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Original Article

OPTIMIZATION OF FORMULATION OF SOLID DISPERSION OF FUROSEMIDE BY FACTORIAL DESIGN

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ABSTRACT

Objective: The present study aimed to improve the rate of dissolution of furosemide by solid dispersion technique.

Methods: Solid dispersion of furosemide was prepared by using hydrogel isolated from the seeds of *Lepidium sativum* as a novel carrier by the solvent evaporation method. Solid dispersion was evaluated to study the improvement in the rate of dissolution. Molecular dispersion of furosemide in the novel carrier was studied by DSC and FTIR studies. Solid dispersion was filled in capsules after stability studies and the formulation was optimized by adopting factorial design.

Results: Solid dispersion of furosemide exhibited dissolution improvement from 13.54 % (plain furosemide) to 69.12% (solid dispersion) in the first 60 min. Improvement in dissolution efficiency was found to be retained after stability studies. Capsules were filled with the formulation of solid dispersion using two different grades of lactose-α lactose monohydrate and anhydrous lactose and were found stable after stabilization studies.

Conclusion: The dissolution improvement of furosemide was attributed to its molecular dispersion in the novel carrier selected for this study. The recrystallization of furosemide was prevented due to intermolecular interaction between the novel carrier and furosemide. This was confirmed by FTIR. Evaluation of the dissolution data of factorial batches was analyzed by ANOVA. Analysis of the data revealed that selected levels of α lactose monohydrate and anhydrous lactose would be useful to navigate design space.

Keywords: Furosemide, Dissolution, Hydrogen bonding, Solid dispersion

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INTRODUCTION

Furosemide is a BCS class IV drug and is a weakly acidic loop diuretic used for oral treatment of edema and hypertension. It shows the variable rate and extent of absorption resulting in poor oral bioavailability (37%–51%). It is a substrate for the P-gp efflux system expressed in lower GIT and hence it is poorly permeable. Since poor permeability of furosemide is due to its efflux in the lower small intestine; enabling dissolution of furosemide to the extent to ensure its adequate absorption through upper GIT is sufficient to improve its bioavailability [1, 2]. Solid dispersion is a widely adopted formulation approach to enable dissolution because of its feasibility, reproducibility, and ease of optimization. Molecular dispersion of furosemide in a selected novel carrier was prepared in the present study. It is reported that if water-soluble carriers ate preferred; the incidence of recrystallization of a molecularly dispersed drug is reduced. Therefore molecular dispersion of furosemide was prepared with hydrogel isolated from the seeds of *Lepidium sativum* as a novel hydrophilic carrier [3, 4]. In an attempt to improve the dissolution of a drug through its molecular dispersion in a hydrophilic carrier; the recrystallization of a drug during storage is a point of major concern. This problem can be mitigated by proper polymer selection. Suitable material that is capable of interacting with drug molecules through hydrogen bonding is expected to prevent the recrystallization. The hydrogel was isolated from the seeds of *Lepidium sativum* (gel) and used in this study as novel material as it was studied as a disintegrating agent and reported by Patel *et al.*; 2011 [5-8].

The stability of molecular dispersion of furosemide was confirmed and its formulation to be filled in capsules was developed and optimized by adopting factorial design. Lactose is routinely used diluent/filler in capsule dosage forms. Crystalline α-lactose monohydrate and crystalline anhydrous lactose are the most frequently used forms of lactose in the pharmaceutical industry. The present work aimed to improve the dissolution of furosemide. Hence, the influence of lactose as one of the major components of the formulation; on the dissolution efficiency of molecularly dispersed furosemide was necessary to be assessed. The grade of lactose was selected as one variable factor and amount of silicon dioxide as the second variable factor. Silicon dioxide is a hydrophobic lubricant; the study of its effect on the dissolution of furosemide was required [9, 10]. Design Expert (Demo version 11-Stat-Ease, Inc, USA) was used for the analysis of the effect of each variable on the designated response i.e. dissolution efficiency. The analysis of data suggested that the selected levels of factors (two grades of lactose and the amount of silicon dioxide) can be used to navigate the design space [11].

