ORIGINAL ARTICLE

Enhancing Perphenazine Dissolution Profile through Innovative Solid Dispersion Techniques: A Comprehensive Study

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Abstract

Objective: Using the hydrophilic polymer polyethylene glycol 6000 (PEG 6000) and chitosan, the solid dispersion (SD) technique is used to increase the solubility and dissolution of perphenazine. **Materials and Methods:** SDs of perphenazine were prepared with polymers PEG 6000 and chitosan, using different methods of preparation: (1) Solvent evaporation and (2) dropping technique method along with different drug: carrier ratios. Performance of the prepared formulations was evaluated for solubility, Fourier transform infrared (FTIR) spectroscopy. **Results:** Perphenazine's solubility was improved in all SDs. Both solubility and carrier concentration were positively correlated. When prepared using the dropping method, the concentration of the perphenazine- SD PPD2 1:2 demonstrated improved water solubility. **Conclusion:** According to the investigations, PEG 6000 and chitosan later form an amorphous state in SD, which FTIR confirms. The SD containing perphenazine (dropping method) demonstrated high solubility and drug release.

Key words: Bioavailability, chitosan, polyethylene glycol 6000, perphenazine, solid dispersion

INTRODUCTION

Atypical antipsychotic medication is perphenazine. Chemically speaking, it belongs to the piperazinyl phenothiazine class. It was initially provided as Trilafon in the United States and has been utilized in therapeutic settings for decades.[1] Perphenazine is regarded as a medium-potency antipsychotic due to its about ten times more efficacy of the dopamine-2 receptor than chlorpromazine.[2] Perphenazine is typically used twice or thrice daily in divided doses. Its oral bioavailability is around 40% and a half-life of 8–12 h that may extend up to 20 h.[3] To increase hypnotic influence throughout at night and less at daytime sedation and lower blood pressure without losing therapeutic action, 1/3 during breakfast and 2/3 of the daily dose at bedtime can be administered.[4]

It is used in small doses to treat increased depression in conjunction with an anti-depressant. There are predetermined combinations of perphenazine with the tri-cyclic anti-depressant amitriptyline of various dose ratios.[5] As soon as the clinical circumstances allow, perphenazine is stopped being used to treat depression. There is no intrinsic antidepressive action of phenazine. Even though fluoxetine interacts with perphenazine's metabolism and leads to higher plasma concentration and a long half-life, studies demonstrate the combination of perphenazine and fluoxetine (prozac) in patients with neurotic depression is most promising.[6] Together, the early agitation caused by fluoxetine and the powerful antiemetic effects of perphenazine minimize the emesis it causes.[7] Either option might be advantageous for many patients.

MATERIALS AND METHODS

Materials

Perphenazine was procured from Rimore Healthcare, Pune. Polymers PEG-4000 and PVPK-30 and all chemicals required are of analytical research grade in use.

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Methods

Ultraviolet (UV) spectroscopic study

Construction of standard curve for perphenazine

The band-aid is kept in an alloyed silica cuvette 10 mm. The UV-visible (UV-vis) spectrum will be carried in the ambit of 200–400 nm on a UV-vis spectrophotometer at 1 cm aperture width.[8]

Standard calibration curve of perphenazine

Determination of absorption maxima

A combination including 10 µg/mL of perphenazine in pH 6.8 phosphate buffer is subjected to a UV-vis spectrum using a double-beam UV-vis spectrophotometer. The solution is scanned between 200 and 400 nm. Contents of calibration are given in Table 2.[9]

Calibration curves of perphenazine in phosphate buffer 6.8 at λ max 257 nm

Accurately measured in a 10-mL volumetric flask, 10 mg of perphenazine (Trilafon) was dissolved in 1 mL of ethanol to create a stock with a concentration of 100 g/mL. A phosphate buffer solution with a pH of 6.8 was then added to the remaining volume. Standard volumetric flasks (10 mL) were used to dilute the standard solution with a pH 6.8 phosphate buffer solution to generate various dilutions (0, 5, 10, 15, 20, 25 g/mL).[10] 200–400 nm was the wavelength range used to scan the dilution. Between 0 and 25 g/mL, a linear correlation was seen. Absorbance was measured at 257 nm using a blank of phosphate buffer with a pH of 6.8. Plotting the absorbance versus the drug concentration produced a calibration graph. The Plotted Graph of calibration is shown in Figure 2.[11]

