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Original Article

FORMULATION AND OPTIMIZATION OF CURCUMIN SOLID DISPERSION PELLETS FOR IMPROVED SOLUBILITY

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ABSTRACT

Objective: The present study was aimed at designing of solid dispersion based pellets of curcumin (Cu) for improving its solubility.

Methods: Solid dispersion (SD) of Cu was prepared by the melt method using Poloxamer 407 (Pol 407) at a different weight ratio of Cu-Pol 407 (1:2, 1:3, 1:5, 1:7, 1:10). The solid dispersion was characterised by FTIR, SEM, DSC, XRD and evaluated for saturation solubility in water, drug content and *in vitro* dissolution. The pellets of Cu solid dispersion were prepared by extrusion spheronization technique and optimization was performed by 3^2full factorial design. The pellets were evaluated for size distribution, flow properties, hardness, disintegration and *in vitro* drug dissolution.

Results: From the phase solubility analysis, Pol 407 was selected as a Solid dispersion carrier. The formation of Cu-SD by melt method using Pol 407, was confirmed from FTIR and DSC studies. XRD studies indicated a change of Cu from crystalline to amorphous form. There was a significant increase of Cu when formulated as SD compared to plain Cu. The optimization of extrusion spheronization process revealed the significant effect of Cu-Pol 407 ratio ($p<0.0001$) on *in vitro* dissolution of pellets. Higher Cu dissolution was obtained with Cu-SD pellets compared to plain Cu pellets.

Conclusion: The present study demonstrated the potential of Cu-SD pellets in improving the solubility of poorly soluble Cu.

Keywords: Curcumin, Poloxamer, Solid dispersion, Pluronic, Factorial design

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INTRODUCTION

Curcumin (Cu) is a phenolic phytoconstituent from the curcuminoid group and is obtained from curcuma Longa (family, zingiberaceae), traditionally known as turmeric. It is widely used in Indian and Chinese traditional medicine [1] and also has been extensively studied for its anti-inflammatory [2], anticancer [3], antioxidants [4], antibacterial and wound healing activity [5]. The efficacy of Cu in hepatoprotection [1], inflammatory bowel disease [4] and lifestyle associated diseases is also reported. The clinical potential of Cu is limited owing to its low aqueous solubility and poor permeation resulting in lower bioavailability and extensive metabolism. As a result, Cu is classified into the BCS Class IV compound and its therapeutic potential is limited due to its instability in physiological conditions[6]. Various formulation approaches have been extensively utilized to address the problems of solubility and permeability of Cu, out of which, improving solubility and dissolution of Cu has been a major area of interest. Solid dispersion (SD) of Cu using various water-soluble polymers, polyvinylpyrrolidone (PVP) [7], D α-tocopheryl polyethylene glycol 1000 succinate [8], chremophore and polyethylene glycol (PEG), Eudragit E100 [9], carboxymethyl cellulose acetate butyrate [10], hydroxypropyl methylcellulose (HPMC) [11], and hydroxypropyl methylcellulose acetate succinate [12] and polyethylene glycol-15-hydroxy stearate (Solutol HS 15) [13] are reported.

However, the efficiency of Cu to form a stable complex with polymer is questionable and a large amount of polymers are needed to obtain a desirable effect. With the availability of self-emulsifying and surface-active carrier with low melting point, the major focus is now shifted to SD formulation using these carriers. One of the interesting strategy is the combination of nanotechnology and SD [14]. Nanomicellization is achieved with the help of amphiphilic carrier that can solubilize the drug in its hydrophobic core and also helps in improving the drug stability and solubility. Parika *et al.* [15] Reported self nanomicellizing SD of Cu using soluplus as the carrier. However, the use of a high amount of polymer in the self-nanomicellizing SD may pose a problem in handling and dispensing of this formulation. As pellets allow great design flexibility, ease of handling, can be easily packed in capsules, free-flowing and therefore commercially preferable, the pellet formulation of solid dispersion can address this problem.

In the present study, we have explored the potential of poloxamer 407 (Pol 407) as a carrier for the solid dispersion (SD) of the Cu. The solid dispersion of Cu was loaded on the pellet formulation and optimization was performed using design of experiment (DOE). The solid-state characterization of SD was done using FTIR, DSC, XRD AND SEM and the self micellizing properties were confirmed by particle size and zeta potential measurement. Pellet formulation was optimized on the basis of size distribution and *in vitro* dissolution.

MATERIALS AND METHODS

Materials

Curcumin (Phyto Life Science Pvt Ltd Gujrat, India) was received as a gift sample. Hydroxypropyl-β-cyclodextrin (HPβCD), PVP K30, PEG 6000, microcrystalline cellulose, lactose, and crosscarmellose Sodium were purchased from Himedia, Mumbai, India. Poloxamer 407 (Pol 407) (Kolliphor P 407, BASF Mumbai) and Poloxamer 188 (Pol 188) (Kolliphor P 188, BASF Mumbai) were received as gift sample. All the solvents of analytical grade were used in the study.

Methods

Phase solubility analysis

A series of solutions (5, 10, 15, 20, 25, 30 mmol) of different carriers, HPβCD, Pol 188, Pol 407, PVP K30, and PEG 6000 were prepared in 0.1 N HCL. An excess amount of Cu was added to each carrier solution and the dispersion was kept to achieve equilibrium at 25 °C for 72 h with shaking at 100 rpm in an orbital shaker (Remi, CIS24b2, India). The dispersions were filtered through 0.45 µ membrane filter, suitably diluted with 0.1 N HCL and the drug concentration in solution was analyzed at 429 nm by UV spectrophotometry (Shimadzu, UV 1700, Japan). The experiment was performed in triplicate [16, 17].

Preparation of solid dispersion by melt method

Solid dispersions of Cu were prepared with different weight ratio, 1:2, 1:3, 1:5, 1:7 and 1:10 of Cu-Pol 407. The carrier was melted at 55 °C, and then the Cu was dispersed to molten carrier with constant

stirring followed by quick cooling. The obtained dried mass was then passed through sieve # 85 and stored in a refrigerator at 4 °C until further use [18, 19].

Characterization of Cu-SD

Solid state characterization of Cu-SD and plain Cu were characterized by FTIR, DSC and XRD. The morphological characterization was done using SEM.