MATERIALS AND METHODS

Materials

Furosemide was obtained as a gift sample from Cipla Ltd., Kurkhumbh, India. Seeds of *Lepidium sativum* were purchased from a local source and were authenticated CSIR-National Botanical Institute (authentication number-LWG-46) and deposited in National Repository, Lucknow, India. All other chemicals used in the analysis were of analytical grade and others were at least of pharmaceutical grade and used without further purification.

Methods

Isolation of hydrogel from the seeds of *Lepidium sativum*

The hydrogel was isolated from whole seeds of *Lepidium Sativum* by soaking them in demineralized water. The entire bulk was homogenized and passed through a muslin cloth to obtain the gel.

FTIR of hydrogel obtained from the seeds of *Lepidium sativum*

The gel was isolated from the seeds of *Lepidium Sativum*, and dried in hot air oven (at 80 °C for sufficient time to remove the water completely) and taken for FTIR analysis. Powder of potassium bromide (KBr) was heated for 1.5 h. to remove moisture at 160 °C. Dried Gel was mixed thoroughly with KBr in the proportion of 1:1.

The FTIR spectrum was recorded using a JASCO FTIR instrument. The result was obtained in the form of a graph of % Transmittance vs. Wave no. Then the mixture was scanned over the 400-4000 cm^{-1}.

Preparation of solid dispersion of furosemide

Gel (mucilage) isolated from the seeds of *Lepidium sativum* was used in the preparation of solid dispersion of Furosemide. Solid dispersion of Furosemide was prepared by adopting the solvent evaporation method [12]. Furosemide was dissolved in ethanol (50 ml). Sufficient amount of gel was mixed with an ethanolic solution of furosemide in to attain 1:1, 1:2 and 1:3 proportions by weight of furosemide and dried Gel. The mixture was homogenized for 30 min and then was dried in an oven for 50 min at 80 °C. These solid dispersions were characterized and evaluated for dissolution studies.

Characterization and evaluation of solid dispersion of furosemide

Uniformity of content of furosemide in solid dispersion

The sufficient amount of solid dispersion equivalent to 40 mg of furosemide was weighed accurately. The actual amount of furosemide present in solid dispersion was determined by dissolving it in 50 ml of dimethyl-formamide to which has been added 3 drops of Bromothymol blue T. S. which previously has been neutralized 0.1 N NaOH; titrated with 0.1N NaOH [13].

FTIR analysis of solid dispersion

FTIR of solid dispersion recorded to study molecular interaction between furosemide and gel. Potassium bromide (KBr) was heated for 1.5 hr. at 160 ° C to remove moisture. Solid dispersion was mixed thoroughly with KBr in the proportion of 1:1. The FTIR spectrum of the solid dispersion was recorded using a JASCO FTIR instrument. The result was obtained in the form of a graph of % Transmittance vs. Wave no. Then the mixture was scanned over the 400-4000 cm^{-1}.

Determination of dissolution efficiency of solid dispersion of furosemide

Solid dispersion equivalent to the 40 mg of furosemide was weighed accurately and put in the vessel of the USP II dissolution apparatus containing 900 ml of phosphate buffer pH 5.8. The dissolution medium was maintained at 37 °C±0.5 °C. The speed of the rotating shaft was 50 rpm. The aliquots of 5 ml were withdrawn at predetermined time intervals, filtered and diluted sufficiently. The absorption was measured at 277 nm and the cumulative amount dissolved was calculated. The dissolution efficiency (D. E.) of solid dispersion is the area under the dissolution curve of the rectangle described by 100% dissolution in the same time [14]. It was calculated by the following equation-

$$\text{D. E.} = \frac{0\int \text{ty} \times \text{dt}}{\text{y100} \times \text{t}} \times 100 \text{----------Eq. n 1}$$

Where 'y' is the drug percent dissolved at the time 't'.

Stability study

Stability studies were conducted for the solid dispersion of Drug: Gel in 1:3 proportions to confirm the dissolution improvement even after the stability period. Solid dispersion was packed in aluminum foil and exposed to 40°C/75% RH for two months according to the guidelines from the International Council for Harmonization (ICH) [15]. Solid dispersion was evaluated for the parameters as uniformity of content, dissolution efficiency and DSC.

