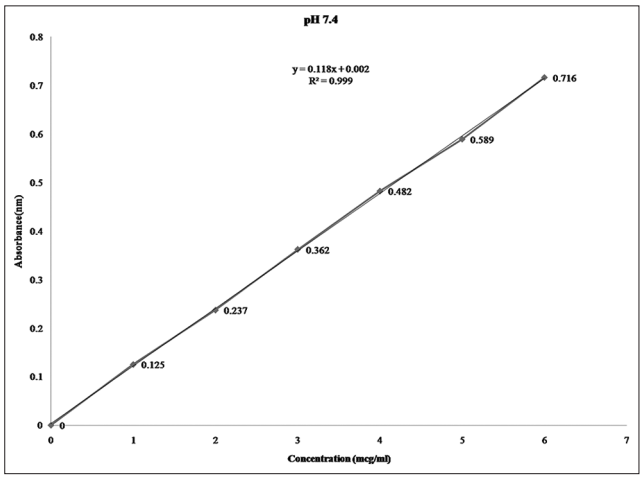

Figure 5: Calibration curve of praziquantel in phosphate buffer of pH 7.4

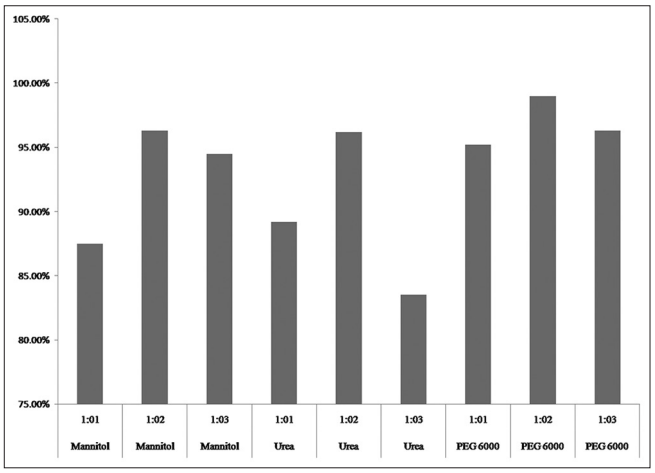

Figure 6: Study of drug content

Table 5: Solubility of PZQ in different solvent

Media	Solubility (mcg/ml)
Acidic buffer (pH 1.2)	40.07
Phosphate buffer (pH 6.8)	30.15
Water (pH 7)	12.20
Phosphate buffer pH 7.4	16.05

PZQ: Praziquantel

Table 6: Stability study of plain PZQ

Time (h)	Concentration (mcg/ml)	Absorbance (nm)
After 0	6	0.941
After 1	6	0.943
After 3	6	0.947
After 6	6	0.939
After 12	6	0.944
After 24	6	0.948

PZQ: Praziquantel

was obtained. In addition, the SDs showed different surface characteristics that varied with the compositions of the SDs.

Evaluation of tablets

Preliminary test

Analysis of data by design expert software

A 2^3 randomised full factorial design was used in the present study. In this design three factors are evaluated, each at two levels, and experimental trials are performed in all eight possible combinations. The MCC (X_1), magnesium stearate (X_2), crospovidone was selected as independent variables. The hardness, friability and disintegration time were selected as dependent variables. The design matrix and coded levels are mentioned in actual values as shown in Tables 3 and 9. The Hardness, friability, disintegration time were selected as dependent variables. Based on the factorial design 8 formulations were devised as shown in Table 10.

The avicel pH 101 (MCC) (X1), Magnesium stearate (X2) and crospovidone (X3) were selected as independent variables. The design matrix and coded levels are mentioned in actual values as shown in Table 10. The Hardness, Friability, Disintegration time were selected as dependant variables in a 2^3 randomised full factorial design to evaluate the responses.