Scanning electron microscopy

The surface morphology of Cu-SD formulation was studied using field emission scanning electron microscopy (FESEM) (FEI, Nova Nano SEM 450, USA). The samples were coated with platinum layer of 20 nm to make them electrically conductive and the coated samples were then randomly scanned in the FESEM chamber at an acceleration voltage of 5.00 KV. The photomicrographs were obtained at different magnifications [16].

FT-IR study

IR absorption spectra of Cu, its physical mixture with excipients and SD formulation were recorded by potassium bromide dispersion technique in which dry samples and potassium bromide were placed in the sample holder and infrared spectrum was recorded using FTIR Spectrophotometer (Shimadzu, 8400S, Japan) over a range of 400-4000 cm^{-1}[20].

Differential scanning calorimetry study

In order to study the physical state of Cu and Pol 407, DSC (PerkinElmer, DSC 4000, USA) study was conducted for Cu, Pol 407 and Cu-SD. Accurately, 1 mg sample was weighed and placed in a sealed aluminum pan, and the sample was heated under nitrogen flow (20 ml/min) at a scanning rate of 10 °C per min from 30 to 350 °C. An empty aluminum pan was used as reference [10].

X-ray diffraction study

X-ray diffraction (Rigaku, Miniflex 600, Japan) was performed using Cu K 2α rays with a voltage of 40 kV and a current of 15 mA. Samples were scanned for 2θ from 20 ° to 80 °. Diffraction patterns for Cu, Pol 407 and SD of Cu-Pol 407 were obtained [21].

Characterization of Cu-SD for self-micellizing property

Particle size measurement

The particle size of Cu-SD was determined using dynamic light scattering (Horiba, SZ 100, Japan). Cu-SD was dissolved in 0.1 N HCL, and ultrasonicated for 10 min followed by measurement at fixed angle of 90 ° at 25 °C, carried out in triplicate [22].

Drug content study

Cu-SD equivalent to 5 mg of Cu was transferred to 50 ml volumetric flask, ultrasonicated to 15 min, and diluted to 50 ml with methanol. The solution was appropriately diluted by methanol and absorbance was noted at maximum wavelength, 419 nm. Drug content was determined using the calibration curve in methanol at the same wavelength. All the trials were done in triplicate [23, 24].

Saturation solubility

The solubility of Cu and Cu-SD was determined in 0.1 N HCL. An excess amount of the Cu or Cu-SD was added into 5 ml of 0.1 N HCL up to saturation. Then the glass vials were placed into a water bath shaker for 72 h at 37 °C±0.5 and 100 rpm. The supernatant solutions were then passed through whatman filter paper and analyzed by UV spectrophotometry at 419 nm. All solubility measurements were performed in triplicate [25].

***In vitro* dissolution study**

In vitro dissolution study was carried out using USP apparatus I (basket assembly). Accurately weighed sample equivalent to 20 mg of Cu-Pol 407 SD was filled into capsule and placed in a basket of dissolution vessel containing 900 ml of 0.1 N HCL as dissolution medium, maintained at 37±0.5 °C and 100 rpm. At each time interval, 5 ml of the sample was withdrawn and appropriately diluted. The equal volume of fresh dissolution medium was immediately replaced. The concentration of Cu in the sample was analyzed spectrophotometrically at 429 nm. The dissolution experiments were conducted in triplicate.

Preparation of Cu-SD pellets

The pellets of Cu and Cu-SD were prepared using extrusion and spheronization technique. The Cu or Cu-SD was mixed with all other excipients, except PVP K30 in a mortar. PVP K30 was dissolved in a mixture of IPA and water (2:1 ratio). The PVP solution was added to the powder mixture to form a damp mass. The wet mass was then passed through sieve number 18 (1000 μm) to obtain cylindrical extrudates. The extrudates were placed in a spheronizer (Shakti, SSP 120, India) fitted with the cross-hatched plate (2 mm) and spheronized for 5 min at varying rpm (1100, 1200, 1300 rpm). The resulting pellets were dried at 30 °C in a vacuum oven (Bio technique, BTI29, India) for 30 min [27]. The composition of pellet formulation is shown in table 1.

Table 1: Composition of Cu-SD pellets

Ingredient	Quantity (%w/w)
Solid dispersion (Cu-Pol 407) powder	30
Microcrystalline cellulose	30
Lactose	30
Sodium croscarmellose,	5
Polyvinyl pyrrolidone K30	5
Isopropyl Alcohol and Distilled water	Quantity Sufficient (2:1 ratio)

Table 2: 3^2 full factorial design for optimization of Cu-SD pellets

Run	Batches	(X1) (Cu-Pol 407 ratio)	(X2) (Speed in rpm)
1	F1	-1 (1:0)	-1 (1100)
2	F2	-1 (1:0)	0 (1200)
3	F3	-1 (1:0)	1 (1300)
4	F4	0 (1:3)	-1 (1100)
5	F5	0 (1:3)	0 (1200)
6	F6	0 (1:3)	1 (1300)
7	F7	1 (1:7)	-1 (1100)
8	F8	1 (1:7)	0 (1200)
9	F9	1 (1:7)	1 (1300)

Experimental design

The optimization of the formulation was performed using 3^2 full factorial design. The design consisted of 2 variables at 3 levels. The first independent variable (X_1) was Cu-Pol 407 ratio, (1:0, 1:3, 1:7) and the other variable (X_2) was spheronization speed (1100, 1200, 1300 rpm). Total of nine formulations were prepared (table 2) and the effect on geometric mean diameter (Y_1) of pellets, and drug

release after 2 h (Y_2) was evaluated. The data from 9 trial runs was analyzed using Design-Expert software (Stat-Ease, version 9.0, USA). The contour plots and 3-D surface response plots were generated in order to study the influence of independent variables on responses.

Characterization of Cu-SD pellet

Particle size distribution

The particle size distribution of pellets was carried out by sieve analysis, using a set of USP standard sieves. Sieves set of #12, 16, 18, 22, 24, 30, 36 and 44 were used along with a pellet load of 10 g. The sieve set was then mechanically shaken for 10 min. The net weight retained on each sieve was determined and these values were used for calculation of the particle size distribution [28].

Scanning electron microscopy

The surface morphology of Cu-SD pellet formulation was studied using field emission scanning electron microscopy (FESEM) (FEI, Nova Nano SEM 450, USA). The samples were coated with a platinum layer of 20 nm to make them electrically conductive and the coated samples were then randomly scanned in the FESEM chamber at an acceleration voltage of 5.00 KV. The photomicrographs were obtained at different magnifications

Micromeritic properties

Micromeritic properties like bulk and tapped density, Carr's index, compressibility index and angle of repose of pellet formulation were evaluated as per standard procedure mentioned in USP [28].