Fourier transform infrared (FTIR)-spectroscopy

Using the "Alpha Bruker" FTIR spectrophotometer and the FTIR spectroscopy approach, the drug moiety was identified. The drug moiety was positioned between 4000 and 400 cm^{-1} for the attenuated total reflectance scan at transmission.[12] Thus, the wave numbers of peaks in the FTIR spectra of the drug moiety as obtained are compared with the theoretical values of the wave numbers related to the structure and functional group of pharmaceuticals.[13]

Formulation of perphenazine solid dispersion (SD) using solvent evaporation technique

In this technique, perphenazine together with polyethylene glycol 6000 (PEG 6000) and chitosan, respectively, was prepared at distinct ratios 1:1, 1:2, and 1:3. Weigh accurately 16 mg of perphenazine mixed with 16, 32, and 48 mg of PEG 6000 and chitosan were dissolved and mixed in methanol with continuous stirring.[14] SD is prepared by evaporating the solution under low pressure. Then, an accurately weighed 10 mg solvent evaporated of perphenazine was taken to carry out the dissolution test.[15,16]

Formulation of SD by dropping technique

Perphenazine, PEG 6000, and chitosan are produced individually using the dropping method in three distinct ratios: 1:1, 1:2, and 1:3. 16 mg of perphenazine were precisely weighed, along with 16, 32, and 48 mg of PEG 6000 and chitosan.[17] Pipette-out solid particles of melted perphenazine and carrier were subjected to drop onto a plate as they crystallized to circular or spherical shapes. The dissolving medium's surface was then sprinkled with 10 mg of precisely weighed perphenazine drops.[18] Data are shown in Table 1. In addition, dissolving studies were performed.

SD investigations using micromeritics

The following particle properties were analyzed: Hausner's Ratio, Carr's index for compressibility, bulk density and

Table 1: Perphenazine solid-dispersion

Formulation-code	Drug : Carrier ratio	Drug content (milligram)	Carrier content (milligram)	Method of preparation
PCS 1	Perphenazine: chitosan (1:1)	16	16	Solvent evaporation method
PCS 2	Perphenazine: chitosan (1:2)	16	32	Solvent evaporation method
PCS 3	Perphenazine: chitosan (1:3)	16	48	Solvent evaporation method
PPS1	Perphenazine: PEG 6000 (1:1)	16	16	Solvent evaporation method
PPS 2	Perphenazine: PEG 6000 (1:2)	16	32	Solvent evaporation method
PPS 3	Perphenazine: PEG 6000 (1:3)	16	48	Solvent evaporation method
PCD1	Perphenazine: Chitosan (1:1)	16	16	Dropping method
PCD 2	Perphenazine: Chitosan (1:2)	16	32	Dropping method
PCD 3	Perphenazine: Chitosan (1:3)	16	48	Dropping method
PPD 1	Perphenazine: PEG 6000 (1:1)	16	16	Dropping method
PPD2	Perphenazine: PEG 6000 (1:2)	16	32	Dropping method
PPD 3	Perphenazine: PEG 6000 (1:3)	16	48	Dropping method

PEG 6000: Polyethylene glycol 6000

tapped density, flow property, angle of repose, and percentage yield (i.e., % recovery) of SD produced.[19]

Studies on solubility

In distilled water, the solubility of SD was tested. The samples were transferred to a flask, and added distilled water. Place it on a mechanical shaker. The SD samples are subjected to assay using a double-beam UV-vis photometer.[20,21]

Drug content

The complete formulation of the created SDs, or roughly 16 mg of perphenazine, is carefully weighed and dissolved in 100 mL of pH 6.8 phosphate buffer in a different volumetric flask. The mixture is filtered and then appropriately diluted with the same solvent.[22] Pharmaceuticals have been detected at 257 nm using a UV-photometer.[23]

RESULTS AND DISCUSSION

Perphenazine calibration curve in a pH 6.8 phosphate buffer

A UV spectrophotometer was used to get the UV-vis spectrum of pure perphenazine, and it was found that the absorption maxima was 257 nm. Figure 1 plotting of the perphenazine calibration curve data is done.

FTIR compatibility studies for drugs and polymers

The peak spectra of the physical combination [Figure 3] were compared to the original FTIR spectra. The fact that identical peaks were seen suggests that the drug and the polymers PEG 6000 [Figure 5] and chitosan [Figure 4] did not interact molecularly.

