Department of Pharmaceutical Technology[1]; Department of Medicinal Chemistry and Pharmacognosy[2], Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan

Dissolution enhancement of gliclazide using ultrasound waves and stabilizers in liquid anti-solvent precipitation

S. S. AL-Nimry[1], A. M. Qandil[2], M. S. Salem[1]

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Dr. Suhair S. Al-Nimry, Pharmaceutical Technology Department, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box 3030-Irbid-22110-Jordan
ssnimry@just.edu.jo

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The absorption rate of gliclazide is slow and variable among subjects probably due to poor dissolution from the dosage form. The objective of this study was to enhance the dissolution rate of gliclazide by reducing the particle size. Gliclazide was precipitated from an acetone solution by adding an antisolvent (water) containing stabilizers. A combination of jets (flow rate of 20 ml/min), ultrasound, HPMC 4000, and sodium dodecyl sulfate was used to control particle size and particle size distribution. The effects of concentration of stabilizers, initial drug concentration in solution, time of insonation, antisolvent-to-solvent ratio, and ultrasound power on particle size and particle size distribution were studied. Precipitated drug particles were characterized by laser diffraction particle size analysis, SEM, FTIR spectroscopy, DSC, powder x-ray diffraction and *in-vitro* dissolution. With increasing almost all the studied parameters, the particle size of gliclazide initially decreased, exhibited a minimum, and then increased. Drug particles of glicazide with a mean particle size of 1.56 ± 0.09 μm and a narrow size distribution ($d_{10}/d_{50}/d_{90} = 0.67/1.67/2.26$) were precipitated as compared to unprocessed gliclazide with a mean particle size of 10.67 ± 0.04 μm and a wide size distribution ($d_{10}/d_{50}/d_{90} = 4.53/9.88/18.03$). SEM images indicated changes in the particle morphology. Powder x-ray diffraction patterns and DSC curves indicated no changes in the chemical properties but only decrease in crystallinity and/or particle size. The dissolution rate was enhanced 2.55-fold. In conclusion, drug particles with small size and narrow size distribution were precipitated by selecting favorable process conditions, and dissolution was enhanced several folds.

1. Introduction

Gliclazide, [1-(3-azabicyclo(3,3,0)oct-3-yl)-3-p-tolylsulfonylurea] is a hypoglycemic agent that belongs to the sulfonylurea group and is used in treating type II diabetes mellitus. It is considered a drug of choice in long term sulfonylurea treatment of type II diabetes mellitus (Biswal et al. 2008). An oral hypoglycaemic agent should be rapidly absorbed after oral administration in order to prevent a sudden increase in blood glucose level after food ingestion. Unfortunately, the absorption rate of gliclazide is slow and variable among subjects. The time to reach maximium plasma concentration (t_{max}), varies from 2 to 8 h following oral administration of a tablet dosage form (Ambrogi et al. 2009). Slow and variable absorption rates usually result from poor dissolution of drugs from the formulation or poor permeability of drugs across the gastrointestinal membranes. According to the Biopharmaceutical Classification System (BCS), gliclazide belongs to class-II drugs because the rate of oral absorption is controlled by the dissolution rate rather than the permeability (Biswal et al. 2008). The slow dissolution results partly from the hydrophobicity of the drug (Biswal et al. 2008). The solubility of gliclazide in distilled water is very low (1.5 μg/ml at room temperature (Ambrogi et al. 2009) and 55 μg/ml at 37 °C (Alkhamis et al. 2003)). Furthermore, it is a weak acid (pKa = 5.8) and its solubility depends on the pH of the gastric fluid which is variable within the same subject and from one subject to another (Ambrogi et al. 2009). This suggests that enhancing dissolution will increase GIT absorption and reduce variability in bioavailability.

A variety of pharmaceutical formulation strategies were used to enhance dissolution rate and oral bioavailability of gliclazide. These include solubilization in micellar solutions (Alkhamis et al. 2003); co-solvent solubilization (Seedher and Kanojia 2009), complexation with cyclodextrins (Lo et al. 2007; Abou-Auda et al. 2006; Patil et al. 2010; Hiremath et al. 2008; Sharma et al. 2011), or cyclodextrin-hydroxypropylmethyl cellulose (HPMC) (Aggarwal et al. 2002); manipulation of the solid state of a drug substance by decreasing crystallinity through formation of solid solutions; and solid dispersions (using polyethylene glycol (PEG) 4000 (Shavi et al. 2010; Biswal et al. 2009a; Patil and Gaikwad 2009; Sateesha et al. 2010), PEG 6000 (Biswal et al. 2008; Shavi et al. 2010), PEG 8000 (Biswal et al. 2009b), polyvinyl pyrolidone (PVP) K 30 (Shavi et al. 2010; Sateesha et al. 2010; Barzegar-Jalali et al. 2010; Ingle et al. 2011), HPMC (Sateesha et al. 2010, Ingle et al. 2011), cross povidone and microcrystalline cellulose (Sateesha et al. 2010; Barzegar-Jalali et al. 2010), Poloxamer 407 (Bandarkar et al. 2011), and croscarmellose sodium (Sateesha et al. 2010)).

