Effect of Hydrophilic Swellable Polymers on Dissolution Enhancement of Carbamazepine Solid Dispersions Studied Using Response Surface Methodology

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ABSTRACT

The objective of this work was to study dissolution enhancement efficiency and solid dispersion formation ability of hydrophilic swellable polymers such as sodium carboxymethyl cellulose (Na-CMC), sodium starch glycolate (SSG), pregelatinized starch (PGS), and hydroxypropylmethyl cellulose (HPMC) with carbamazepine using 3^2 full factorial design for each of the polymers. Solid dispersions of carbamazepine were prepared using solvent evaporation method with around 70% solvent recovery. The independent variables were the amount of polymer and organic solvent. The dependent variables assessed were percentage drug dissolved at various time points and dispersion efficiency (ie, in terms of particle size of solid dispersion). Solid dispersions were evaluated for percentage drug dissolved, wettability, differential scanning calorimetry, scanning electron microscopy, and angle of repose. Multiple linear regression of results obtained led to equations, which generated contour plots to relate the dependent variables. Similarity factor and mean dissolution time were used to compare dissolution patterns obtained in distilled water and simulated gastric fluid United States Pharmacopeia (USP) XXVI of pH 1.2. Maximum drug dissolution was obtained with polymer order Na-CMC>SSG>PGS>HPMC. Particle size of drug was reduced ~10–15, 3–5, 5–7, and 10–25 times in Na-CMC, SSG, PGS, and HPMC solid dispersions, respectively; whereas wettability of solid dispersions was found in the order of Na-CMC>HPMC>PGS>SSG. Angle of repose was found to be in the range of 29° to 35° for all solid dispersions, which shows good flowability characteristics. HPMC showed increase in drug dissolution up to an optimized level; however, further increase in its concentration decreased drug dissolution.

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KEYWORDS: Solid dispersion, factorial design, similarity factor, mean dissolution time, carbamazepine, multiple linear regression, simulated gastric fluid.

INTRODUCTION

The rate of oral absorption of poorly soluble drugs is often controlled by their dissolution rate in the gastrointestinal tract.[1] Thus solubility and dissolution rate are the key determinants of oral bioavailability, which is the concluding point drawn for fate of oral bioavailability.[2,3] Carbamazepine (CBZ) is a widely prescribed antiepileptic drug having poor water solubility (~170 mg/L at 25°C).[4] Because of having poor water solubility, its absorption is dissolution rate limited, which often results in irregular and delayed absorption.[5]

For improvement of solubility and dissolution rate of poorly soluble drugs, numerous commercially viable techniques such as liquisolid, in which drug in solution state or dissolved drug is adsorbed over insoluble carriers,[6-8] nanomorph, a patented technology by Soliqs for controlled crystallization of drug,[9] in situ micronization,[10,11] and coprecipitation using antisolvent,[12] are available. Surfactants can also be used in formulations to improve wettability and solubility of many lipophilic substances.[13] Micronization of drug is not preferred because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution.[14] But ahead of all, solid dispersion is the most promising method to formulators because of its ease of preparation, ease of optimization, and reproducibility.[15-18] Poorly soluble drugs are dispersed in an inert hydrophilic polymer or matrix by melting, solution formation, or solvent melting to yield solid dispersion.[15,17]

Usually, solid dispersions (SDs) are prepared with water soluble low melting point synthetic polymers such as polyvinylpyrrolidone (PVP), mannitol, or polyethylene glycols (PEGs).[19] These polymers show superior results in drug dissolution enhancement, but the amount of these polymers required is relatively large, around 1:2 to 1:8 (drug/polymer) ratio.[20] In certain similar experiments it has been observed that, PVP and PEG get dissolved first in dissolution media (owing to their high water solubility) leaving the drug back in undissolved state. In such case, though the drug is in controlled crystallization state or amorphous state, the

polymers are unable to provide wetting ability to the drug particles. In such cases, there may be the possibility of rapid reversion of amorphous drug to the more stable crystalline state in presence of small amount of plasticizers such as water.[21]

Literature survey reveals that certain hydrophilic swellable polymers such as sodium carboxymethyl cellulose (Na-CMC), sodium starch glycolate (SSG), and pregelatinized starch (PGS) have still been unexplored for their potential to form solid dispersion in order to improve dissolution properties of poorly soluble drugs. For this reason, in the present work, water-swellable polymers or normal excipients of solid dosage forms were used. These polymers were supposed to hold the drug in intimate contact with water (owing to their water retention potential) and increase its wettability. Solid dispersions were prepared with modified solvent evaporation technique.

Full factorial experimental design is one of the best tools to study the effect of different variables on the quality determinant parameters of any formulation. In the present study, independent variables were assigned to the amount of polymer and the amount of solvent at 3 different levels, whereas responses or dependent variables for them were assigned to percentage drug dissolved at various time points and dispersion efficiency (ie, in terms of particle size of solid dispersion). Q_{30} (ie, percentage drug dissolved at 30 minutes) was determined for 2 different dissolution media (ie, distilled water and SGF without enzymes [USP XXVI]). The multiple linear regression (MLR) analysis of results led to equations that adequately described the influence of the independent variables on the selected responses. Polynomial regression equations and contour plots were used to relate the dependent variables. As part of the optimization process, the main effects, interaction effects, and quadratic effects of the amount of polymer and amount of solvent on percentage drug dissolved of solid dispersion were investigated.