Hardness

The measurement of Hardness of pellets was done using a digital hardness tester (Veego, India).

Drug content

Drug content of pellets was estimated using UV visible spectrophotometric method. Pellets were crushed to powder using mortar and pestle. Finely crushed sample equivalent to 5 mg of Cu was transferred to 50 ml methanol, ultrasonicated to 15 min and after appropriate dilution, absorbance was noted at 419 nm. The experiment was performed in triplicate and drug content was calculated using a previously developed calibration curve in methanol [29].

***In vitro* dissolution study**

In vitro dissolution study of pellets was performed using the same method as mentioned in the characterization of Cu-SD.

Stability study

The stability study of pellet formulation was performed at conditions as per ICH guidelines for Zone IV. Pellet sample was filled in capsules, which was further placed in HDPE container. The samples were maintained in the stability chamber with accelerated conditions (40 °C±2 °C, 75±5% RH), and intermediate condition (30 °C±2 °C, 65±5%). The sample were analyzed for appearance, drug content and *in vitro* drug release at 0 and 1 mo time points at both the conditions.

RESULTS AND DISCUSSION

Phase solubility analysis

The solubility of Cu in 0.1 N HCL was observed as 0.0018 mmol. With increasing carrier concentration over the range of 5 to 30 mmol, the Cu solubility was found to be increased in a linear fashion in all the carriers as shown in fig. 1. The sudden increase in solubility was observed with Pol 407 and PVP K30 as compared to other carriers. At 30 mmol concentration of Pol 407, the solubility of Cu was observed as 1.659 mmol. Thus, 921.6 fold increase in solubility of Cu was observed. Pol 407 is an amphiphilic coblock polymer with a large number of polyethylene oxide chains representing hydrophilic portion and polypropylene oxide units representing the hydrophobic part. At higher concentrations, it forms micelles, thus allowing solubilization of hydrophobic drugs in its core resulting in improved drug solubility. Considering this, for further study, Pol 407 was selected as SD carrier.

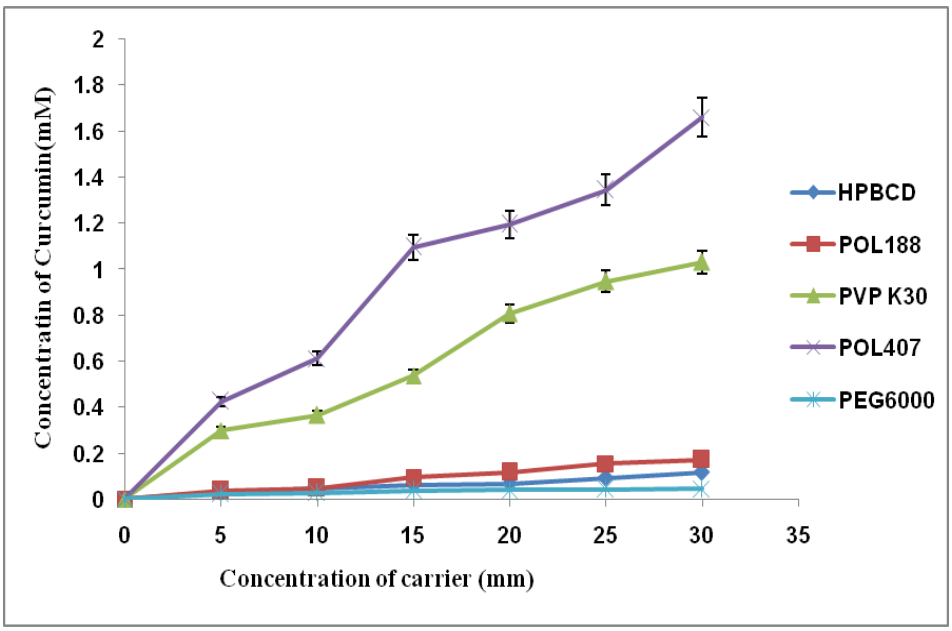

Fig. 1: Phase solubility analysis of Cu in different carriers, *error bars represent standard deviations of three replicates

Formulation and evaluation of Cu-SD

From the phase solubility plots, considering the high molecular weight of Pol 407, Cu solid dispersions were prepared with Cu-Pol 407 weight ratio of 1:2, 1:3, 1:5, 1:7, 1:10 instead of molar ratio.

Scanning electron microscopy

Scanning electron micrograph of Cu revealed its crystalline structure and Pol 407 appeared as perfectly spherical smooth-surfaced particles (fig. 2). The SEM of Cu-SD showed agglomerated particles with a rough surface.