Optimization of the capsule as a dosage form by factorial design

Bulk formulations of solid dispersion were prepared by mixing the appropriate quantity of solid dispersion with 62.5% lactose (α monohydrate and anhydrous) as a filler/diluent and silicon dioxide 1.5% as a glidant for 10 min. A 2^2full factorial design was used for the optimization of the composition of the bulk of solid dispersion to be filled in capsules [16, 17]. According to the model it contained 2 independent variables at 2 levels,+1,-1. According to the model, the total four formulations are possible, the composition of the different formulation is shown in table 1. The different independent variables were α lactose monohydrate or anhydrous lactose (X1) and the amount of colloidal silicon dioxide (X2). The factor levels were chosen to their relative alteration was acceptable to have powder bulk with flow property (i.e. if the angle of repose was between 28 to 34) and compressibility (i.e. Hausner's ratio between 1.12 to 1.2). The dependent factor included dissolution efficiency at 60 min after stability studies. Stability studies of all the factorial formulations were conducted. All formulations were exposed to 40°C/75% RH for three months according to the guidelines from the International Council for Harmonization (ICH) and were evaluated for dissolution studies. Design Expert (Demo version 11-Stat-Ease, Inc, USA) was used for the analysis of the effect of each variable on the designated response i.e. dissolution efficiency. The significant response polynomial equations generated by Design Expert were used to validate the statistical design. Response surface plots were generated to visualize the simultaneous effect of each variable on each response parameter. The constant and regression coefficients were also calculated using the software.

Table 1: Composition of powder blend for preparation of factorial batches

Ingredients (mg/capsule) formulation code	FRU SD equivalent to 40 mg of CLA	Lactose*	Colloidal silicon dioxide	Total weight of the tablet
F1 (-,-)	160	100	4	264
F2 (+,-)	160	100	4	264
F3 (-,+)	160	100	8	268
F4 (+,+)	160	100	8	268

* F1 and F3 were prepared by using α lactose monohydrate and F2 and F4 were prepared by using anhydrous lactose.

Table 2: Translation of coded value in actual unit

Variable level	–	+
X1= Grade of lactose	α lactose monohydrate	Anhydrous lactose
X2 = Colloidal silicon oxide	04 mg	08 mg

RESULTS AND DISCUSSION

Isolation of hydrogel from the seeds of lepidium sativum

The hydrogel was isolated from whole seeds of *Lepidium Sativum and* the appearance of the gel was translucent and brownish. The specific gravity of the gel was found to be 1.009 and was comparable to water revealing very high water uptake by the gel-forming material.

FTIR of hydrogel obtained from the seeds of Lepidium sativum

The composition of Gel is reported in the literature. It contains arabinose, xylose and rhamnose and the highest amount of uronic acid (galacturonic acid+glucuronic acid). FTIR spectrum of the dried is shown in fig. 1. The spectra exhibited all typical bands and peaks characteristic of polysaccharides. The major identical peaks are similar and in good agreement with those reported for *Lepidium*

sativum seed mucilage. A band around 2921 cm^{-1} (3000-2800 cm^{-1}) referred to C-H vibrations, which included CH, CH2 and CH3 stretching and bending vibrations, symmetric, and asymmetric and occasionally doubles overlapping with O-H. The characteristic bands around 1668 cm^{-1} and 1463 cm^{-1} were attributed to the asymmetrical and the symmetrical COO-stretching vibrations, respectively. The peak at 1066 cm^{-1} indicated the presence of carbohydrates [18, 19].