Gohel and Panchal[22,23] recently proposed a similarity factor (S_d) for the comparison of dissolution profiles, which is more simple and flexible than similarity factor (f_2) because data can be expressed either as the amount of drug dissolved or as the percentage of drug dissolved. Another advantage is that, unlike the similarity factor (f_2), linear interpolation can be used to accurately express the results. The dissolution profiles of optimized batch in distilled water and simulated gastric fluid (SGF) without enzymes of pH 1.2 were compared using similarity factor (S_d).

Materials and Methods

Chemicals

Analytical grade chemicals were used as received. Carbamazepine was received as gift from Relax Pharmaceuticals Ltd, Vadodara, India. Polymers were purchased from S. D. Fine Chemicals Ltd, Mumbai, India. Deionized double-distilled water was used throughout the study.

Preparation of Solid Dispersion

Solid dispersions of all the polymers were prepared by modified solvent evaporation method,[10] wherein drug was dissolved in acetone at its saturation solubility with continued stirring up to 30 minutes. Polymer was suspended in sufficient amount of water (up to wet mass of polymer). The drug solution was poured at once into polymer suspension. The entire solvent was evaporated under reduced pressure at 60°C to 70°C with Rotavapor (Heidolph, Germany) with solvent recovery. The recovered solvent was used for the next batch. The solid dispersion was obtained in a flask, which was dried at 70°C to 80°C and stored in a desiccator for 24 hours.

Solubility Determination

For the determination of solubility of carbamazepine, excess material was placed in contact with 7 mL of solvent in sealed glass tubes. The tubes were shaken on a vortex mixer and were maintained at 25°C for 24 hours. The saturated solution was centrifuged and the supernatant was filtered through 0.45-μm Whatman filter paper (Whatman Ltd, Middlesex, UK) diluted suitably with water and analyzed by UV spectrophotometer at 285 nm (model UV-1601, UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan).

Experimental Design

To study all the possible combinations, 3 levels full factorial design (3^2) was constructed and conducted in a fully randomized order.[24] The dependent variables measured were percent drug dissolved at various time points and particle size of solid dispersion at three different levels. Independent variables of the 3^2 full factorial design with their coded and actual values are shown in Table 1. The range of a factor was chosen in order to adequately measure its effect on the response variables. This design was selected as it provides sufficient degrees of freedom to resolve the main effects as well as the factor interactions. MLR analysis was used to find out the control factors that affects significantly on response variables.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) thermograms of pure CBZ, CBZ: Na-CMC, CBZ: SSG, CBZ: PGS, CBZ: HPMC solid dispersions were measured using differential scanning calorimeter (DSC 60, Shimadzu) previously

Table 1. Matrix of Independent Variables and Responses for 3^2 Factorial Design for Each Polymer*

	Variables With Levels†		Response Values				
Batch	X_1	X_2	Q_{30} for % Drug Dissolved in Water	Q_{30} for % Drug Dissolved in SGF	Particle Size of Optimized Batch (μm)	Angle of Repose for Optimized Batch (°)	Wettability Time for Optimized Batch (minutes)
Polymer: Na-CMC							
A_1	–1	–1	66.58	64.25	15–17	29.43	03.15
A_2	–1	0	70.21	68.45			
A_3	–1	1	71.35	67.21			
A_4	0	–1	82.64	76.85			
A_5	0	0	87.63	83.54			
A_6	0	1	88.54	85.65			
A_7	1	–1	93.58	91.14			
A_8	1	0	95.21	93.47			
A_9	1	1	95.64	94.69			
Polymer: SSG							
B_1	–1	–1	64.25	61.26	138–158	34.56	04.49
B_2	–1	0	67.51	65.24			
B_3	–1	1	67.85	65.36			
B_4	0	–1	76.36	74.21			
B_5	0	0	78.21	75.29			
B_6	0	1	78.62	76.91			
B_7	1	–1	83.64	80.24			
B_8	1	0	84.25	82.91			
B_9	1	1	85.65	83.16			
Polymer: PGS							
C_1	–1	–1	65.36	63.59	10–200	30.65	03.86
C_2	–1	0	67.63	65.37			
C_3	–1	1	68.62	66.69			
C_4	0	–1	75.54	73.16			
C_5	0	0	75.69	73.26			
C_6	0	1	77.25	74.36			
C_7	1	–1	76.58	75.91			
C_8	1	0	82.01	78.12			
C_9	1	1	82.35	79.19			
Polymer: HPMC							
D_1	–1	–1	65.68	62.46	2–79	33.25	03.56
D_2	–1	0	66.54	64.23			
D_3	–1	1	66.25	65.28			
D_4	0	–1	68.35	66.47			
D_5	0	0	73.52	70.25			
D_6	0	1	74.56	72.19			
D_7	1	–1	70.21	71.25			
D_8	1	0	69.25	69.69			
D_9	1	1	69.58	70.58			

*Na-CMC indicates sodium carboxymethyl cellulose; SSG, sodium starch glycolate; PGS, pregelatinized starch; and HPMC, hydroxypropylmethyl cellulose.

†Independent variables levels: low (–1), medium (0), high (1); amount of polymer (1 g, 2 g, 3 g); and amount of solvent (150 mL, 200 mL, 250 mL).

calibrated using indium. The samples ~2 to 3 mgs were accurately weighed into solid aluminum pans with seals and crimped. Reference pan was an empty sealed aluminum pan. The measurements were obtained at a heating rate of 10°C/min with purging of dry nitrogen at a constant rate of 20 mL/min.