MICROMERITICSTUDIES OF PERPHENAZINE SD

Angle of repose values ranged from 15.80 to 23.42, and compressibility index (%) results ranged from 9.13 to 14.4, respectively. The results of bulk and tapped densities are in the range of 0.44 ± 0.20–0.59 ± 0.97 and 0.48 ± 0.18–0.69 ± 0.56, respectively. Hausner found that these ratios were related to inter-particulate friction and could be utilized for the prediction of powder flow properties. In general, a lesser value than 1.25 indicates better flow properties, which is equivalent to 20% value of Carr's index,as given in Table 3.

With formulated SD, the yield percentage was found to be good. The maximum yield for the batch (PPD 2) is 96.46%. The total yield for the remaining batches is >82.86%. When

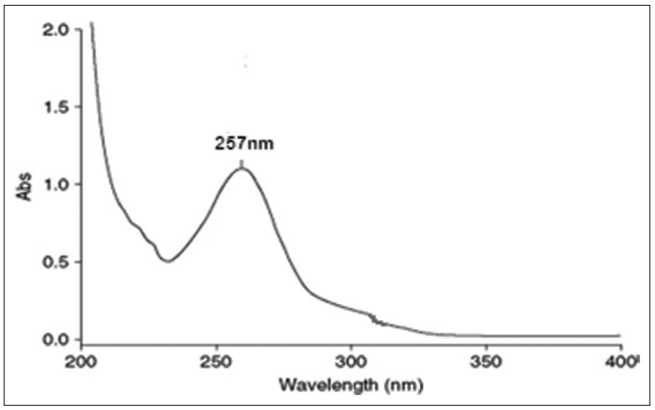

Figure 1: Calibration curve of perphenazine in phosphate buffer (pH 6.8)

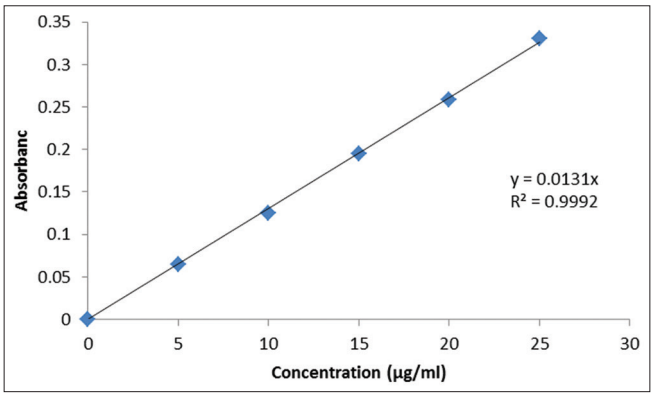

Figure 2: Calibration curve of perphenazine (trilafon)

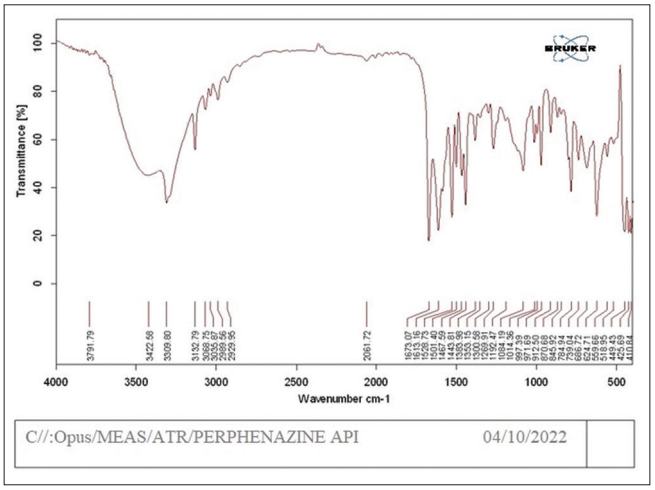

Figure 3: Infrared spectra of perphenazine (Trilafon)

compared to a pure medication, the formulated SD exhibits poor flow characteristics.