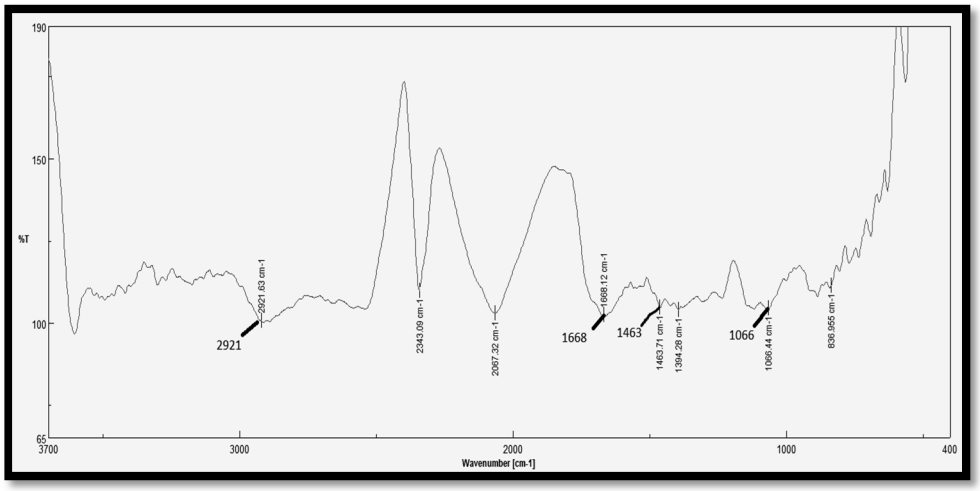

Fig. 1: FTIR spectrum of dried mucilage of *Lepidium sativum*

Preparation of solid dispersion of furosemide

Uniformity of content of furosemide in solid dispersion

Solid dispersion was prepared in three lots and was faint brown in appearance. The yield was calculated and it was found to be more than 95%. The uniformity of the content of furosemide in its solid dispersion form was found to be 96.12%±1.74. Further calculations were done with necessary corrections accordingly.

FTIR analysis of solid dispersion

FTIR spectra of plain furosemide (fig. 2) and its solid dispersion (fig. 3) were compared and revealed hydrogen bonding between them. The characteristic peak of the primary amine (NH_2) group that was observed at 1568 cm^{-1} in FTIR of plain furosemide was downshifted at1430 cm^{-1} in FTIR of solid dispersion of furosemide. Similarly, the characteristic peak of the ketone carbonyl group that was observed at 1678 cm^{-1} in FTIR of plain furosemide was downshifted at1611 cm^{-1} in FTIR of solid dispersion of furosemide. The broadening of the absorption band in the OH stretching region also indicated intermolecular hydrogen bonding [20, 21].

Determination of dissolution efficiency of solid dispersion of furosemide

In an attempt to design a scalable manufacturing method of solid dispersion, the amount of carrier needed to achieve the desired improvement in dissolution characteristics of the drug is a major factor. The gel was selected as a novel carrier in the present study. Hence, the solid dispersion of Drug: Gel was prepared by using gel in increasing proportions and its influence on dissolution characteristics of the furosemide was carefully studied. As the proportion of gel was increased in the preparation of solid dispersion, dissolution was found to be gradually increased. There was an increase in the dissolution efficiency of furosemide in its solid dispersion form (in proportion 1:3) when compared to that with plain furosemide as from 13.54% to 69.12% in first 60 min (table 3 and fig. 4). This improvement was statistically significant [22]. This might be due to the well-reported wetting effect of the hydrophilic gel that is used as a novel carrier in the present study and molecular dispersion of the furosemide in the carrier system [23].