Scanning Electron Microscopy

To observe the surface morphology of CBZ and its SDs with Na-CMC, SSG, PGS, and HPMC scanning electron microscopy (SEM) studies were performed using Jeol JSM-5610 LV (Jeol Corp, Tokyo, Japan). CBZ and SDs were individually glued on the brass sample holder with the help

Table 2. Quantitative Solubility Data for Pure Carbamazepine in Different Solid Dispersion Systems and Polyethylene Glycol 400*

	Solvents		Solid Dispersion System			
Solubility of CBZ (mg/mL)	Water	PEG 400	Na-CMC	HPMC	PGS	SSG
0.0061	0.1782	0.1903	0.1411	0.1168	0.0962	

*CBZ indicates carbamazepine; PEG, polyethylene glycol; Na-CMC, sodium carboxymethyl cellulose; HPMC, hydroxypropylmethyl cellulose; PGS, pregelatinized starch; and SSG, sodium starch glycolate.

of double-sided adhesive tape. The images were captured at an excitation voltage of 15 kV at varying magnifications from original magnification ×50 to ×650.

In Vitro Dissolution Study

The dissolution study was performed using 2 media, distilled water and SGF without enzymes. Accurately weighed amount of solid dispersion, containing equivalent 100 mg of pure drug was placed in basket of USP XXIV dissolution apparatus (Type I, TDT-06P, Electrolab, Mumbai, India) with 900 mL deaerated dissolution medium. Deaeration of dissolution media was done by ultrasonication (Ultrasonics - 2.2, Mumbai, India) of dissolution medium for 15 minutes. The dissolution apparatus was run at 100 rpm at constant temperature 37°C ± 1°C. Samples (5 mL) were withdrawn at 0, 5, 10, 15, 20, 25, and 30 minutes, filtered through 0.45-μm Whatman filter paper, diluted suitably and analyzed spectrophotometrically at 285 nm (model UV-1601 UV-visible spectrophotometer, Shimadzu). An equal volume of fresh dissolution medium kept at the same temperature was added to maintain the sink conditions. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r^2 = 0.9998). The dissolution test was performed in triplicate for each batch.

Similarity Factor S_d

The similarity factor S_d is defined by Equation 1.

$$S_d = \frac{\sum_{t=1}^{n-1} |Log((AUC_{Wt})/(AUC_{Gt}))|}{n-1} \qquad (1)$$

where n is the number of data points collected during the in vitro dissolution test; AUC_{wt} and AUC_{Gt} are the areas under curves of the dissolution profiles of the solid dispersion in distilled water and SGF without enzymes, respectively, at time t. For the dissolution profiles in distilled and SGF without enzymes, to be identical, the S_d value should be zero.[22,23]

Wettability Studies

Pure drug, weighing ~1 g was placed in sintered glass funnel of 27 mm internal diameter. Bridge was formed at the neck of the funnel with the help of cotton plug. The funnel was held in upright position in a beaker filled with water such that the water level in the beaker just touched the cotton plug. Methylene blue powder was layered over the surface of pure drug in the funnel. The time required to raise the water through the drug till wetting of methylene blue powder occurred was recorded.[25] The procedure was followed for all the SDs.

Angle of Repose

To get an idea about flowability properties of the solid dispersions, angle of repose for all the batches of experimental design was determined. If the angle exceeds 50°, the material will not flow satisfactorily, whereas materials having values near the minimum flow easily and well. The rougher and more irregular the surface of the particles, the higher is the angle of repose.[26] The angle of repose was measured by passing SD through a sintered glass funnel of internal diameter 27 mm. on the horizontal surface. The height (h) of the heap formed was measured with a cathetometer, and the radius (r) of the cone base was also determined. The angle of repose (Φ) was calculated from Equation 2.

$$\Phi = \tan^{-1}\left(\frac{h}{r}\right) \qquad (2)$$

Results and Discussion

Quantitative solubility data for carbamazepine in water, polyethylene glycol 400, and Na-CMC, PGS, SSG, and HPMC solid dispersion systems is given in Table 2. Solubility of carbamazepine in Na-CMC solid dispersion increased to 0.1903 mg/mL from its 0.0061 mg/mL aqueous solubility.

Stepwise multivariate linear regression was performed to evaluate the relationship obtained between response and independent variables. For each polymer 3^2 full factorial design was applied. The independent and dependent factors, their levels, and the matrix of variables and responses for 3^2 factorial design of each polymer are shown in Table 1.