Table 7: Data of micromeritics study

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio
F1	2.5±0.03	2.2±0.03	21.80±0.1	13.63±0.04	0.88±0.03
F2	4.4±0.04	0.4±0.02	33.42±0.1	10.00±0.03	0.90±0.08
F3	5.8±0.03	4.6±0.01	29.68±0.02	26.08±0.04	0.79±0.05
F4	2.0±0.05	1.3±0.02	27.92±0.02	53.84±0.08	0.65±0.03
F5	4.0±0.05	0.3±0.03	26.56±0.02	23.8 0±0.05	0.80±0.04
F6	5.2±0.05	4.2±0.035	40.36±0.03	33.33±0.04	0.75±0.04
F7	1.8±0.04	1.6±0.03	19.29±0.03	12.5±0.09	0.88±0.04
F8	3.4±0.05	2.8±0.05	26.56±0.07	21.42±0.04	0.82±0.05
F9	4.2±0.03	3.6±0.03	30.96±0.08	16.66±0.08	0.85±0.04

Table 8: Percentage drug content

Batch	Carrier	Drug: Carrier ratio	Percentage drug content
F1	Mannitol	1:1	87.5
F2	Mannitol	1:2	96.3
F3	Mannitol	1:3	94.5
F4	Urea	1:1	89.2
F5	Urea	1:2	96.2
F6	Urea	1:3	83.5
F7	PEG 6000	1:1	95.2
F8	PEG 6000	1:2	98.5
F9	PEG 6000	1:3	96.3

PEG: Polyethylene glycol

Table 9: Design matrix of independent variables

Formulations	Coded levels (mg)		
	X_1	X_2	X_3
F1	−1	−1	−1
F2	−1	1	1
F3	1	1	1
F4	1	−1	−1
F5	−1	−1	1
F6	−1	1	−1
F7	1	1	−1
F8	1	−1	1

Calculation of coefficient for hardness, friability and disintegration time

The coefficients of the polynomial equations generated using multiple linear regressions analyses (MLRA) hardness, friability and disintegration time of tablet studied with the values of r^2. Nine coefficients ($ß_0$ to $ß_9$) were calculated with B_0 as the intercept. The coefficients $ß_0$ to $ß_9$ represent various quadratic and interaction terms, but are denoted as such in equation due to their simplicity.

The general equation in terms of coded factors is:

$$\text{Hardness} = ß_0 - ß_1 \times 1 + ß_2 \times 2 + ß_3 \times 3 + ß_4 \times 1\ X\ 2 + ß_5 \times 1\ X\ 3 - ß_6 \times 2\ X\ 3 + ß_7 \times 1^2 + ß_8 \times 2^2 + ß_9 \times 3^2$$

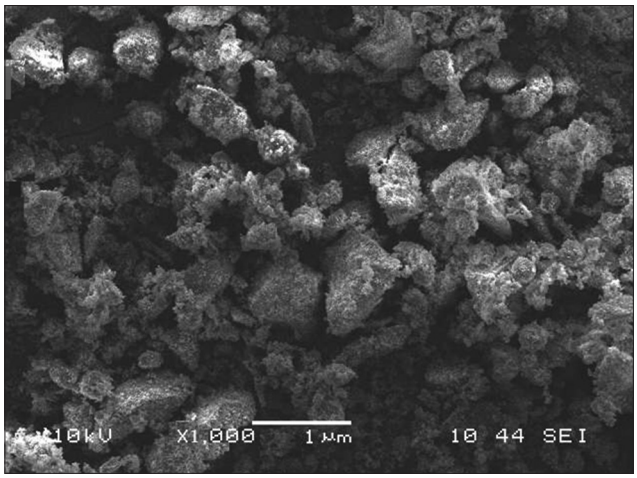

Figure 7: Scanning electron microphotograph of optimised batch F8

$$\text{Friability} = ß_0 - ß_1 \times 1 + ß_2 \times 2 - ß_3 \times 3 + ß_4 \times 1\ X\ 2 + ß_5 \times 1\ X\ 3 - ß_6 \times 2\ X\ 3 - ß_7 \times 1^2 - ß_8 \times 2^2 - ß_9 \times 3^2$$

$$\text{Disintegration time} = ß_0 - ß_1 \times 1 + ß_2 \times 2 - ß_3 \times 3 + ß_4 \times 1\ X\ 2 + ß_5 \times 1\ X\ 3 - ß_6 \times 2\ X\ 3 - ß_7 \times 1^2 - ß_8 \times 2^2 - ß_9 \times 3^2$$

Whereas $ß_0$ is intercept and $ß_1$. $ß_9$ is the coefficient of variables which represented various quadratic and interaction terms, but are denoted as such in equation due to their simplicity while $X_1 \times 2\ X_3$ are the response variables.