Study on solubility of perphenazine SD

Pure drug had poor solubility was the solubility study result. Comparing the solubility to the addition of other excipients, solid dispersion greatly improves the solubility of drug moiety with PEG 6000. During SD cooling, PEG 6000

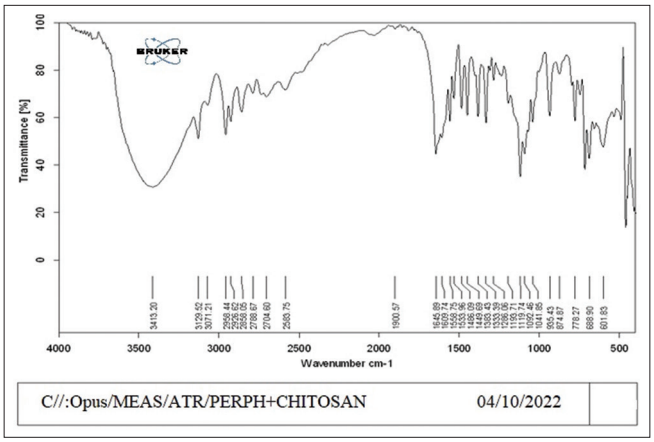

Figure 4: Infrared spectra of perphenazine with chitosan

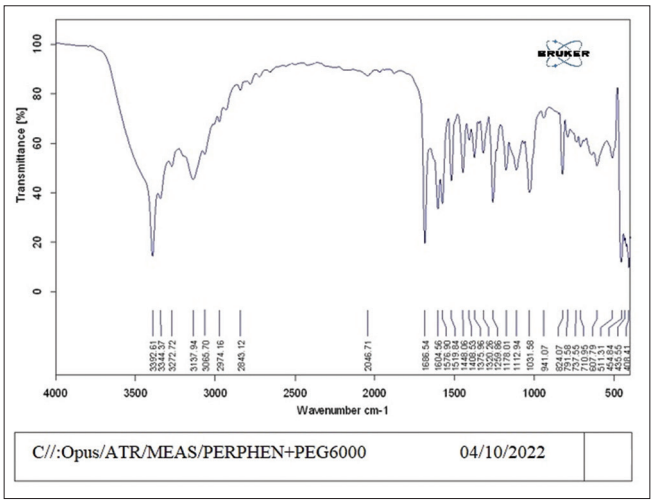

Figure 5: Infrared spectra of perphenazine with polyethylene glycol 6000

avoids re-crystallization, hence increasing the solubility of the drug by PEG 6000. Solubility increases as the PEG 6000 concentration increases; in the PPD2 formulation, the maximum solubility observed as in Table 4.

Drug content

A UV spectrophotometer was used to assess each formulation batch's percentage medication content. Calculations are made based on the percent drugs present in the absorbance. All formulations' percentage drug content ranged from 92.29% to 99.85%, in Table 5 which is within pharmacopoeial bounds.

In vitro drug release study of pure perphenazine

The drug release pattern is given in Table 6, and the graph is plotted for the same in Figure 6.

In vitro release of perphenazine SD

Table 7 shows the *in vitro* percentage of medication released from the perphenazine SD of batches PPD 1, PPD 2, and

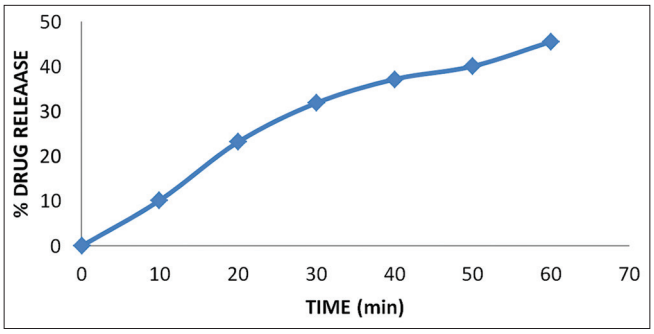

Figure 6: *In vitro* drug release of pure perphenazine

Table 2: Calibrationdata of perphenazine (trilafon) (phosphate buffer at pH 6.8)

S. No.	Concentrations (µg/mL)	Absorbances
1	0	0
2	5	0.065
3	10	0.125
4	15	0.195
5	20	0.259
6	25	0.331

PPD 3. Figure 7 plots the three batches' percentage medication release.