The statistical evaluation of dependent variables was performed by analysis of variance (ANOVA) using Microsoft Excel Version-2003. The ANOVA results (P value) of the variables on percentage drug dissolved of solid dispersion

Table 3. Analysis of Variance Results (*P* value) Effect of the Variables on Percentage Drug Dissolved of Solid Dispersions*

		For Dissolved in Water		For Dissolved in SGF	
Polymer	Factor	Coefficient	*P* Value	Coefficient	P Value
Na-CMC	X_1	12.7	.00	13.2	.00
	X_2	2.12	.01	2.55	.05
	X_1^2	–4.18	.01	–2.15	.23
	X_2^2	–1.30	.15	–1.86	.28
	X_1X_2	–0.68	.25	0.15	.89
SSG	X_1	8.99	.00	9.08	.00
	X_2	1.31	.02	1.62	.02
	X_1^2	–2.21	.02	–2.44	.02
	X_2^2	–0.60	.29	–0.96	.19
	X_1X_2	–0.40	.31	–0.30	.51
PGS	X_1	6.56	.00	6.26	.00
	X_2	1.79	.05	1.26	.03
	X_1^2	–2.39	.10	–2.12	.03
	X_2^2	–0.84	.47	–0.10	.86
	X_1X_2	0.63	.44	0.05	.91
HPMC	X_1	1.76	.15	3.26	.02
	X_2	1.03	.35	1.31	.16
	X_1^2	–4.22	.08	–2.39	.14
	X_2^2	–0.66	.71	–0.02	.99
	X_1X_2	–0.30	.81	–0.87	.38

*SGF indicates simulated gastric fluid; Na-CMC, sodium carboxymethyl cellulose; SSG, sodium starch glycolate; PGS, pregelatinized starch; and HPMC, hydroxypropylmethyl cellulose.

are shown in Table 3. The detailed summary of results of regression analysis of SDs for all the polymers is shown in Table 4. The significant parameters in the equations can be selected using a stepwise forward and backward elimination for the calculation of regression analysis. However, in the present study full model having both significant and nonsignificant *P* values were used in obtaining dependent variables.[23] The coefficients for the equations representing the quantitative effect of the independent variables on percentage drug dissolved in distilled water and SGF without enzymes for each polymer are shown in Table 3. The equations for each polymer can be generated by putting values of coefficients in Equation 3.

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2 \qquad (3)$$

Coefficients with one factor indicate the effect of that particular factor, while the coefficients with more than one factor and those with second-order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign of the term indicates positive (additive) effect, while negative sign indicates negative (antagonistic) effect of the factor on the response.[21]

It can be concluded from the equations that x_1 (amount of polymer) showed the largest positive effect, whereas the term x_2 (amount of solvent) showed statistically insignificant positive effect on percentage drug dissolved. The quadratic terms of x_1 and x_2 also had significant positive effect on percentage drug dissolved. The effects of term x_1 and x_2 on particle size of SDs were significant; however, high values for standard deviation were observed.

Figure 1 shows the contour plots for percentage drug dissolved of SDs in distilled water and SGF without enzymes of Na-CMC, SSG, PGS, and HPMC at 30 minutes (Q_{30}), respectively. The contour lines indicated that higher the amount of polymer, the more significant is the dissolution enhancement. However, for HPMC this was not observed, which may be attributed to controlled release matrix forming ability of HPMC.[27]

The reliability of the equations that described the influence of factors on percentage drug dissolved was assessed by preparing 3 additional check points SDs (batch C_1, batch C_2, and batch C_3) in triplicate using the amount of x_1 and x_2 −0.5, 0.25, and 0.75 level.[28] The experimental values and predicted values of each response are shown in Table 5. Equation 4 was used to calculate the percentage relative

Table 4. Summary of Results of Regression Analysis of All Polymers*

Polymer	Response: Q_{30} for Dissolution Medium	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Na-CMC	Water	87.13	12.72	2.12	–4.18	–1.30	–0.68
	SGF	83.25	13.23	2.55	–2.15	–1.86	0.15
SSG	Water	78.13	8.99	1.31	–2.21	–0.60	–0.40
	SGF	76.11	9.08	1.62	–2.44	–0.96	–0.30
PGS	Water	76.70	6.56	1.79	–2.39	–0.84	0.63
	SGF	73.66	6.26	1.26	–2.12	–0.10	0.05
HPMC	Water	72.58	1.76	1.03	–4.22	–0.66	–0.30
	SGF	69.65	3.26	1.31	–2.39	–0.02	–0.87

*Na-CMC, sodium carboxymethyl cellulose; SGF, simulated gastric fluid; SSG, sodium starch glycolate; PGS, pregelatinized starch; and HPMC, hydroxypropylmethyl cellulose.