Other strategies proposed for improving gliclazide dissolution rate include reducing particle size to the micron (microniza-

Table 1: Effect of polymer concentration on particle size and size distribution (n = 2)

HPMC concentration (mg/ml)	Particle size (μm)	Std Deviation (μm)	Size distribution (μm) $D_{10}/D_{50}/D_{90}$
0.0125	3.31	0.14	1.55/3.10/5.56
0.025	2.56	0.04	1.69/2.47/3.49
0.05[(1)]	2.36	0.14	1.27/2.33/3.28
0.1	2.45	0.16	1.79/2.37/3.20
0.2	3.02	0.10	2.07/2.80/4.22
0.4	3.10	0.04	1.91/2.86/4.81

[(1)] n = 4

Table 2: Effect of SDS concentration on particle size and size distribution (n = 2)

SDS concentration (mM)	Particle size (μm)	Std Deviation (μm)	Size distribution (μm) $D_{10}/D_{50}/D_{90}$
0.00[(1)]	2.98	0.13	1.55/2.68/5.02
0.078[(2)]	2.79	0.13	1.97/2.61/3.58
0.156[(3)]	2.90	0.21	1.89/2.66/4.33
0.312	2.97	0.15	1.91/2.74/4.30
1.56	3.14	0.01	1.69/2.78/5.36
6.24	3.41	0.10	1.96/3.16/5.29

[(1)] n = 4, [(2)] n = 6, [(3)] n = 4

tion) or submicron range (nanosizing) to increase surface area. Normally size reduction is achieved by precipitation or by mechanical processes (Patel et al. 2008). In the precipitation method, the substance is dissolved in an appropriate solvent then precipitated from the solution by various methods like the pH change method (Talari et al. 2009), the solvent change method (Varshosaz et al. 2008), and the solvent evaporation method (Lo et al. 2007). In mechanical processes, the substance is subjected to mechanical forces using grinding equipments (ball mill, roller mill, colloid mill, etc.) (Patel et al. 2008).

Liquid AntiSolvent (LAS) precipitation technique is advantageous in comparison with the many techniques available for size reduction. Using this technique, the particle size and morphology can be controlled and the technique can be scaled-up easily through the impinging-jet technique. In LAS technique, the solid solute is precipitated by adding an antisolvent. This increases the molar volume of liquid mixture and decreases the solvent power for the solute. The steps involved in LAS precipitation are 1) nucleation due to supersatuartion attained by mixing and 2) simultaneous growth of nuclei by coagulation and condensation (Fig. 1). Accordingly, increasing nucleation rates results in low or negligible growth and in production of small particles (submicrometer range). Ultrasound and high stream velocities can be applied to enhance the mixing and produce rapid and uniform supersaturation and high nucleation rate. The stability of the precipitated particles in colloidal solution depends on agglomeration or flocculation. These are driven by hydrophobic effects, electrostatic interactions, and weak van der Waals attractive forces and are described by the Deryagin-Landau-Verwey-Overbeek (DLVO) theory (Dalvi and Dave 2009). Therefore, in order to obtain stable particles with small size and narrow particle size distribution (PSD), the nucleation rate must be increased, the particle growth must be inhibited, and the agglomeration of particles by steric or electrostatic stabilization must be controlled by the addition of stabilizers (polymers and/or surfactants).

Table 3: Effect of drug concentration on particle size and size distribution (n = 2)

Gliclazide concentration (mg/ml)	Particle size (μm)	Std Deviation (μm)	Size distribution (μm) $D_{10}/D_{50}/D_{90}$
2.5	5.75	0.01	2.10/4.77/10.93
5	4.56	0.12	1.78/4.02/8.24
10	3.78	0.00	1.95/3.32/6.19
15	2.97	0.10	1.91/2.74/4.30
20	3.09	0.00	1.57/2.77/5.30
30	3.19	0.00	1.60/2.77/5.64
35	3.50	0.07	1.86/2.98/6.43

This novel technique was used successfully to precipitate very small particles of griseofulvin, a model drug of class II drugs (Dalvi and Dave 2009). In this research the same technique was applied to another drug belonging to the same class with the objective of, in addition to controlling the particle size and the PSD, enhancing the dissolution.