The final polynomial equation for hardness, friability and disintegration time of tablet generated in terms of coded factors using MLRA is:

$$\text{Hardness} = +4.08 - 0.060 \times 1 + 0.31 \times 2 + 0.000 \times 3 + 0.03 \times 1\ X\ 2 + 0.13 \times 1\ X\ 3 - 0.12 \times 2\ X\ 3$$

$$+0.48 \times 1^2 + 0.26 \times 2^2 + 0.050 \times 3^2$$

$$\text{Friability} = +0.72 - 0.042 \times 1 + 0.020 \times 2 - 003 \times 3 + 0.06 \times 1 \times 2 + 0.42 \times 1 \times 3 - 0.82 \times 2 \times 3 - 0.16 \times 1^2 - 1.43 \times 2^2 - 0.049 \times 3^2$$

Disintegration time = $+37.50 - 3.54 \times 1 + 1.77 \quad X2 - 4.60 \times 3 + 3.35 \times 1 X 2 + 1.98 \quad X1 \times 3 - 1.29 \times 2 \times 3 - 1.75 \times 1^2 - 3.00 \times 2^2 - 4.50 \times 3^2$

ANOVA for selected factorial model (hardness)

The statistical evaluation was performed by one-way ANOVA and results are shown in data it was evident that *P* value was < 0.0041 in all formulations. X1 (MCC) factor shows negative effects, X2 (Magnesium stearate) factor shows positive effect while combine effect of X1 × 2 X 3 factor shows positive effects from this data it was cleared that the given model for Hardness was significant. Therefore, it can be derived that the change in MCC had a significant effect on the Hardness of tablet, while (X2) change in magnesium stearate ratio shows a negative effect.

Response surface plots for measured responses

Three-dimensional response surface plots are presented in Figure 8 these types of plots are useful in the study of the effects of two factors on the response at one time [Figure 9] shows that hardness of tablet increases with increasing concentrations of magnesium stearate and MCC later on decreases.

ANOVA for selected factorial model (friability)

The statistical evaluation was performed by one-way ANOVA and results are shown in data it was evident that *P* value was < 0.0041 in all formulations. X1 (MCC) factor shows positive effects, X2 (Magnesium) factor shows negative effect while combine effect of X1 × 2 X 3 factor shows positive effects from this data it was cleared that the given model for friability was significant. Therefore it can be derived that the change in MCC had significant effect on the friability of tablet while (X2) change in magnesium stearate ratio shows positive effect.

Response surface plots for measured responses

Three-dimensional response surface plots are presented in Figure 10 these types of plots are useful in the study of the effects of two factors on the response at one time [Figure 11] shows

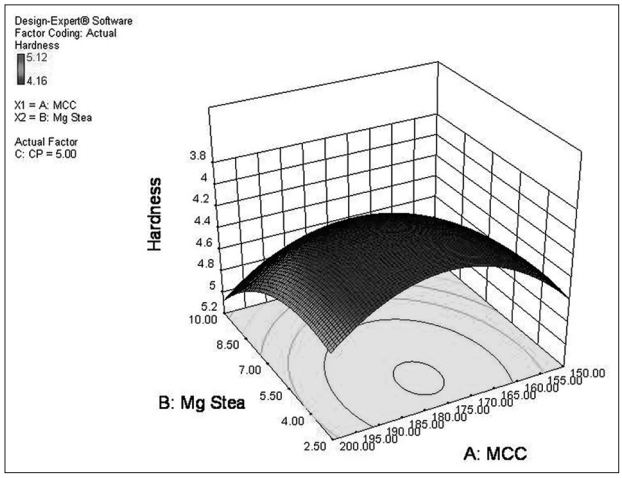

Figure 8: Response surface plots showing the effect of drug carrier ratio on the hardness from formulation