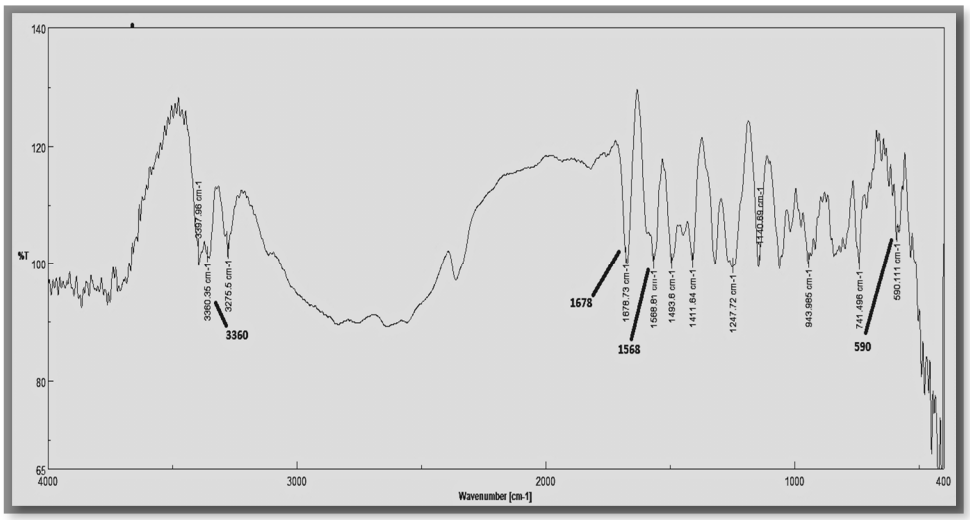

Fig. 2: FTIR spectrum of furosemide

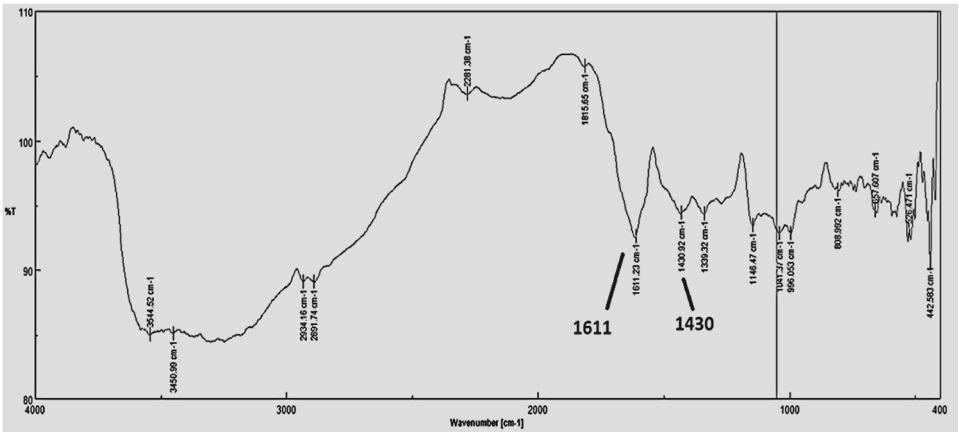

Fig. 3: FTIR spectrum of solid dispersion of furosemide

Table 3: Percent cumulative dissolution data for SD of furosemide and plain furosemide

Time (min)	Plain furosemide	% Cumulative dissolution for solid dispersions of various proportions of the drug: gel*		
		1:1	1:2	1:3
00	00	00	00	00
05	5.88±0.19	29.55±0.29	25.85±0.12	40.17±0.11
10	8.61±0.31	32±0.23	36.83±0.21	54.77±0.23
15	11.01±0.11	33.38±0.12	49.9±0.25	60.83±0.06
20	13.5±0.23	38.94±0.12	62.14±0.13	63.40±0.20
25	14.86±0.49	39.77±0.15	66.47±0.32	68.22±0.10
30	15.16±0.17	40.33±0.22	66.13±0.08	74.35±0.30
45	16.19±0.33	40.55±0.20	71.19±0.12	84.38±0.21
60	18.55±1.6	43.33±0.18	75.65±0.23	93.55±0.21

*All values indicate mean±SD (n=3)