2. Investigations, results and discussion

2.1. Optimization of process variables

Effects of increasing HPMC 4000 concentration, sodium dodecyl sulfate (SDS) concentration, drug concentration, time of insonation, antisolvent-to-solvent ratio, and amplitude on particle size and size distribution were evaluated and are presented in Tables 1, 2, 3, 4, 5, and 6, respectively.

As can be noticed from Tables 1 and 2, as polymer and surfactant concentrations in the solution increased, the particle size and PSD of gliclazide decreased, went through a minimum (at a polymer concentration of 0.05 mg/ml and a surfactant concentration of 0.078 mM), then increased. They both enhance the formation of stable particles with a small size and a narrow PSD probably by firstly adsorbing at the solid-liquid interfaces reducing interfacial tension and interfacial surface free energy of new surfaces and increasing the nucleation rate. The reduction in surface tension and interfacial free energy was more significant in the case of surfactants; secondly by forming a film around suspended particles, reducing attractive forces between them, and offering steric and/or electrostatic stabilization, thus preventing growth and agglomeration. Polymers form multilayered films while surfactants form monolyaered films. SDS is negatively charged and provides steric and electrostatic hindrance while HPMC 4000 polymer is a neutral polymer and provides only steric hindrance. Polymers increase the viscosity of the solution causing decreased collision among the particles again preventing growth and agglomeration. The increase in particle size at higher polymer and surfactant concentrations is probably due to bridging flocculation of the particles in the suspension (Dalvi and Dave 2009; Patrick 2006).

SDS was used to stabilize the microcrystals and enhance wetting rather than to solubilize the drug through the formation of micelles. Therefore, the concentrations used were far below the critical micelle concentration (CMC) in pure water at 25 °C, which is 0.0082 M (Moldes et al. 2013).

As can be noticed from Table 3, as gliclazide concentration in solution increased, the particle size and PSD of gliclazide decreased, went through a minimum at 15 mg/ml, then increased. At low gliclazide concentrations, supersaturation was not attained and hence resulted in a low nucleation rate thus increasing the particle size. At higher concentrations, the supersaturation increased and hence resulted in an increase in the nucleation rate thus decreasing the particle size. Increasing

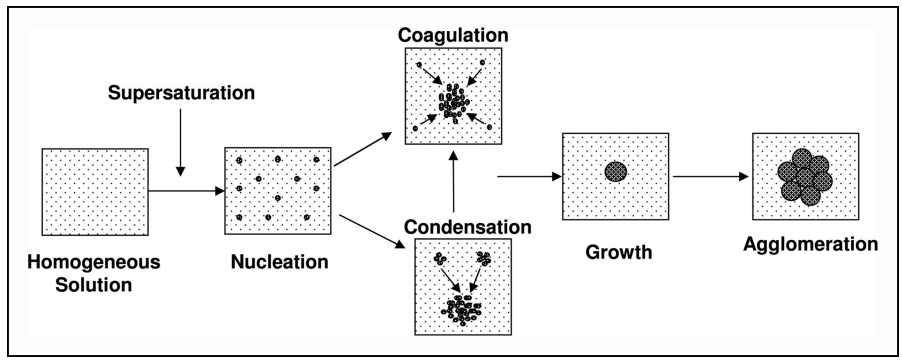


Fig. 1: Schematic of particle precipitation process (Dalvi and Dave 2009).

Table 4: Effect of time of insonation on particle size and size distribution (n = 2)

Time of insonation (min)	Particle size (μm)	Std Deviation (μm)	Size distribution (μm) $D_{10}/D_{50}/D_{90}$
2.5	3.08	0.24	2.07/2.85/4.42
5.0	2.97	0.15	1.91/2.74/4.30
7.5	2.62	0.01	1.87/2.52/3.43
10.0[(1)]	2.86	0.43	2.05/2.73/3.79
12.5	2.90	0.08	1.84/2.76/4.05
15	3.23	0.15	1.86/3.024/4.91

[(1)] n = 3

Table 5: Effect of antisolvent:solvent ratio on particle size and size distribution (n = 2)

Antisolvent: solvent ratio	Particle size (μm)	Std Deviation (μm)	Size distribution (μm) $D_{10}/D_{50}/D_{90}$
5:1	2.97	0.03	2.05/2.79/4.12
10:1	2.49	0.06	1.71/2.42/3.31
15:1[(1)]	2.10	0.22	1.08/2.11/2.88
20:1	2.05	0.12	0.89/2.06/2.90

[(1)] n = 3

gliclazide concentration further probably decreased the distance between particles and increased the number of collisions leading to flocculation and formation of large particles.