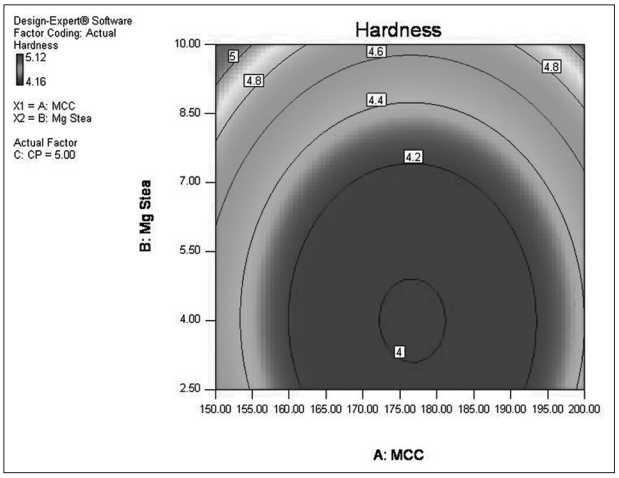

Figure 9: Counter plots showing the effect of drug carrier on the hardness from formulation

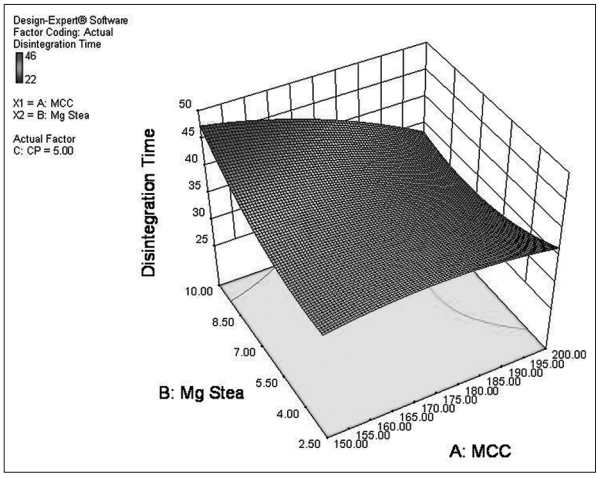

Figure 10: Response surface plots showing the effect of drug carrier ratio on the hardness from formulation

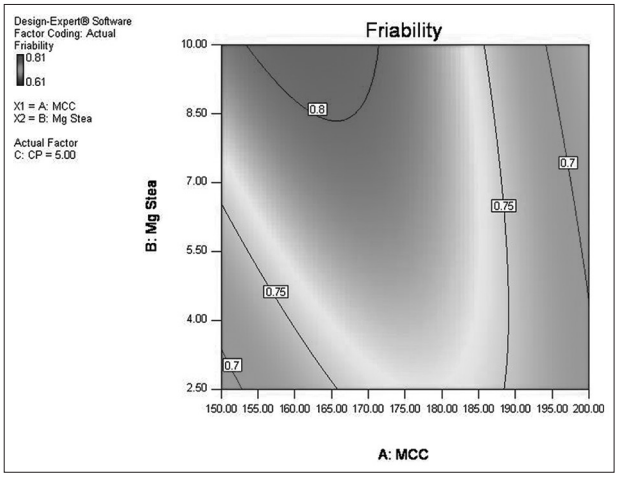

Figure 11: Counter plots showing the effect of drug carrier on the friability from formulation

that friability of tablet increases with increasing concentrations of magnesium stearate later on decreases and increases while increases in the concentration of magnesium stearate.

ANOVA for selected factorial model (disintegration time)

The statistical evaluation was performed by one-way ANOVA, and results are shown in data it was evident that *P* value was < 0.0041 in all formulations. X1 (MCC) factor shows positive effects, X2 (magnesium) factor shows positive effect while combine effect of X1 × 2 × 3 factor shows positive effects from this data it was cleared that the given model for disintegration time was significant. Therefore, it can be derived that the change in MCC concentration had a significant effect on the disintegration time of tablet while (X2) change in magnesium stearate ratio showed a positive effect.