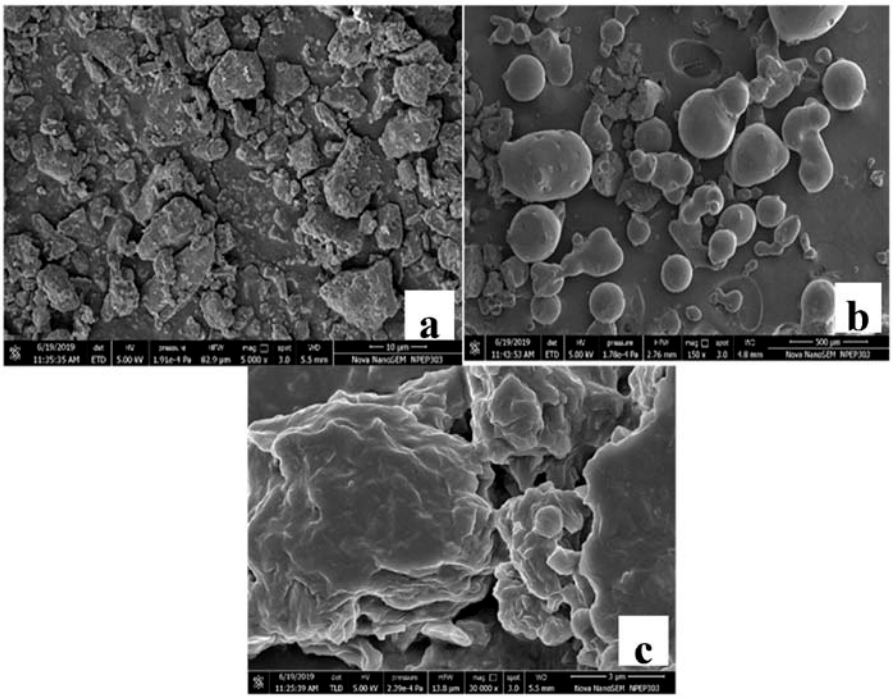

Fig. 2: Scanning electron micrograph of (a) Cu (b) Pol 407 (c) Cu-SD

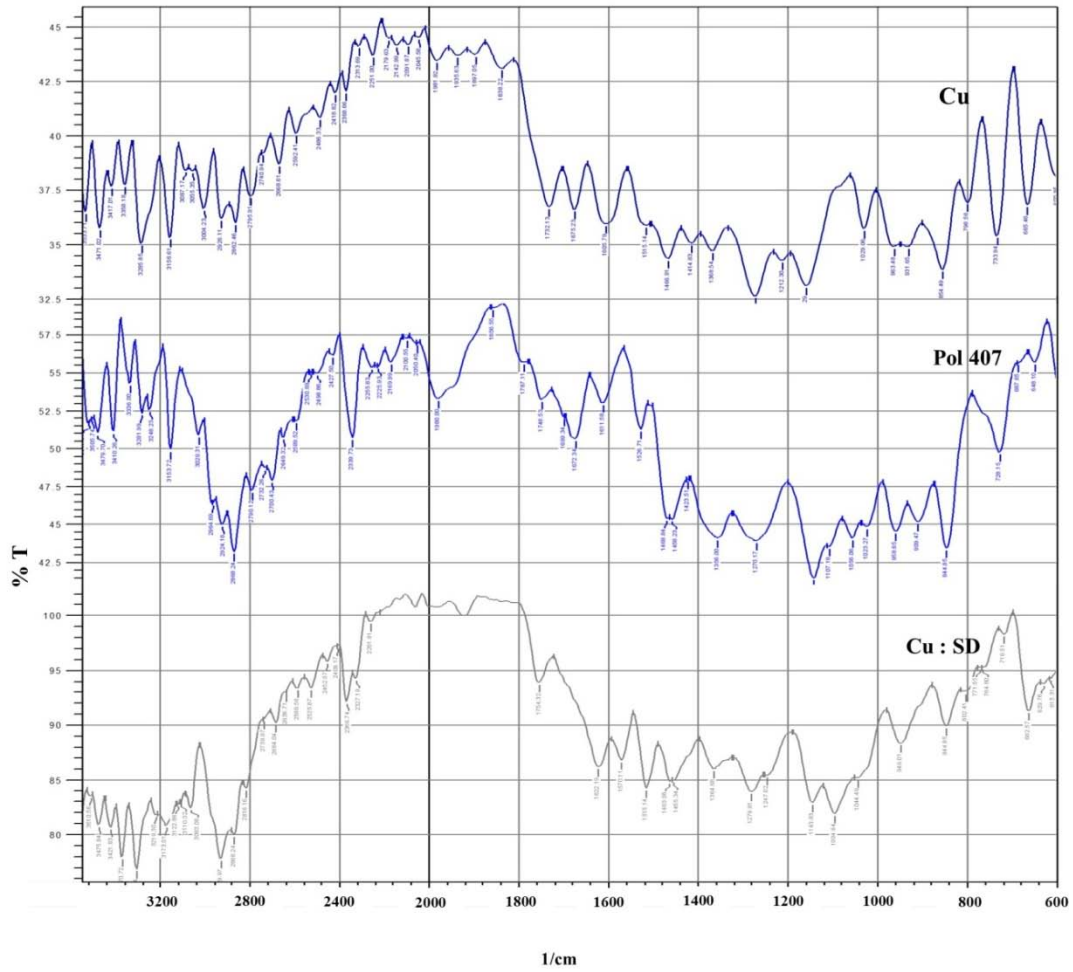

Fig. 3: FTIR spectra of (a) Cu (b) Pol 407 (c) Cu-SD

FT-IR study

The IR spectra of pure Cu (fig. 3) presented characteristic peaks at 3471.02-3285.85 cm^{-1} (O-H stretching), 3156.61 cm^{-1} (C-H stretching), 3004.23 cm^{-1} (aromatic C–H stretching), 2926.11-2862.46 cm^{-1} (asymmetric symmetric stretching of–CH_3 group), 1732.13-1675.23 cm^{-1} (C=O and C=C stretching in aromatic) and 733.94 cm^{-1} (C–H bonding of aromatic group). The IR spectra of pure Pol 407 showed peaks at 3153.72 (O–H group stretching), 2924.18-2868.24 cm^{-1} (asymmetric and symmetric Stretching of–CH_3 and CH_2 group) and 1140.93 cm^{-1} (C-O Single bond stretching).

Cu in its free form has two hydroxyl group with their frequencies at 3471.02-3285.85 cm^{-1} and Pol 407 has one hydroxyl group at 3153.72 cm^{-1}. In the IR spectra of Cu-SD, the decrease in the frequencies of hydroxyl group in the range 3510.56-3173.01 cm^{-1} is attributed to hydrogen bonding between Cu and Pol 407. This confirms the Cu and Pol 407 interactions during the formation of Solid dispersion.

Differential scanning calorimetry study

The solid-state changes in Cu-SD were studied by comparing DSC of Cu, Pol 407, and Cu-Pol 407 SD (fig. 4). The crystallinity in Cu was confirmed by sharp endothermic peak at 178.66 °C. DSC of Pol 407 demonstrated endotherm at 54.9 °C. The endothermic peak was observed at 53.16 °C in Cu-SD. The peak for Cu was not observed. This confirmed molecular dispersion of Cu in Pol 407 carrier.