As can be noticed from Table 4, as time of insonation increased, the particle size and PSD of gliclazide decreased, went through a minimum at 7.5 min, then increased. Increasing the time of insonation enhanced mixing due to cavitation. Rapid and uniform supersaturation was generated by ultrasound waves and resulted in the formation of fine particles. Increasing the time of insonation further probably increased mixing and the number of collisions leading to flocculation and formation of large particles.

As can be noticed from Table 5, particle size and PSD decreased and experienced a minimum at an antisolvent-to-solvent ratio of 20:1. The increase in the ratio increased the total volume of the liquid mixture and decreased mixing due to the decrease in the ultrasound energy per unit volume. This was expected to increase the particle size and the PSD. On the other hand, increasing the ratio lowered the % of solvent and Ostwald ripening therefore smaller particles were attained. Higher ratios of antisolvent-to-solvent were tried but the results were not reproducible.

As can be noticed from Table 6, the mean particle size and PSD decreased from 34.44 to 3.78 μm and from 23.84/32.97/46.53 to 2.20/3.26/6.04, respectively, with using an ultrasound power of 25% of 500 W. However, increasing the ultrasound energy further only resulted in a small decrease in the particle size and PSD. A minimum was obtained at an operating power of about 75 % of 500 Watt. Further increase in amplitude to 100% of 500 W, slightly increased particle size and PSD slightly. This is probably due to an increase in energy of particles resulting in a higher number of collisions, promoting flocculation and formation of larger particles.

Table 6: Effect of amplitude on particle size and size distribution (n = 2)

Amplitude %	Particle size (μm)	Std Deviation (μm)	Size distribution (μm) $D_{10}/D_{50}/D_{90}$
0	34.44	2.99	23.84/32.97/46.53
25	3.78	0.00	2.20/3.26/6.04
50	3.16	0.01	1.88/2.77/5.23
75	2.97	0.10	1.91/2.74/4.3
100	3.02	0.03	1.72/2.62/5.11

Accordingly, the optimum conditions for obtaining small crystals with a mean particle size of 1.56 ± 0.09 μm and a narrow size distribution ($d_{10}/d_{50}/d_{90} = 0.67/1.67/2.26$) as compared to unprocessed gliclazide with a mean particle size of 10.67 ± 0.04 μm and a wide size distribution ($d_{10}/d_{50}/d_{90} = 4.53/9.88/18.03$) were: HPMC 4000 concentration of 0.05 mg/ml, gliclazide concentration of 15 mg/ml, SDS concentration of 0.078 mM, time of insonation of 7.5 min, antisolvent-to-solvent ratio of 20:1, and amplitude of 75% of 500 watt. The results were reproducible (18 different batches were prepared under the same conditions, n = 18). Representative cumulative frequency under size plots for unprocessed gliclazide and precipitated drug particles at optimum conditions are shown in Fig. 2.

Precipitated drug particles at optimum conditions were prepared and further used for the characterization and *in vitro* release experiments.

2.2. Characterization of precipitated drug particles

Scanning Electron Microscope (SEM) images of unprocessed gliclazide and precipitated drug particles were obtained and are presented in Fig. 3. Both unprocessed gliclazide and precipitated drug particles were crystalline and the crystals were euhedral or idiomorphic (bound by plane faces) but they showed different crystal habits. Crystals of unprocessed gliclazide were platy while crystals of precipitated drug particles were prismatic and the prisms were elongated and looked like needles.