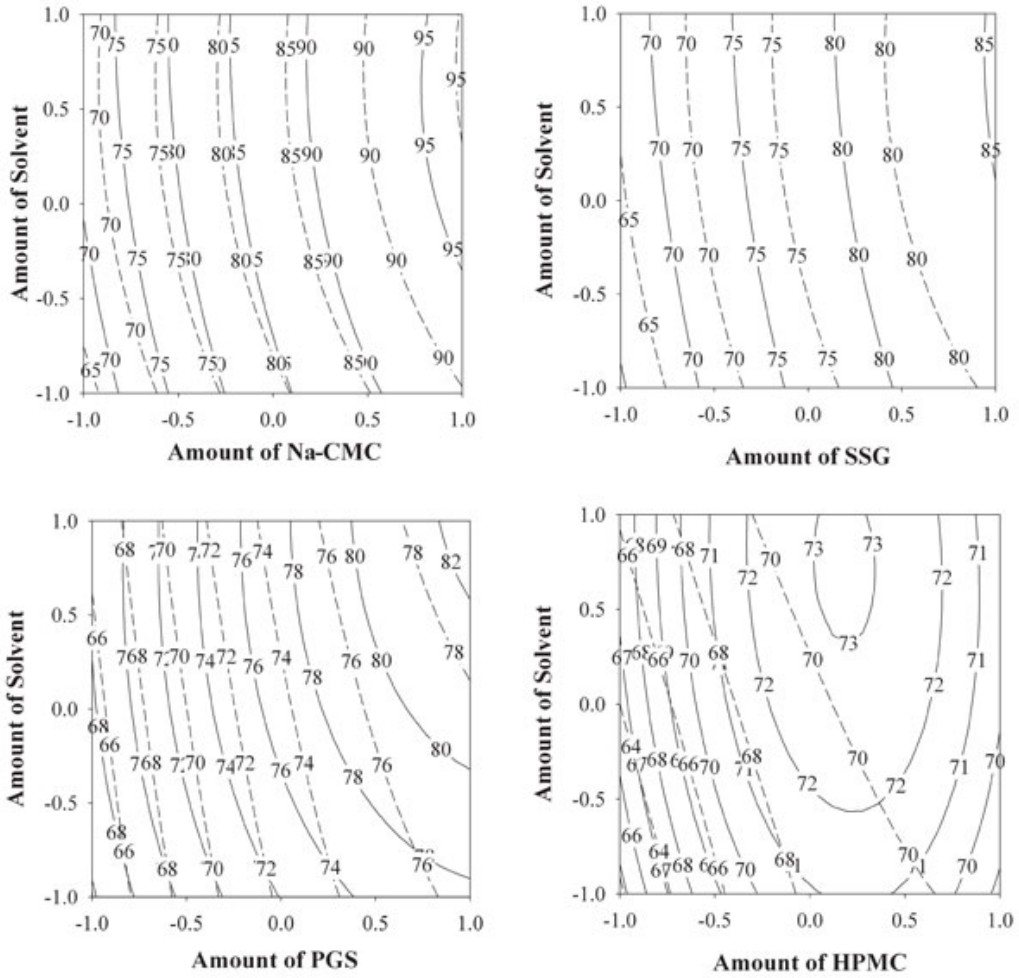

Figure 1. Contour plots showing (1) percentage drug dissolved in distilled water (solid line), and (2) percentage drug dissolved in simulated gastric fluid (SGF) (dashed line) for solid dispersions prepared with sodium carboxymethyl cellulose (Na-CMC), sodium starch glycolate (SSG), pregelatinized starch (PGS), and hydroxypropylmethyl cellulose (HPMC).

error between predicted values and experimental values of each response.

$$\% \text{ Relative error } = \left(\frac{|\text{Predicted value} - \text{Experimental value}|}{\text{Predicted value}} \right) \times 100 \quad (4)$$

The percentage relative error obtained from checkpoint batches was in the range of 0.0637 to 6.6983. Low values of the relative error showed that for all the polymers there was a reasonable agreement of predicted values and experimental values. This proved the validity of model and ascertained the effects of Na-CMC, SSG, PGS, HPMC and the amount of solvent on percentage drug dissolved.

Particle sizes of pure drug and SDs were determined using Malvern Mastersizer (Malvern Mastersizer, Worcestershire, UK) with petroleum ether as dispersion medium for sample. Results of particle size analyses are shown in Figure 2. Particle size of pure drug was found to be in a broad range of 150 to 600 μm. SDs with Na-CMC were observed with most uniformity in particle size, which ranged from 15 to 17 μm. SDs of CBZ with HPMC also showed considerable decrease in the particle size of CBZ; however, it was spread over a wide range. In the case of SDs with SSG there were 2 particle size distributions first in the range of 138 to 158 μm and the other in 1000 to 2500 μm. The latter can be very well attributed to particle size of plain SSG, whereas first can be credited to decreased particle size of drug. In case of SDs with PGS a small volume fraction was found in the range of 3 to 10 μm and a large volume fraction in the range of 100 to 200 μm, whereas in case of SDs with HPMC there were also 2 distributions but both of them represented drug because the difference in particle size was much less. This finding shows that SDs of CBZ with Na-CMC, SSG, PGS, and HPMC showed considerable decrease in the particle size of CBZ.

The release of drug from SDs was analyzed in distilled water and SGF without enzymes. Similarity factor was calculated to compare both dissolution profiles for each SD

Table 5. Cross-validation of Model Obtained Using Observed and Predicted Results of Checkpoint Batches*

Polymer	Dissolution Media	X_1	X_2	Predicted Values	Experimental Values	% Relative Error
Na-CMC	**Water**	–0.50	0.75	80.85	85.25	5.44
		0.25	0.50	90.70	84.67	6.65
		0.75	–0.50	93.19	93.25	0.06
	SGF	–0.50	0.75	76.91	80.25	4.34
		0.25	0.50	87.25	88.67	1.62
		0.75	–0.50	90.17	87.65	2.80
SSG	**Water**	–0.50	0.75	73.88	75.57	2.29
		0.25	0.50	80.69	82.64	2.41
		0.75	–0.50	82.97	78.15	5.81
	SGF	–0.50	0.75	71.74	76.36	6.43
		0.25	0.50	78.75	82.37	4.59
		0.75	–0.50	80.60	78.21	2.97
PGS	**Water**	–0.50	0.75	73.46	75.68	3.02
		0.25	0.50	78.96	80.26	1.64
		0.75	–0.50	78.93	82.61	4.66
	SGF	–0.50	0.75	70.87	68.21	3.76
		0.25	0.50	75.71	72.65	4.04
		0.75	–0.50	76.49	78.65	2.82
HPMC	**Water**	–0.50	0.75	71.15	68.15	4.22
		0.25	0.50	73.06	70.36	3.70
		0.75	–0.50	70.96	75.28	6.09
	SGF	–0.50	0.75	68.72	64.12	6.70
		0.25	0.50	70.86	66.29	6.44
		0.75	–0.50	70.42	72.67	3.20

*Na-CMC indicates sodium carboxymethyl cellulose; SGF, simulated gastric fluid; SSG, sodium starch glycolate; PGS, pregelatinized starch; and HPMC, hydroxypropylmethyl cellulose.