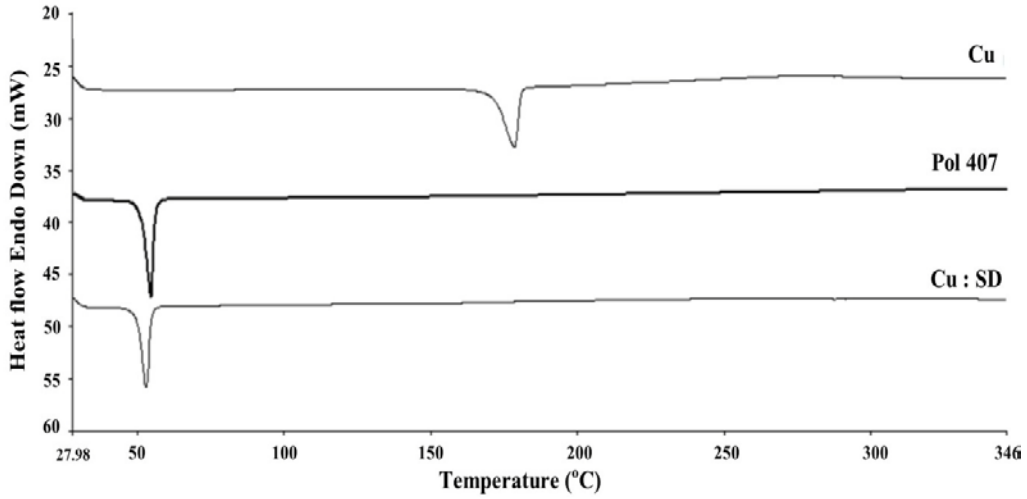

Fig. 4: Differential scanning calorimetry of (a) Cu (b) Pol 407 (c) Cu-SD

X-ray diffraction study

The changes in the crystallinity of Cu in SD formulation were further confirmed by XRD. Fig. 5 represents X-Ray diffractogram of Cu, Pol 407, and Cu-SD. The sharp characteristic peaks of Cu were observed at 2θ, 21.12 °, 23.3 °, 25.52 °, 25.56 °, and 28.92 ° in raw Cu sample. This confirmed the crystalline nature of Cu. Pol 407 indicated a sharp peak in the range, 22.88 ° to 23.78 °. In Cu-SD sample, the sharp peaks of Pol 407 in the range of 23.12 ° to 23.82 ° were observed but there was a complete disappearance of Cu peaks. This indicated a complete change of Cu from crystalline to amorphous form. This can be correlated with the enhanced solubility and dissolution of Cu-SD as compared to raw Cu.

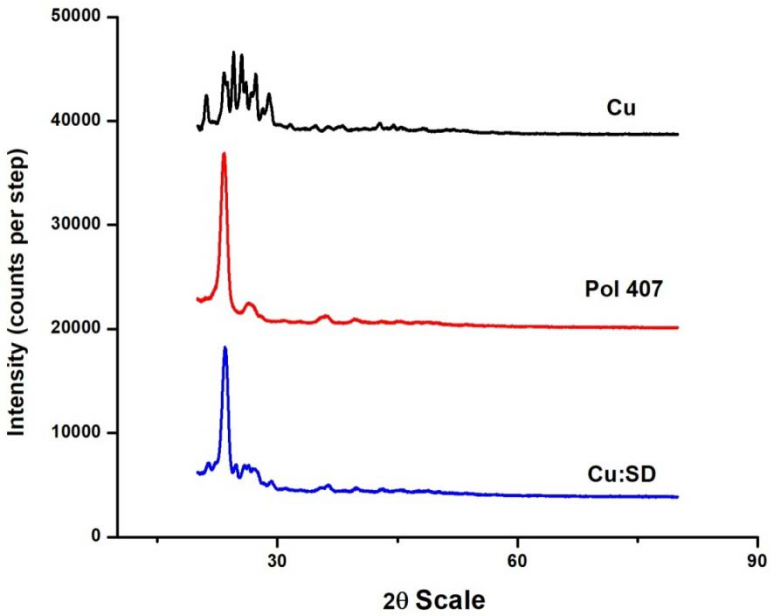

Fig. 5: XRD of (a) Cu (b) Pol 407 (c) Cu-SD

Characterization of Cu-SD for self micellizing property

Pol 407 is a block copolymer with poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO) units. Above critical micelle concentration of $2.8x10^{-6}$M at 37 °C it forms micelles with PPO unit aggregated in the core and PEO units oriented towards the external aqueous phase. Micellar solubilization of lipophilic drugs could result in an increase in drug solubility. In order to confirm the formation of micelles by Pol 407, the particle size distribution was conducted after dispersion of SD in water (table 3).

The solid dispersion formulation showed mean size of micelles in the range 721.4 to 1311.7 nm and PDI in range 0.409 to 1.612. Parikh *et al.* [15] reported similar nanomicellizing formulations where the size of micelles was obtained as 63.05±5.24 nm with polydispersity index of 0.09±0.04. In these formulations they used Soluplus and Solutol HS-15 as polymers. The higher values of the polydispersity index in our reported formulations could be the result of excessive Pol 407 present in higher Cu-Pol407 ratios. High concentration of Pol 407 may result in increase in number of micelles and their size. This could result in uneven size distribution of micelles. The drug content of Cu-SD was found to be in range 81.56 to 92.02%.

Saturation solubility

The result of saturation solubility is depicted in fig. 6. The SD with ratio 1:3 demonstrated significant increase in solubility of Cu (158.71 mg/ml) as compared to only Cu (0.692 mg/ml) and SD with ratio 1:7 demonstrated solubility value of 333.72 mg/ml. Thus, the solubility of Cu was significantly increased with increasing ratio of Cu-Pol 407. This could be attributed to increase in formation of micelles with increase in Cu-Pol 407 ratio.

Table 3: Characterization of Cu-SD for particle size and drug content

Batch	Mean size (d90) (nm)	PDI	Drug content (%)*
SD1	721.4	0.409	82.58±0.78
SD2	878.1	0.759	86.0±0.33
SD3	1156.6	0.975	88.40±0.20
SD4	1266.6	1.015	92.27±0.15
SD5	1311.7	1.612	93.74±0.24

*Values are expressed as mean±SD (n=3)

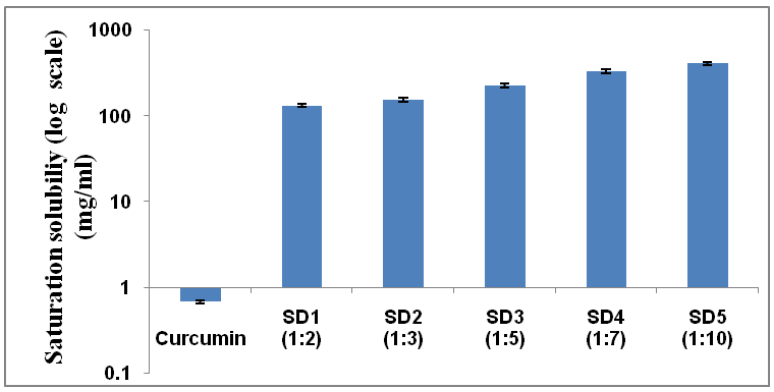

Fig. 6: Saturation solubility (mg/ml) (log scale) of Cu and Cu-SD in 0.1 N HCL, *error bars represent standard deviations of three replicates