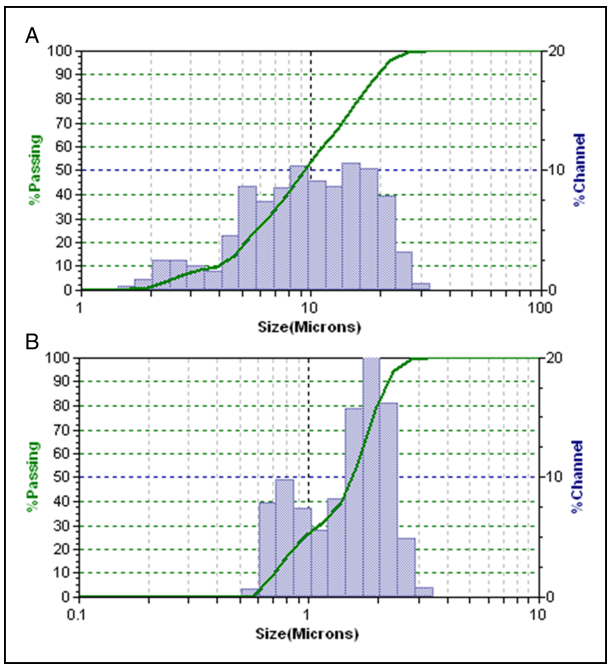
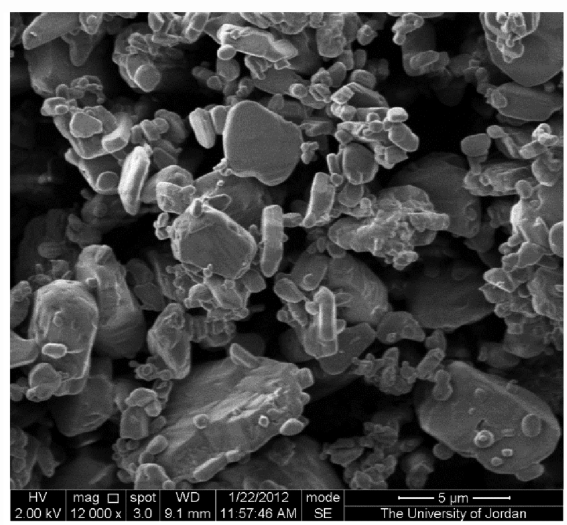


Fig. 2: Cumulative frequency under size plots of (A) unprocessed gliclazide; (B) precipitated gliclazide particles.



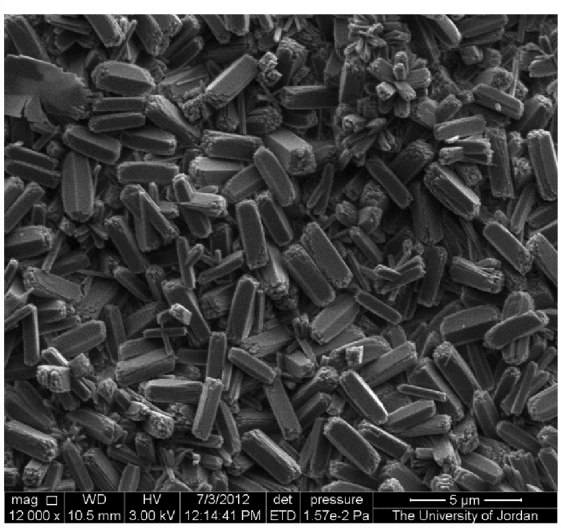


Fig. 3: SEM images of A) unprocessed gliclazide; B) precipitated drug particles.

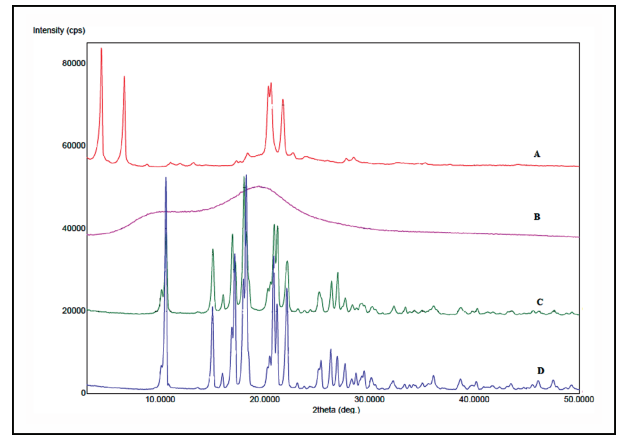


Fig. 4: PXRD patterns of A) SDS; B) HPMC 4000; C) precipitated drug particles; and D) unprocessed gliclazide.