Response surface plots for measured responses

Three-dimensional response surface plots are presented in Figure 12 these types of plots are useful in the study of the effects of two factors on the response at one time [Figure 13] showed that disintegration time of tablet steady with increasing concentrations of MCC while increases when magnesium stearate concentration increases.

***In vitro* drug release study**

A total of 500 mg of drug-loaded solid dispersion tablet containing solid dispersion of PZQ equivalent to 100 mg were put into 900 ml of 0.1N HCl, pH 1.2. At various time points (30 min, 1, 2, 3, 4, 5, 6 h), 1 ml aliquots were drawn for drug analysis and replaced with an equal volume of dissolution medium. The samples were analysed spectroscopically at 210 nm to determine the concentration of drug present. The results were expressed as the percent drug released with respect to the theoretical value [Figure 14].

Stability study

Tablet was packed in suitable packaging condition and stored in following conditions for a period according to ICH guidelines.

Accelerated stability studies

Accelerated stability studies are carried out at 40 ± 2°C and RH 75 ± 5% for a period of 0, 7, 15, 21, 30, 45, 60 days in a stability chamber. The optimised formulations were placed in an amber colour bottles the sample were withdrawn after these days and evaluated for the physical characterization that is tablet defect, hardness, friability, disintegration time, drug content, dissolution and *in vitro* drug release [Table 11].

At room temperature

Tablet was packed in suitable packaging material at room temperature for a period of 0, 7, 15, 21, 30, 45, 60 days after these days sample withdrawn and evaluated for the physical characterization that is tablet defect, hardness, friability, disintegration time, drug content, dissolution and *in vitro* drug release [Table 12].

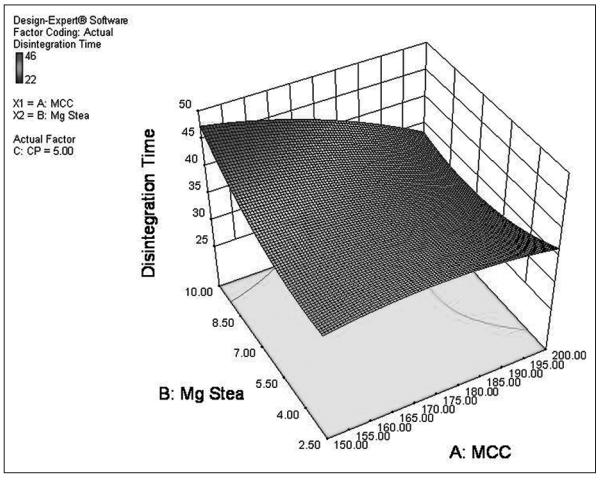

Figure 12: Response surface plots showing the effect of drug carrier ratio on the disintegration time from formulation

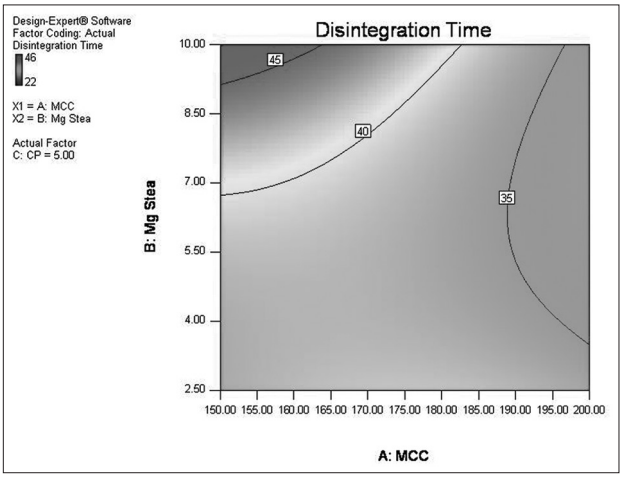

Figure 13: Counter plots showing the effect of drug polymer on the disintegration time from formulation