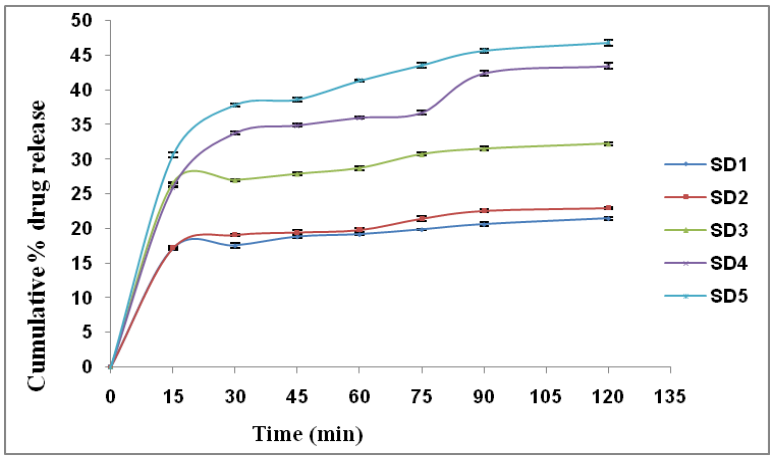

Fig. 7: *In vitro* dissolution study of Cu-SD formulation, *error bars represent standard deviations of three replicates

***In vitro* dissolution study of Cu-SD**

Fig. 7 represents *in vitro* dissolution of Cu solid dispersion formulations. Cu-SD demonstrated higher drug release as compared to raw Cu. When Cu-Pol 407 ratio was increased from 1:2 to 1:3 there was no significant increase in drug release. However, with increase in ratio to 1:7 and 1:10, the drug release was significantly increased. This is in agreement with the reports of Paradkar *et al.*

[30] in which authors reported a solid dispersion system of Cu and PVP at different weight ratio. The drug release of solid dispersion was significantly higher than pure Cu and ratio 1:7 and 1:10 demonstrated a significant increase in drug release as compared to lower ratios, 1:1, 1:3 and 1:5.

Considering the results of saturation solubility, particle size and *in vitro* dissolution, the solid dispersion ratios of 1:3 and 1:7 were selected for the formulation of solid dispersion loaded pellets.

Characterization of Cu-SD pellets

Pellet formulations of Cu-SD were prepared by extrusion spheronization technique in order to overcome the problems of agglomeration and poor flowability of solid dispersion due to higher poloxamer concentration. Cu-SD was 30% w/w and other excipients were 70% w/w in the pellet formulation. Pellet formulation by extrusion spheronization takes place through various stages, attrition, plastic deformation and agglomeration resulting into shape change from cylindrical dumbbells, ellipsoid to finally spherical shape pellets. Preliminary trials were performed in order to optimize the solvents for the pelletization process. Water: IPA (isopropyl alcohol) in 1:4 ratio was used as solvent. Increase in water proportion resulted in sticky product whereas use of only IPA resulted in friable pellets. From the preliminary trials, the spheronization speed was set in the range of 1100 to 1300 rpm.

The feasibility of extrusion spheronization process for the formulation of pellets containing Cu in free form and in complex form with Pol 407 was studied using Design of Experiments (DOE). (table 4) depicts the effect of independent variables Cu-Pol 407 ratio (X_1) and spheronization speed (X_2) on evaluation parameters. The pellet formulation indicated good flow properties and compressibility as evident from Hausner ratio and compressibility index. As the spheronization speed was increased from 1100 to 1300 rpm, there was decrease in the values of angle of repose. For Cu pellets without SD (1:0 ratio), the d_{geo} (geometric mean diameter) of pellet increased with increase in spheronization speed (fig. 8). However, with Cu-SD pellets, there was no significant change in d_{geo} with change in spheronization speed. During Cu pellet formation, higher speed of spheronization resulted in higher attrition producing large amount of fines. These fines, during dumbbell phase got deposited in the waist region resulting in formation of larger pellets. In Cu-SD pellet, presence of Pol 407 in high amount imparted excess cohesion and plasticity, thus decreasing the fine production. This resulted in narrow size distribution as compared to only Cu pellets. At higher speed, due to the deposition of excess fines, the pellet surface was rough resulting into increase in the value of angle of repose. The drug content for all the pellet formulation was in the range 81.69 to 93.69 %.

Table 4: Effect of independent variables on responses

Run	Batches	(Y1) (Geometric mean diameter in µm)	(Y2) (Drug release %)*
1	F1	927.89	19.62±0.32
2	F2	943.4	19.13±0.07
3	F3	1066.59	18.55±0.20
4	F4	954.11	51.45±0.13
5	F5	955.43	51.94±0.28
6	F6	934.11	52.15±0.18
7	F7	916.22	56.3±0.16
8	F8	905.73	58.29±0.17
9	F9	964.94	57.5±0.17

*Values are expressed as mean±SD (n=3)

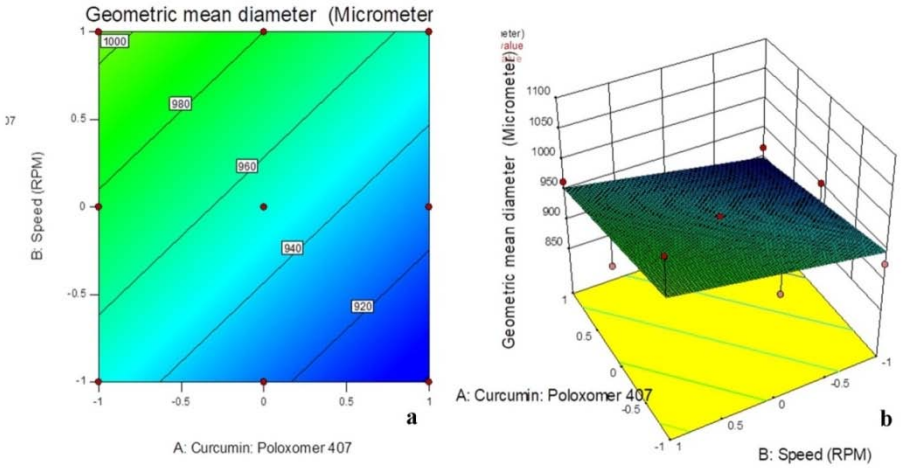

Fig. 8: (a) contour plot (b) Surface response plot showing effect of Cu-Pol 407 ratio and speed on geometric mean diameter

In order to check the relationship between independent variables and the responses, multiple liner regression analysis was carried out. The significance of the model was checked by ANOVA followed by student t-test. Form the ANOVA data, the effect of variables on pellet size was observed as insignificant whereas independent variables contributed significantly ($p<0.050$) to drug release after 2 h.