Optimization of perphenazine SD by using experimental design

Perphenazine SD preparations were assessed in accordance with the options chosen for the study's design. The statistical tool known as an analysis of variance (ANOVA) is used to estimate processes like variance. It is applied to the analysis of mean differences. This kind of testing involves a statistical hypothesis. The outcome was determined using the null hypothesis. $P = 0.05$ was used to define the null hypothesis' significance value. It denotes variation across all variables without an impact on the outcomes. Different method parameters were utilized for the response surface plots and the graph plots that the ANOVA examined. The three response variables, i.e., solubility, drug content, and *in vitro* drug releases, are statistically evaluated, which are produced in Table 8.

ANOVA for SD solubility study

The model's importance is underscored by its F-value of 10.15, signifying a mere 1.74% likelihood of noise accounting for an F-value of this magnitude. Model terms achieve significance when the *P*-value falls below 0.0500, yet, as evidenced by Table 8, no pivotal model terms are identified in this instance. A value exceeding 0.1000 renders model terms nonsignificant. To streamline your model, consider model reduction, particularly if it contains superfluous terms that are not essential for scale maintenance. The significance of lack

Table 3: Micromeritics properties of solid dispersion of perphenazine formulation

Parameters	Bulk-density (g/cm³)±S.D	Tapped-density (g/cm³)±S.D	Compressibility index (%)	Hauser's ratio	Angle of repose	% yield
Formulation codes						
PCS 1	0.46±0.18	0.48±0.18	12.1	1.12	16.80	86.17
PCS 2	0.48±0.24	0.52±0.22	14.4	1.12	17.70	82.86
PCS 3	0.52±0.15	0.51±0.56	9.41	1.13	22.56	94.78
PPS 1	0.59±0.97	0.59±0.33	11.42	1.13	21.67	96.37
PPS 2	0.50±0.57	0.60±0.32	9.31	1.14	23.05	92.88
PPS 3	0.54±0.34	0.50±0.28	11.48	1.13	23.30	95.28
PCD 1	0.59±0.95	0.69±0.56	11.03	1.13	21.09	88.66
PCD 2	0.52±0.52	0.67±0.31	10.11	1.11	22.45	92.24
PCD 3	0.54±0.18	0.67±0.49	11.34	1.12	23.42	91.88
PPD 1	0.57±0.11	0.63±0.41	11.29	1.11	22.99	88.99
PPD 2	0.44±0.20	0.48±0.19	12.1	1.12	15.80	96.46
PPD 3	0.54±0.47	0.66±0.19	9.13	1.10	22.78	92.94

Table 4: Solid-dispersions solubility investigations

S. No.	Formulation codes	Solubility (µg/mL)
1	PCS 1	16.76
2	PCS 2	13.56
3	PCS 3	17.16
4	PPS 1	15.76
5	PPS 2	34.82
6	PPS 3	18.16
7	PCD 1	16.88
8	PCD 2	43.82
9	PCD 3	18.21
10	PPD 1	18.76
11	PPD 2	44.82
12	PPD 3	24.82

Table 5: Drug content estimation

S. No.	Formulation codes	% drug content
1	PCS 1	98.24
2	PCS 2	97.45
3	PCS 3	98.62
4	PPS 1	94.13
5	PPS 2	95.21
6	PPS 3	98.34
7	PCD 1	96.19
8	PCD 2	92.29
9	PCD 3	95.56
10	PPD 1	97.47
11	PPD 2	99.85
12	PPD 3	93.72

Table 6: *In vitro* release of pure perphenazine

S. No.	Time in (min)	% drug release
1	0	0
2	10	10.2±0.74
3	20	28.2±0.74
4	30	31.9±0.07
5	40	37.2±0.57
6	50	39.1±0.43
7	60	45.6±0.36

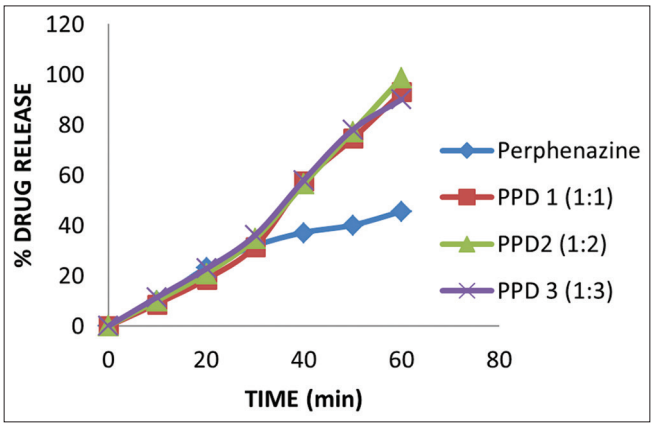

Figure 7: Perphenazine solid dispersion *in vitro* drug release

of fit is highlighted by its F-value of 993.02, with only 0.10% of cases attributing a significant lack of fit F-value to noise.