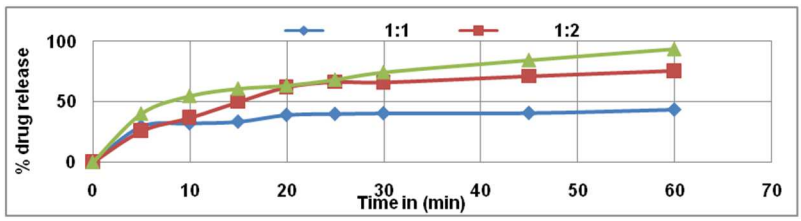

Fig. 4: Percent cumulative drug release of different furosemide: gel ratio's

Stability study

In the overall developments in amorphous solid dispersions, re-crystallization of the drug in solid dispersion form i.e. physical stability of the dispersion is a factor of serious concern. The strategy to stabilize the molecular dispersion/amorphous form of a drug in its solid dispersion demands interactions such as hydrogen bonding between the drug and hydrophilic polymer used in the solid dispersion [24]. FTIR study already revealed hydrogen bonding between furosemide and gel. Therefore stability studies were planned and conducted to confirm the stability of molecular dispersion/amorphous form of a drug in its solid dispersion. Uniformity of content of furosemide remained above 95% even when the solid dispersion was exposed to 40°C/75%RH i.e. after stability testing studies for two months. Dissolution efficiency was found to be 68.33%. Differential Scanning calorimetry was performed to confirm the amorphous nature of the drug in solid dispersion. The DSC scans of furosemide in its solid dispersion recorded at the end of stability studies revealed that the drug exothermic characteristic peak (fig. 5) disappeared completely. This might be explained based on the homogeneous dispersion of furosemide in hydrophilic carrier i.e. gel [25]. Therefore it was concluded that the marked improvement in the dissolution of furosemide was due to molecular dispersion/amorphization of the furosemide in the hydrophilic gel. The recrystallization of furosemide was mitigated due to intermolecular hydrogen bonding between the furosemide and novel carrier selected in the present study. Solid dispersion of Furosemide: gel in 1:3 proportions was taken further to develop its suitable dosage form.

Optimization of the capsule as a dosage form by factorial design

Recrystallization of the amorphous form of a drug is promoted due to the application of the compression force [26]. Also, most of the formulations are filled into the capsules for the conduct of clinical trials. Therefore capsules as drug delivery systems were selected in the present study. The formulation to be filled in the capsules requires a specific flow and density profile. Lactose is a well-accepted excipient, widely used as a diluent, filler-bulking agent in the capsule as a solid oral dosage form. It is available in various grades with different physical properties. Various grades of lactose are available and are routinely used in the bulk formulations to be filled in the capsules. The process demands a specific grade of lactose to make the bulk free-flowing to somewhat cohesive for a specific formulation. Two different grades of lactose-α lactose monohydrate or crystalline anhydrous lactose were selected as diluents to prepare the bulk of solid dispersion to be filled in capsules [27]. The levels of lactose were selected based on the evaluation of preliminary bulk formulations and the recommended amounts for BCS class IV compounds [28]. Preliminary bulk

formulations were prepared by mixing lactose of either grade in the proportion reported to be appropriate for BCS class IV API (furosemide). The bulk formulations that exhibited acceptable flow properties, as well as compressibility, were further selected for optimization of the formulation by adopting factorial design. Silicon dioxide was used as a glidant. Capsules were evaluated for contents of the active ingredient and were found 98.85% w/w. Three capsules from each factorial batch were taken for measurement of dissolution efficiency and the results are reported in table 4.

The data obtained after evaluation of factorial batches were analyzed by using the demo version of commercially available software Design Expert (Version 11). To describe the response surface curvature (fig. 5), the design was evaluated by the quadratic model, which bears the form of the equation–

$$D.E.(Y) = 68.34 + 0.45X1 - 0.02X2 - 0.01X1X2 \text{ ----------Eq. n 2}$$

Anhydrous lactose exhibited faster dissolution than when lactose monohydrate was used; as indicated by the positive coefficient of X_1. As the amount of silicon dioxide was increased in the formulation the dissolution rate slowed down; as indicated by the negative coefficient of X_2. The high numerical value of the coefficient of X_1 indicated that the grade of lactose used in the formulation has more impact on dissolution than the amount of silicon dioxide added. The interaction between factor X_1 and X_2 was not considerable and both were found to negate the effect of each other to some extent. It was obvious by the negative coefficient of X_1X_2.

Analysis of the evaluation data generated for dissolution efficiency by applying ANOVA suggested that the significant factors affecting dissolution efficiency were the grade of lactose and the amount of silicon dioxide. F value for silicon dioxide and the interaction term was at $p \geq 0.05$ and suggested low confidence in the inference drawn. Thus, the effect of silicon dioxide on the dissolution efficiency of solid dispersion has to be planned with logical modifications to refine the results. Design space is applicable to scale up and to a site change and working within a design space is not considered as a change. As per ICH Q8 (R2) guidelines, the factorial design was adopted to establish design space. The fit statistics (table 5) suggested that the selected levels of factors (two grades of lactose and the amount of silicon dioxide) can be used to navigate the design space.