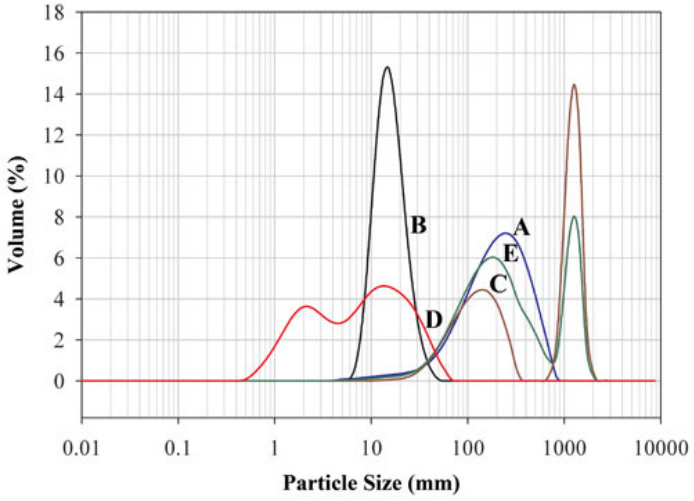

Figure 2. Particle size analyses: (A) Pure CBZ, (B) SD of CBZ with Na-CMC, (C) SD of CBZ with SSG, (D) SD of CBZ with PGS, and (E) SD of CBZ with HPMC. CBZ indicates carbamazepine; SD, solid dispersion; Na-CMC, sodium carboxymethyl cellulose; SSG, sodium starch glycolate; PGS, pregelatinized starch; and HPMC, hydroxypropylmethyl cellulose.

prepared. Table 6 shows the similarity factor values for all the batches of experimental design of Na-CMC, SSG, PGS, and HPMC polymers. For SDs of all the polymers, the value of S_d varied between 0.0033 and 0.0139, which is in the proximity of zero. This finding shows that there was no significant variation between dissolution of SDs in water and SGF without enzymes. In order to assess comparative extent

Table 6. Similarity Factor Calculated for All the Solid Dispersions Prepared*

Batches		Similarity Factor (S_d) for Systems			
		SDs With Na-CMC	SDs With SSG	SDs With PGS	SDs With HPMC
–1	–1	0.00	0.01	0.01	0.01
–1	0	0.01	0.01	0.01	0.01
–1	1	0.01	0.01	0.01	0.00
0	–1	0.01	0.01	0.01	0.01
0	0	0.01	0.01	0.01	0.01
0	1	0.00	0.01	0.01	0.01
1	–1	0.00	0.00	0.01	0.01
1	0	0.01	0.01	0.01	0.01
1	1	0.00	0.00	0.01	0.01

*S_d indicates similarity factor; SD, solid dispersion; Na-CMC, sodium carboxymethyl cellulose; SSG, sodium starch glycolate; PGS, pregelatinized starch; and HPMC, hydroxypropylmethyl cellulose.

Table 7. Mean Dissolution Time Calculated for All the Batches of Experimental Design for All Polymers*

Batches		Mean Dissolution Time (MDT)							
		CBZ: Na-CMC		SSG		PGS		HPMC	
		Water	SGF	Water	SGF	Water	SGF	Water	SGF
–1	–1	8.29	8.50	8.41	9.29	10.4	11.9	9.46	9.29
–1	0	7.79	9.46	7.92	10.2	9.62	12.2	9.35	9.22
–1	1	8.06	8.79	8.14	9.91	9.83	12.2	10.4	9.19
0	–1	8.49	9.70	7.98	10.7	9.32	12.3	8.71	8.75
0	0	8.03	9.03	7.07	8.76	7.80	10.5	8.53	8.69
0	1	7.78	8.20	6.54	7.85	7.75	9.51	8.36	8.32
1	–1	7.90	8.44	7.37	7.71	6.57	8.99	7.30	7.55
1	0	7.40	8.80	6.51	8.23	7.11	9.40	7.07	7.15
1	1	6.83	7.94	6.34	7.15	6.52	8.58	10.1	9.81

*Na-CMC indicates sodium carboxymethyl cellulose; SSG, sodium starch glycolate; PGS, pregelatinized starch; HPMC, hydroxypropylmethyl cellulose; and SGF, simulated gastric fluid.

of dissolution rate enhancement from its SDs, mean dissolution time (MDT) was calculated. The dissolution data obtained of pure CBZ and SDs of all polymers was treated according to Equation 5.[29]

$$\mathrm{MDT}_{\text{in vitro}} = \frac{\sum_{i=1}^{n} t_{mid}\,\Delta M}{\sum_{i=1}^{n} \Delta M} \qquad (5)$$

where i is dissolution sample number, n is number of dissolution sample times, t_{mid} is time at the midpoint between times t_i and t_{i-1}, and ΔM is the amount of CBZ dissolved (μg) between times t_i and t_{i-1}. The results for MDT calculated are shown in Table 7. The MDT of pure CBZ in water and SGF without enzymes is 13.55 and 14.07, respectively, which was decreased to 6.83 and 7.94 in the case of SD of drug with Na-CMC. This result depicts the fulfillment of the objective of dissolution enhancement of CBZ.