Contour plot and 3D surface plot

The contour plot for solubility study of SD Figure 8 and 3D surface plot for solubility study of SD Figure 9 are plotted for the given data.

Table 7: *In vitro* release of perphenazine solid dispersion

Time (min)	% Drug release			
	Perphenazine	PPD 1	PPD 2	PPD 3
0	0	0	0	0
10	10.2±0.74	8.9±1.2	10.2±1.02	11.5±1.07
20	28.2±0.74	18.6±1.23	20.8±1.04	22.7±1.12
30	31.9±0.07	31.6±1.03	34.7±1.65	36.8±1.09
40	37.2±0.57	57.4±1.01	56.5±1.22	58.2±1.43
50	39.1±0.43	74.5±1.03	77.4±1.23	78.5±1.09
60	45.6±0.36	92.9±1.06	98.7±1.35	90.1±1.29

Table 8: ANOVA of solubility study of solid dispersion

Source	Sum of squares	df	Mean square	F-value	*P*-value	
Model	45.09	2	22.55	10.15	0.0174	significant
A-chitosan	9.10	1	9.10	4.10	0.0988	
B-PEG 6000	5.10	1	5.10	2.30	0.1900	
Residual	11.10	5	2.22			
Lack of fit	11.10	3	3.70	993.02	0.0010	significant
Pure error	0.0074	2	0.0037			
Cor total	56.20	7				

ANOVA: Analysis of variance

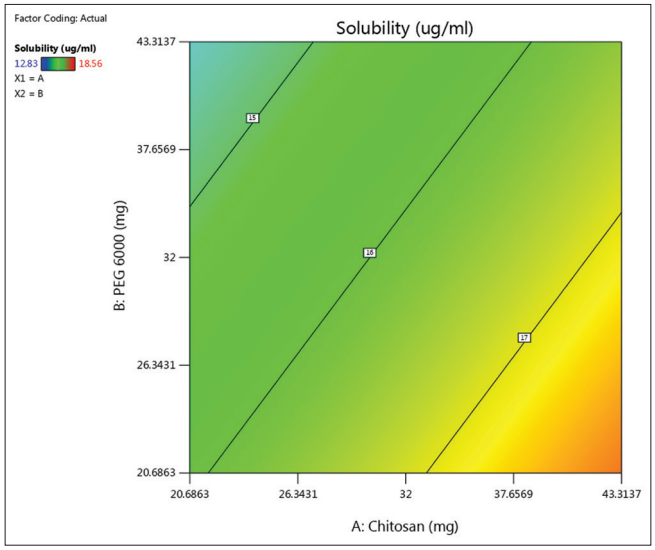

Figure 8: Contour plot for solubility study of solid dispersion

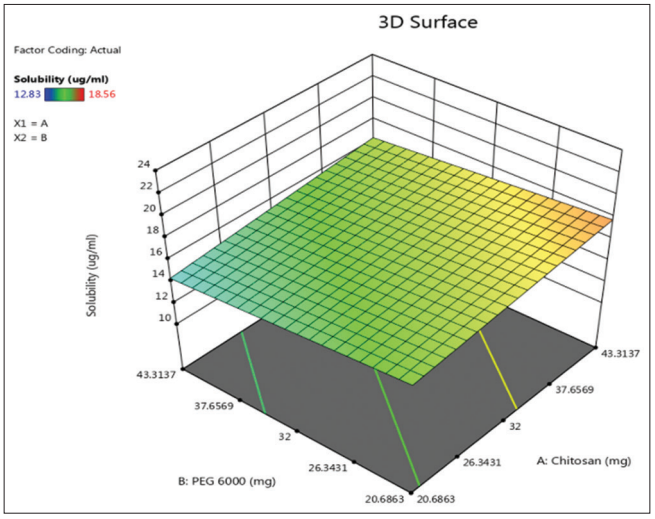

Figure 9: 3D surface plot for solubility study of solid dispersion

ANOVA of drug content

The model demonstrates significance, which is evident in its F-value of 8.89, according to Table 9 ANOVA of drug content. A value of this magnitude is attributable to noise only 2.26% of the time. Model terms achieve significance when the *P*-value falls below 0.0500. The lack of fit is underscored by its F-value of 154.08, with noise accounting for significance in lack of fit F-value merely 0.65% of the time.