Table 10: Factorial design of PZQ tablet

Ingredients mg/tablet	Batch code							
	F1	F2	F3	F4	F5	F6	F7	F8
SDs containing 100 mg PZQ (mg)	250	250	250	250	250	250	250	250
Avicel pH 101 (mg)	150	150	200	200	150	150	200	200
Magnesium stearate (mg)	2.5	10	10	2.5	2.5	10	10	2.5
Crospovidon (mg)	2.5	7.5	7.5	2.5	7.5	2.5	2.5	7.5
Quantity per tablet (mg)	405	427.5	467.5	455	410	412.5	462.5	460

SD: Solid dispersion, PZQ: Praziquantel

At freezer condition

Tablet was packed in suitable packaging material in refrigerator for a period of 0, 7, 15, 21, 30, 45, 60 days after these days sample withdrawn and evaluated for the physical characterisation that is tablet defect, hardness, friability, disintegration time, drug content, dissolution and *in vitro* drug release [Table 13].

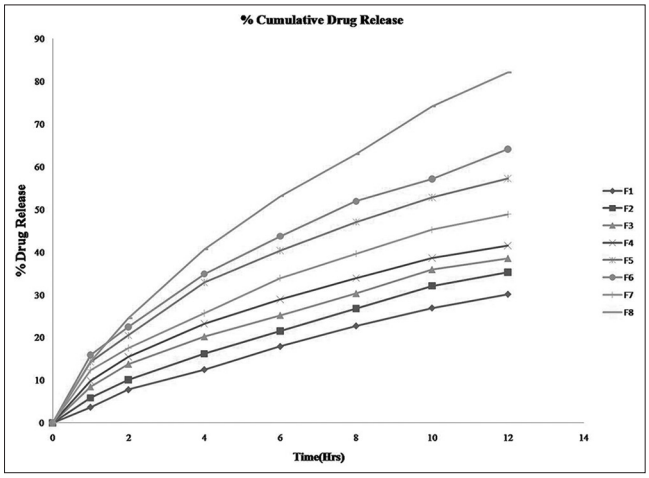

Figure 14: *In vitro* study profile of drug PEG 6000 (12, F8)

CONCLUSION

This study indicates that a solid dispersion is potential carriers system for PZQ. In the present study the solid dispersion was prepared by solvent evaporation using the various solubilisers as carriers like PEG 6000, Mannitol, and Urea. The IR peaks of drug with the carriers resemble almost same structural peaks of pure drug indicating the compatibility between the drug and carriers. Pre-compression parameter was evaluated for Bulk density, Tapped density, angle of repose compressibility index and Hausner's ratios of all samples that indicated that Solid dispersion was free flowing. These properties are suitable for conversion into solid dosage form. The drug content analyses among all formulation were observed, and it was found that F8th formulation contained the maximum amount of drug. The solubilisation effect of the hydrophilic carrier resulted in the reduction of particle aggregation of the drug, elimination of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug particles, and these could be responsible for the enhanced solubility and dissolution rate of praziquantel in the SDs. *In vitro* study indicates that F8 formulation showed highest drug release (82.1%) among all formulations thus results in enhancement solubility. The results of a 2^3 factorial

Table 11: Physicochemical tests

Formulation	Mean±SD					
	Thickness (mm) (*n*=3)	Friability (%)	Hardness (kg/cm^2)	Weight variation (mg)	Disintegration time (s)	Drug content (%)
F1	4.255±0.03	0.74±0.03	3.18±0.5	335.74±2.4	22±0.013	87.5±0.05
F2	5.445±0.06	0.81±0.03	3.55±0.4	417.5±2.8	25±0.038	96.3±0.2
F3	5.858±0.04	0.79±0.35	4.65±0.3	537.5±1.6	30±0.041	94.5±0.07
F4	4.01±0.04	0.80±0.03	3.70±0.7	341.74±2.9	45±0.032	89.2±0.04
F5	4.650±0.05	0.64±0.07	4.68±0.4	463.32±1.8	40±0.046	96.2±0.06
F6	4.74±0.03	0.61±0.04	5.6±0.3	546.12±1.8	55±0.062	83.5±0.07
F7	4.79±0.037	0.72±0.05	4.33±0.3	340.59±2.10	56±0.091	95.2±0.06
F8	5.112±0.03	0.66±0.04	4.25±0.2	498.58±1.27	58±0.017	98.5±0.05
F9	5.142±0.04	0.75±0.04	5.123±0.3	557.5±2.62	60±0.031	96.3±0.03