The amount of the percentage of drug dissolved in 30 minutes (Q_{30}) in distilled water and SGF without enzymes for all the SDs prepared according to experimental design is reported in Table 1. SDs of polymers Na-CMC, SSG, and PGS showed an increase in dissolution rate on increase in amount of polymer. Whereas in the case of HPMC solid dispersions, an increase in the amount of polymer up to a certain level, resulted in enhanced dissolution rate but further addition of polymer resulted in a decrease of dissolution rate, particularly in water. This finding may be correlated to matrix-forming ability of HPMC. SDs with Na-CMC did not show significant difference in dissolution profile carried in water and SGF without enzymes, whereas SD with SSG showed significant difference. In case of SD prepared with PGS, increase in amount of polymer showed significant variation between the dissolution profiles in water and SGF without enzymes. Similarity factor (S_d) was determined for all the experimental batches of SDs with Na-CMC, SSG, PGS, and HPMC. For comparison, the S_d values are shown in Table 6. Figure 3 shows comparative evaluation of dissolution enhancement efficiency of Na-CMC, SSG, PGS, and HPMC in water and SGF without enzymes.

The SEM images for pure drug and SDs of all polymers are shown in Figure 4. Pure drug image showed crystalline drug of irregular shapes and sizes ranging from 50 to 600 μm, whereas images of SD of drug with Na-CMC up to original magnification ×100 did not show any crystalline material. In the case of SDs with SSG, PGS, and HPMC, although a significant decrease in the size of drug crystals was observed, agglomeration of crystals was also observed.

Figure 5 shows the thermograms for pure CBZ, SDs of CBZ with Na-CMC, SSG, PGS, and HPMC. Pure CBZ showed a sharp melting endotherm at 194.43°C. A small endothermic peak at 170.86 was also observed, which can be attributed to the presence of a small amount of polymorphic form of carbamazepine. All thermograms except for SD with PGS showed decrease in the energy change of melting endotherm, which confirms a considerable extent of reduction in crystallinity of drug. In case of thermogram for SD of CBZ with PGS, the melting endotherm for crystalline CBZ disappeared, which ascertains complete amorphization of CBZ.

The time required for rising water through capillary action to wet the methylene blue powder was found to be in the range of 3 to 5 minutes for all the solid dispersions, which was significantly less when compared with 10 to 15 minutes for pure drug. For more accuracy in distinguishing wettability, contact angle measurement is advised.

For all the SDs, prepared angle of repose was determined. It was found to be in the range of 29° to 35°. This illustrates the free flowability of SDs and their ability to be used for formulation into solid dosage forms.

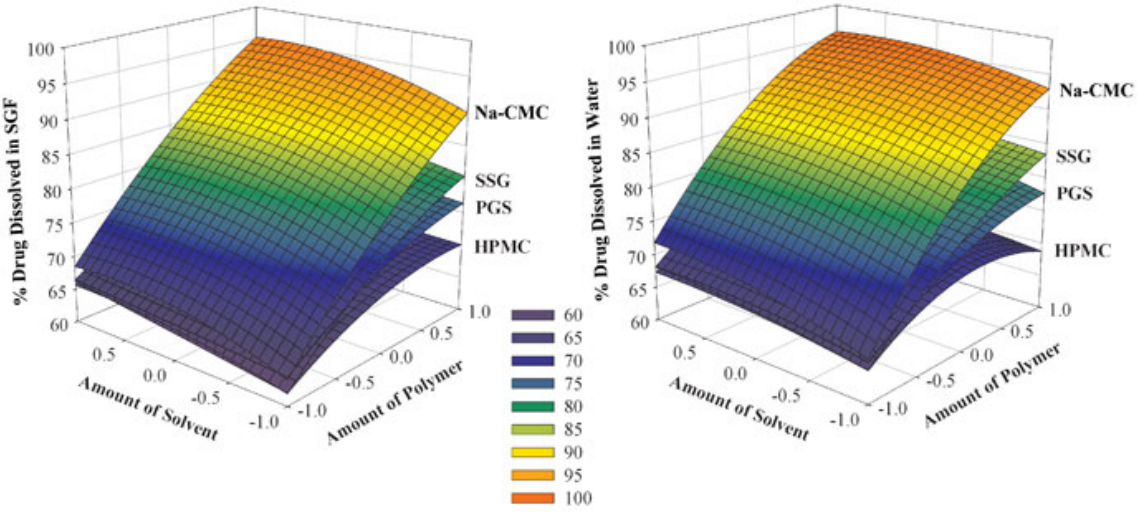

Figure 3. Plot showing comparative evaluation of percentage drug dissolved of solid dispersions of sodium carboxymethyl cellulose (Na-CMC), sodium starch glycolate (SSG), pregelatinized starch (PGS), and hydroxypropylmethyl cellulose (HPMC) with carbamazepine in distilled water and simulated gastric fluid (SGF).