Contour plot and 3D surface plot

Contour plot for drug content Figure 10 3D surface plot for drug content Figure 11 are plotted for the given data.

ANOVA of *in vitro* drug release study

The model's F-value of 9.46 indicates that it is significant, as indicated in Table 10 ANOVA of *in vitro* drug release study,

Table 9: ANOVA of drug content

Source	Sum of squares	df	Mean square	F-value	*P*-value	Significance
Model	25.96	2	12.98	8.89	0.0226	Significant
A-chitosan	2.30	1	2.30	1.58	0.2646	
B-PEG 6000	6.11	1	6.11	4.19	0.0961	
Residual	7.30	5	1.46			
Lack of fit	7.27	3	2.42	154.08	0.0065	Significant
Pure error	0.0314	2	0.0157			
Cor total	33.26	7				

ANOVA: Analysis of variance

Table 10: ANOVA of *in vitro* drug release study

Source	Sum of squares	df	Mean square	F-value	*P*-value	Significance
Model	4.75	2	2.37	9.46	0.0200	Significant
a-chitosan	0.0668	1	0.0668	0.2662	0.6279	
B-PEG 6000	1.92	1	1.92	7.67	0.0394	
Residual	1.25	5	0.2508			
Lack of fit	1.23	3	0.4096	32.77	0.0298	Significant
Pure error	0.0250	2	0.0125			
Cor total	6.00	7				

PEG 6000: Polyethylene glycol 6000, ANOVA: Analysis of variance

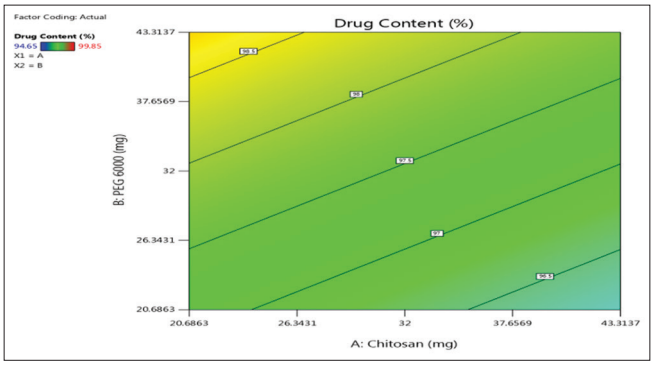

Figure 10: Contour plot for drug content

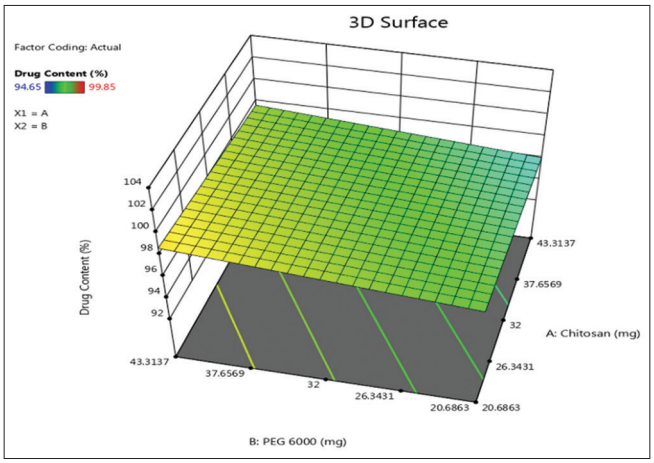

Figure 11: 3D surface plot for drug content

with a mere 2.00% probability of noise causing an F-value of this magnitude. Model terms attain significance when the *P*-value is below 0.0500, and notably, B emerges as a crucial model term in this scenario. Model terms lack significance if the value exceeds 0.1000. The implied significance of lack of fit is conveyed by its F-value of 32.77, with noise accounting for a significant lack of fit F-value in only 2.98% of cases.

Contour plot and 3D surface plot

The contour plot for *in vitro* drug release study Figure 12 and 3D surface plot for *in vitro* drug release study Figure 13 are plotted as per the data.