Equation 1 indicated the effect of independent variables on drug release after 2 h (Y2)

$$\text{Drug release (\%) } (Y_2) = 52.2+19.13X_1+0.14X_2+0.57X_1X_2-13.62X_1^{2}-0.52X_2^{2} \quad \text{----------1}$$

The high F value (1740.31) and p value less than 0.05 ($p = 0.0001$) imply the significance of the model. The predicted R^2 (0.9961) was in reasonable agreement with the adjusted R^2 (0.9991).

Table 5 indicates ANOVA data for response Y_2. ANOVA data indicates significant effect of Cu-Pol 407 on drug release ($p<0.0001$). The higher p

value (p>0.1) indicated a non-significant effect of spheronization speed on drug release. The presence of quadratic tern in the equation indicated non-linearity in the response. Equation 1 suggested that X_1 had positive effect on drug release. The effect was further verified from the response surface and the counterplot as shown in (fig. 9). From the surface response plot, it was observed that when Cu-Pol 407 ratio was changed from 1:0 to 1:3, there was significant increase in the drug dissolution. This was due to presence of Pol 407 as solubility enhancer in the solid dispersion. Further increase in Cu-Pol 407 ratio to 1:7 increased the Cu dissolution, but the change was not very significant. The drug release from, SD pellets with Cu-Pol 407 ratio 1:3 was higher as compared to their SD formulation. This could be due to presence of hydrophilic carriers in pellet formulation. In addition, the uniform size of pellets provided a higher surface area for drug release than the agglomerated SD powdered formulations. There was no significant difference in the dissolution of pellets with different Cu-Pol 407 ratio SD. Change in spheronization speed did not significantly affect the dissolution of pellets.

Table 5: ANOVA data for response Y_2 (%Drug release)

Analysis of variance table [Partial sum of squares-Type III]					
Source	**Sum of squares**	**df**	**Mean square**	**F value**	**p-value Prob>F**
Model	2568.81	5	513.76	1740.31	<0.0001*
X_1-Cu: Poloxomer 407	2196.12	1	2196.12	7439.09	<0.0001*
X_2-Spheronization Speed	0.11	1	0.11	0.39	0.5771
X_1X_2	1.29	1	1.29	4.36	0.1279
X_1^2	370.74	1	370.74	1255.82	<0.0001*
X_2^2	0.55	1	0.55	1.87	0.2652
Residual	0.89	3	0.30		
Cor Total	2569.70	8			

*indicates significance of the model, Counter plot (fig. 9 A) indicated more than 50% Cu release for ratio of 1:3 and higher. Fig. 10 indicates dissolution profile of Cu and Cu-SD pellet.

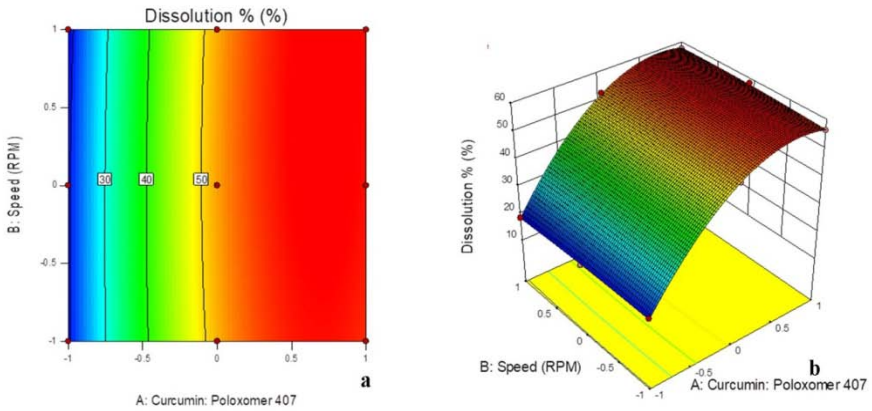

Fig. 9: (a) contour plot (b) Surface response plot showing effect of Cu-Pol 407 ratio and speed on dissolution at 2 h (%)

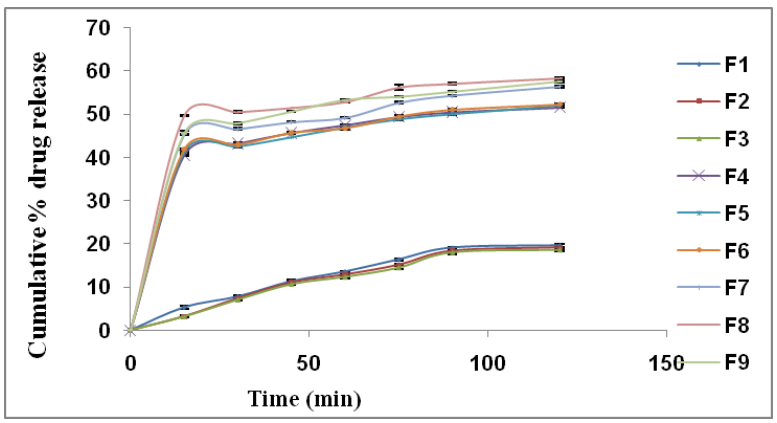

Fig. 10: *In vitro* dissolution profile of Cu-SD pellet formulation, *error bars represent standard deviations of three replicates

The result of micrometric properties indicated good flow and compressibility properties of pellet formulations (table 6). With increase in Cu-Pol 407 ratio in pellet formulation to 1:7, flow properties were adversely affected. Scanning electron micrograph of pellet formulation (fig. 11) confirmed the spherical shape of pellets. The surface of pellets was found to be rough. This could be due to deposition of fines produced by attrition of pellets during spheronization. These results were in agreement with our observation during the optimization of the pelletization process.