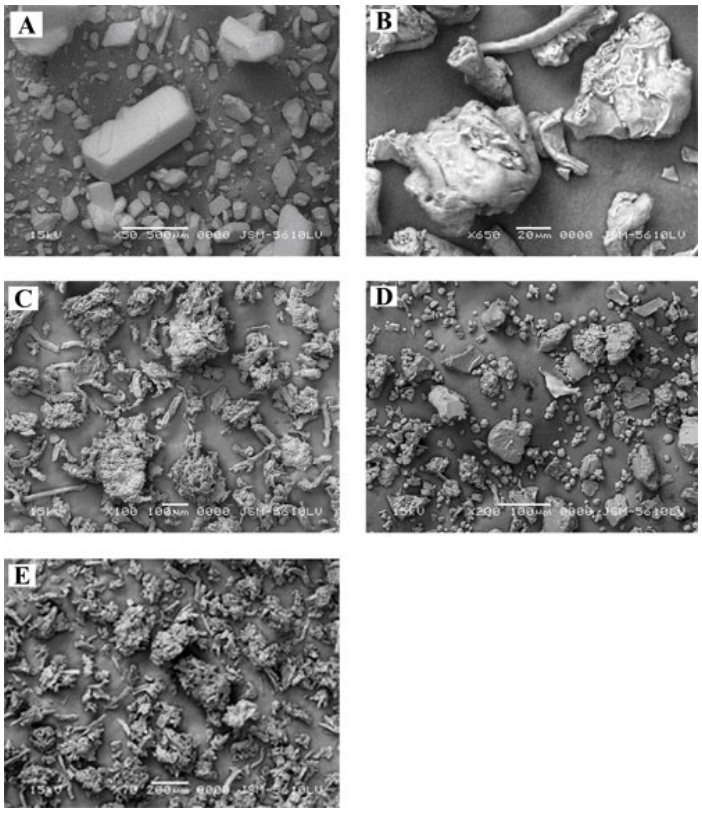

Figure 4. Scanning electron microscope image of (A) Pure crystalline carbamazepine (CBZ), (B) CBZ: sodium carboxymethyl cellulose solid dispersion (SD), (C) CBZ: sodium starch glycolate SD, (D) CBZ: pregelatinized starch SD, (E) CBZ: hydroxypropylmethyl cellulose SD system.

Hydrophilic polymer drug solid dispersions increase drug dissolution because of the following possible reasons:

- usually in solid dispersions, the drug is partially dissolved in melted or dissolved polymer. After drying of these solid dispersions, the drug will not nucleate to form firm crystals resulting in formation of microcrystals. Drug microcrystals are embedded in the water-soluble matrix, where hydrophilic polymers present the ability of rapid wetting and thereby dissolution of drug.[30] Generally PEGs and PVP solid dispersions follow this principle.
- for solid dispersions of SSG, higher dissolution rates observed when compared with other excipients may

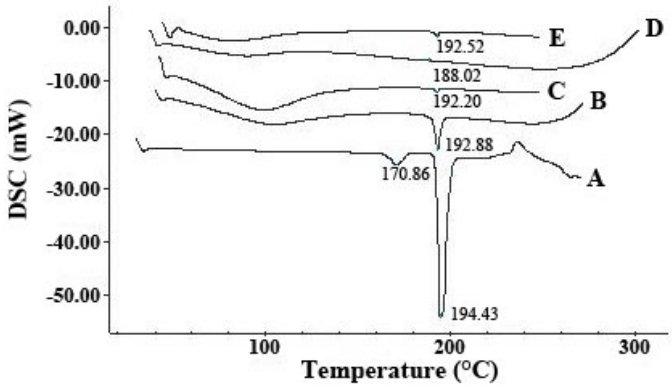

Figure 5. Differential scanning calorimetry thermograms of (A) Pure crystalline carbamazepine (CBZ), (B) CBZ: hydroxypropylmethyl cellulose solid dispersion (SD), (C) CBZ: sodium starch glycolate SD, (D) CBZ: pregelatinized starch, and (E) CBZ: sodium carboxymethyl cellulose SD system. mW indicates molecular weight.

be owing to their easy and rapid dispersibility in the aqueous dissolution fluids.[31]

- solid dispersions of hydrophilic swellable polymers such as CMC and HPMC become gelatinized in the dissolution medium. This gelatinized solid dispersion is constantly crushed by the attrition during stirring, and these finely gelatinized SDs diffuse to bulk solution through the diffusion layer.[32] Being water retentive, gelatinized dispersions also increase wetting of the drug, which attributes to increase in dissolution. However, the gelatinized dispersion formed should not be a barrier for the drug diffusion owing to its viscosity. In the present work, HPMC showed less drug dissolution compared with Na-CMC, which may be owing to the formation of highly viscous barrier layer at the interface of drug and dissolution medium.

CONCLUSION

MLR analysis of results of experimental design illustrated that SD of carbamazepine when prepared with hydrophilic swellable polymers showed marked increase in percentage drug dissolution in water and SGF without enzymes, which was illustrated with the help of mean dissolution time and similarity factor. SDs prepared with Na-CMC showed the highest drug dissolution compared with HPMC, PGS, and SSG owing to its optimum wetting properties by gelatinization and control over particle size of drug. Na-CMC is a popular excipient of tablets and its SD showed good free flowing properties, which may not need extra excipients for compression or filling in hard gelatin capsules.

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