The RS plot and contour plot illustrate the simultaneous impact of factor B (PEG 6000) and factor A (chitosan) on lag time. Low concentrations of chitosan and large concentrations of PEG 6000 were used to get the required results. PEG 6000 had a noticeable impact even at low chitosan concentrations.

Stability study

According to ICHQ1AR, stability studies on a few formulations were conducted for 0, 3, and 6 months as per Table 11 "Stability testing of new drug substances and products", 40°C/75° RH testing routine: Samples underwent evaluations after 0, 3, and 6 months. Various studies on the formulation's stability demonstrate that there is little variation

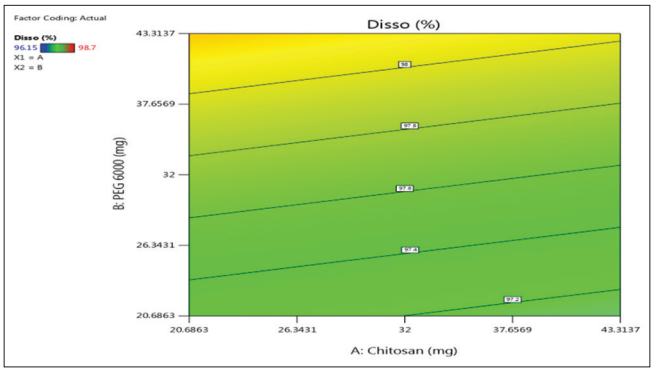

Figure 12: Contour plot for *in vitro* drug release study

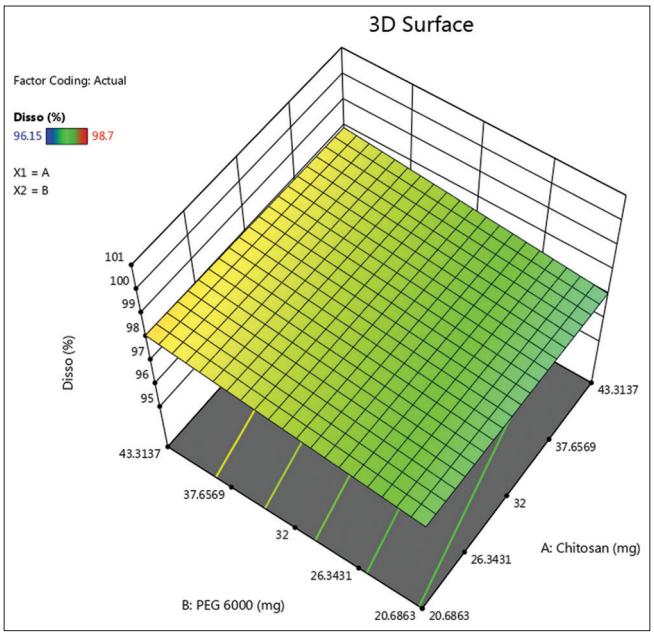

Figure 13: 3D surface plot for *in vitro* drug release study

Table 11: Stability study

Formulation	0 months	3 months	6 months
PPD 1	97.6	97.5	97.3
PPD 2	99.85	99.80	99. 86
PPD 3	99.7	99.6	99.01

in the drug content parameter that was used. The formulation that was created is stable, according to the results. Therefore, by employing these excipients in the correct ratios, we can synthesize the medicine in a variety of dosage forms. The chosen technique, the dropping method, was ideal for creating a SD of perphenazine.

CONCLUSION

Two distinct carriers, such as PEG 6000 and chitosan, were used in the *in vitro* dispersion experiments of pure drug treatment and all three SD formulations with varying ratios of 1:1, 1:2, and 1:3. A dissolution device with 900 mL of 0.1N HCL solution, or USP Type-II, was used as the dissolving medium for the dissolution experiments, which used created solid perphenazine dispersions corresponding to 100 mg of pure medicine. A constant temperature of 37.5 ± 2°C was maintained. Several time intervals, including 0, 10, 20, 30, 40, 50, and 60 min, were used to collect the samples. Additionally, absorbance at 257 nm was detected. The SD comprising pure medication released at a maximum of 98.7% W/V based on these *in vitro* investigations. The SD containing perphenazine (dropping method) demonstrated high release, it was concluded. The research established SD technique as one of the fast-releasing dosage forms for perphenazine, which is weakly water soluble.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

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