Table 6: Micromeritic properties of Cu-SD pellets

Batch	Bulk density	Tapped density	Hausner's ratio	Carr's index %	Hardness g/cm3	Angle of repose (°)
F1	1.05±0.15	1.01±0.17	1.03±0.18	3.8±0.21	1.230±0.41	26.1 °
F2	1.06±0.21	1.14±0.25	1.07±0.16	7.01±0.18	1.310±0.35	29.2 °
F3	0.87±0.20	1.14±0.29	1.12±020	11.40±0.39	1.400±0.42	33.0 °
F4	0.95±0.25	0.98±0.31	1.04±0.22	3.84±0.24	0.800±03.39	25.8 °
F5	0.97±0.15	1.01±0.18	1.11±0.19	3.96±0.15	0.830±0.5	27.1 °
F6	0.95±0.32	0.98±0.30	1.03±0.24	3.06±0.42	0.850±0.25	31.0 °
F7	1.01±0.27	1.12±0.16	1.10±0.32	9.82±0.25	1.00±0.45	30.1 °
F8	1.02±0.29	1.06±0.28	1.03±0.37	3.30±0.36	0.988±0.58	27.0 °
F9	1.06±0.38	1.23±0.35	1.16±0.27	13.82±0.21	0.970±0.25	32.0 °

*Values are expressed as mean±SD (n=3)

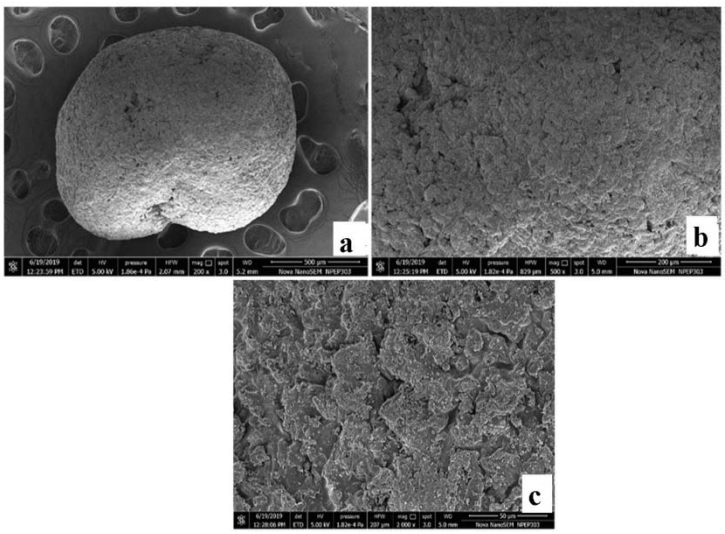

Fig. 11: SEM of the surface of Cu-SD pellet at magnification (a) 200 X (b) 500 X (c) 2000 X

Selection of optimized formulation of Cu-SD pellets

The criteria for the selection of optimized formulations were higher drug release and minimum geometric mean diameter. Based on the results of pellet size distribution and *in vitro* dissolution of pellets, F5 (Cu-Pol 407 ratio 1:3) was selected as an optimized formulation, since at this ratio, the higher release of Cu was obtained and further change in ratio did not significantly change dissolution profile. Fig. 12 indicates an overlay plot and table 7 indicates a comparison of predicted and experimental results. The percentage error in predicted and experimental values was only 0.14% and 0.48% indicating robustness of pellet formulation. This confirms the validation and pellet formulation process.

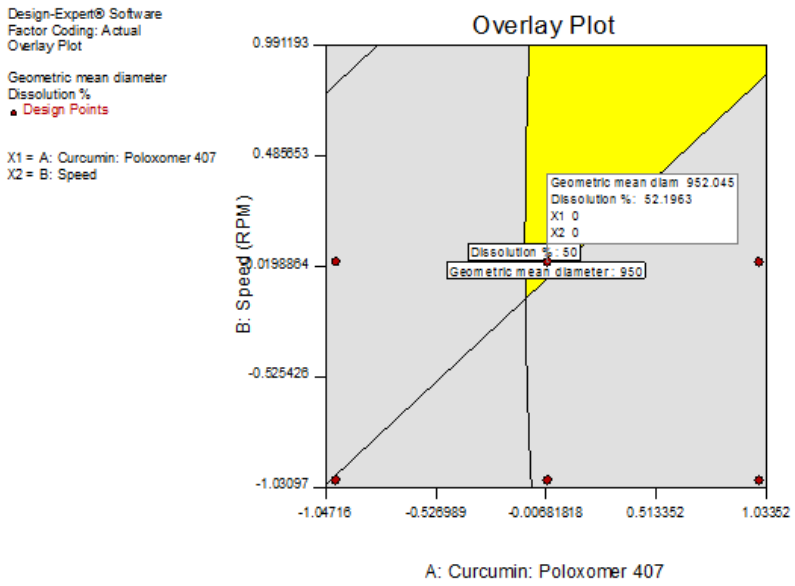

Fig. 12: Overlay plot indicating design space and optimized formulation

Table 7: Comparison of predicted values and experimental value of optimized formulation

Batch	Factor	Responses	Predicted value	Experimental value	Percentage error
	X1 Cu-Poloxamer ratio (1:3)	Geometric Mean Dimeter (µm)	952.04	955.43	0.14%
F5	X2 Speed (rpm) (1200)	Drug Release after 2 h* (%)	52.19±0.21	51.94±0.28	0.48%

*Values are expressed as mean±SD (n=3)

Table 8: Stability data of Cu-SD pellet formulation

	30 °C±2 °C, 65±5%		40 °C±2 °C, 75±5% RH	
	0 d	1 mo	0 D	1 mo
Physical appearance	Yellow colour	No change	Yellow colour	No change
Drug Content (%)*	92.10 ±0.11	91.73 ±0.60	92.10 ±0.11	91.00 ±0.12
Drug Release (%)*	51.94± 0.28	52.42 ±0.38	51.94 ±0.28	52.00 ±0.99

*Values are expressed as mean±SD (n=3)

Stability study

The stability of optimized pellet formulation was studied for 1 mo and results are evident in table 8. From the data, no major change was observed in the appearance, drug content and drug release. This indicated the stability of the formulation at the test temperatures.

CONCLUSION

Cu-SD pellets were prepared by extrusion spheronization technique and the optimization of the formulation was performed by 3^2 full factorial design. Formulation of Cu-SD was confirmed from FTIR and DSC studies. The SD was found to increase the Cu solubility and dissolution significantly. The optimized Cu-SD pellets were spherical with narrow size distribution and indicated significant enhancement in Cu dissolution. The formulation was stable and the process was robust as confirmed from validation results. Conclusively, Cu-SD pellets presents a promising approach indicating an improvement in Cu dissolution.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Authors declare no conflict of interest.

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