Table 4: Dissolution efficiency (%) for factorial batches

Formulation	F1(–,–)	F2(+,–)	F3(–,+)	F4(+,+)
D. E. (%)	67.90±0.32	68.82±0.26	68.16±0.26	68.87±0.21

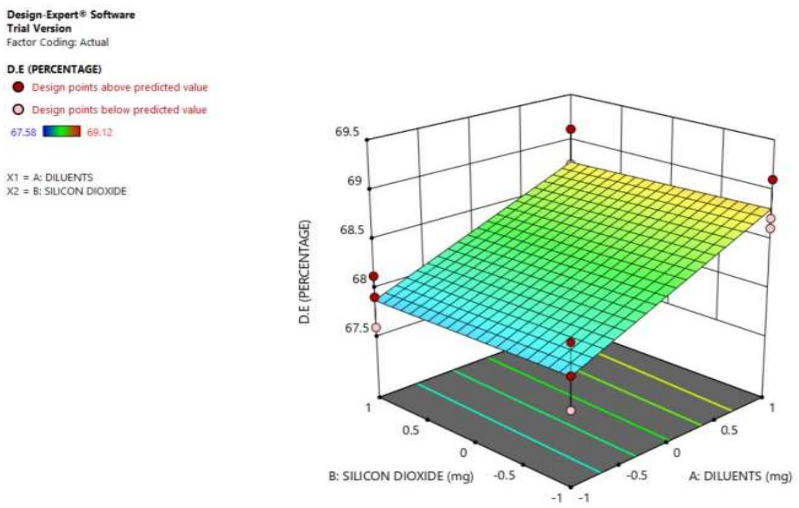

Fig. 5: Surface response curvatures

Table 5: Analysis of data after applying anova

ANOVA for selected factorial model

Response 1: D.E

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2.41	3	0.8034	8.69	0.0067	significant
A-DILUENTS	2.40	1	2.40	26.00	0.0009	
B-SILICON DIOXIDE	0.0061	1	0.0061	0.0657	0.8041	
AB	0.0010	1	0.0010	0.0109	0.9194	
Pure Error	0.7393	8	0.0924			
Cor Total	3.15	11				

Factor coding is **Coded.**
Sum of squares is **Type III - Partial**

The **Model F-value** of 8.69 implies the model is significant. There is only a 0.67% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	0.3040	**R^2**	0.7653
Mean	68.34	**Adjusted R^2**	0.6772
C.V. %	0.4448	**Predicted R^2**	0.4719
		Adeq Precision	5.3559

The **Predicted R^2** of 0.4719 is not as close to the **Adjusted R^2** of 0.6772 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 5.356 indicates an adequate signal. This model can be used to navigate the design space.

CONCLUSION

Solid dispersion of furosemide was prepared by the solvent evaporation technique using hydrogel isolated from the seeds of *Lepidium sativum* (gel) as a novel carrier. Dissolution efficiency of solid dispersion of furosemide (Furosemide: Dried gel in 1:3 proportions) was improved from 13.54 % (plain furosemide) to 69.12% in the first 60 min. Molecular dispersion of furosemide in carrier (in its solid dispersion form) was found to be the major cause of its improved dissolution. Solid dispersion of furosemide was found to be stable and recrystallization was mitigated during stability studies. This was due to the selection of proper hydrophilic carrier and its inclusion in the solid dispersion in appropriate proportion. The stability of amorphous solid dispersion was found to be due to intermolecular interaction between furosemide and novel carrier through hydrogen bonding and confirmed by FTIR studies. Immediate-release capsule formulation of amorphous solid dispersion of furosemide was optimized by adopting factorial design. Data of dissolution efficiency of factorial batches was analyzed by ANOVA by using Design Expert (Demo Version 11) and results revealed that the levels of factors selected would be useful to navigate design space.

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Nil

AUTHORS CONTRIBUTIONS

The research idea was set with guidance of Prof. Dr. Sharwaree R. Hardikar. The research work was done by Shakil S. Mulla. The manuscript was prepared by Shakil S. Mulla and the critical revision of the manuscript was done by Prof. Dr. Sharwaree R. Hardikar. Calculations and data interpretation was supported by Prof. Dr. Sharwaree R. Hardikar.

CONFLICTS OF INTERESTS

Declared none

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