SD: Standard deviation

Table 12: Stability data of optimised batch (F8) at room temperature

Evaluation parameters	Storage time (60 days)						
	0	7	15	21	30	45	60
Hardness (kg/cm^2)	4.05	4.05	4.04	4.02	4.02	4.01	4.00
Drug content (%)	97.5	97.5	97.4	97.2	97.00	97.00	96.8
Friability (mg)	428.58	428.58	428.57	428.56	428.55	428.55	428.53

Table 13: Stability data of optimized batch (F8) at refrigerator

Evaluation parameters	Storage time (60 days)						
	0	7	15	21	30	45	60
Hardness (kg/cm^2)	4.05	4.05	4.04	4.03	4.03	4.01	4.00
Drug content (%)	97.5	97.5	97.5	97.4	97.4	91.3	97.00
Friability (mg)	428.58	428.58	428.58	428.55	428.55	428.53	428.51

design revealed that the amount of PZQ, MCC, Magnesium stearate and crospovidone significantly affect the dependent variables, thickness, hardness, friability, and disintegration time of F8 formulation and also showed uniformity as per IP limits. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Hence, the study concluded that solid dispersion provides a useful solid dosage form for poorly water soluble drugs.

REFERENCES

1. Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersions: A review. Pak J Pharm Sci 2009;22:234-46.
2. Craig DQ. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm 2002; 231:131-44.
3. Zaheer A, Maurya N, Mishra K, Khan I. Solubility enhancement of poorly water soluble drug: A review. Int J Pharm Technol 2001;3:807-23.
4. Breaux J, Jones K, Boulas P. Understanding and implementing efficient, analytical methods development and validation. Pharm Technol Anal Chem Test 2003; 5:6-13.
5. Alfonso RG, Remington: The Science and Practice of Pharmacy. Vol. 2. Lippincott Williams and Wilkins, USA, Philadelphia; 2010. p. 1369.
6. Messareddy RS, Bolmal US, Patil BR, Shah V. Praziquantel loaded sodium alginate microspheres prepared by ionotropic gelation technique: Formulation, evaluation and optimization. Indian J Nov Drug Deliv 2011;3:125-33.
7. Wells J, Aulton ME. Pharmaceutics The Science of Dosage form Design. 3rd ed. Churchill Livingstone Elsevier, Melbourne and New York, Edinburgh, London 1998. p. 224-50.
8. Jain NK. Biodegradable microparticals of peptide drugs using polylactide polymers. Advance in Controlled and Novel Drug Delivery 1st ed. New Delhi, CBS Publishers and Distributors; 2005. p. 12.
9. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. 5th ed. New Delhi: Wolters K, Lippincott Williams and Wilkins; 2009. p. 533-43.
10. Pandey S. Development, Optimization and *in vitro* evaluation of glibenclamide solid dispersion using different polymer, scholars research library Der Pharmacia Lettre, 2009, 1:2, 255-61.
11. Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery system: Effects of CO (2) gas-forming agents. Int J Pharm 2002; 239:81-91.
12. Bagade OM, Kad DR. Consequences and impose of solubility enhancement of poorly water soluble drugs. Res J Pharm Technol 2014;7:598-607.
13. Patel CA. *In vitro* Evaluation and optimization of controlled release floating drug delivery of PZQ. Daru J Pharm Sci 2006;14:57-63.

How to cite this article: Bagade O, Shete A, Dhole S, Pujari R, Raskar V, Kharat P. Design and statistical optimisation of praziquantel tablets by using solid dispersion approach. Asian J Pharm 2015;9:83-92.

Source of Support: Nil. **Conflict of Interest:** None declared.