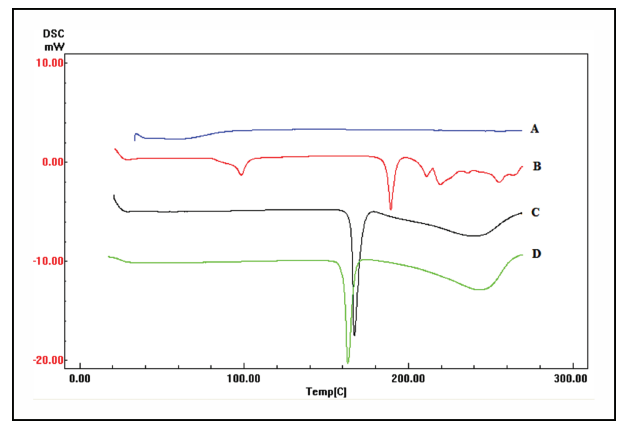


Fig. 5: DSC scans of A) HPMC 4000; B) SDS; C) unprocessed gliclazide; and D) precipitated gliclazide particles.

Powder X-Ray Diffraction (PXRD) patterns, Differential Scanning Calorimetry (DSC) scans, and Fourier Transform Infra Red (FTIR) spectra of unprocessed gliclazide, precipitated drug particles, HPMC 4000, and SDS were also obtained and are presented in Fig. 4, 5, and 6, respectively. The PXRD patterns of unprocessed gliclazide and precipitated drug particles (Fig. 4) were very similar and showed sharp peaks at diffraction angles at 2θ of 10.56, 15.0, 16.86, 17.14, 17.91, 18.22, 18.44, 20.84, 21.16, 22.12, 25.36, 26.3, 26.90 and 29.48° (finger print region). On the other hand, the peak heights for precipitated drug particles were smaller than those for the unprocessed gliclazide. The peak height is affected by crystal size and crystallinity (Talari 2009). Accordingly, smaller peak heights indicate reduced crystal size and crystallinity. This is in agreement with the results of the laser diffractometer (mean particle size decreased from 10.67 µm for unprocessed gliclazide to 1.56 µm for precipitated drug particles).

DSC curves (Fig. 5) indicated a reduction in melting point and enthalpy changes of precipitated drug particles as compared to the unprocessed drug probably due to size reduction. The melting point of unprocessed gliclazide was 167·37 °C and the enthalpy was -340.80 mJ, whereas the melting point of precipitated drug particles was 163.43 °C and the enthalpy was -281.78 mJ. The results also indicated that the drug and stabilizers are compatible (Talari et al. 2009).

The FTIR spectra of unprocessed gliclazide and of precipitated drug particles (Fig. 6) were almost the same and the main absorption bands of gliclazide appeared in both spectra. The NH group located at 3273 cm^{-1}, the C = O stretching located at 1710 cm^{-1}, the S = O located at 1352 cm^{-1} and 1165 cm^{-1},

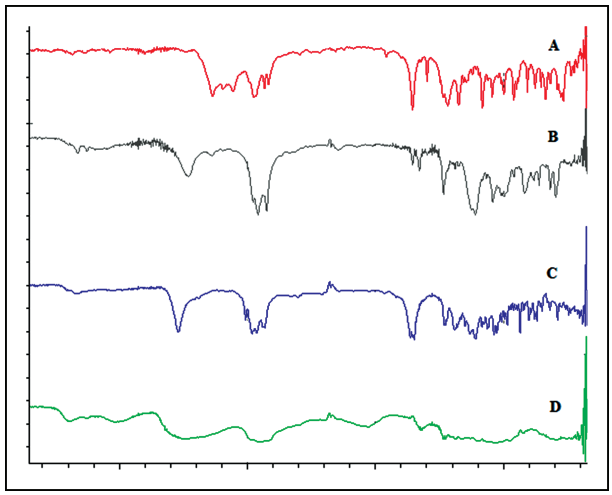


Fig. 6: FTIR spectrum of A) precipitated gliclazide particles; B) SDS; C) unprocessed gliclazide; and D) HPMC 4000.

Table 7: Flow properties of unprocessed gliclazide and precipitated drug particles (n = 3)

	Unprocessed gliclazide	Precipitated drug particles
Bulk density	0.29±0.01	0.33±0.01
Tapped density	0.44±0.01	0.47±0.02
Compressibility index	33.32±0.97	29.70±4.27
Hausner ratio	1.50±0.02	1.43±0.08

the C = (CH)^2 bending located at 1088 cm^{-1}, the C = C bending located at 997 cm^{-1}, the aromatic p- susbtitution phenyl located at 920 cm^{-1} and the aromatic ring located at 669 cm^{-1} in unprocessed gliclazide spectrum were not shifted in precipitated drug particles spectrum. This indicated the absence of any difference in the internal structures and conformation of these two samples (Varshosaz et al. 2008) and the absence of any interaction between the drug, the polymer and the surfactant.

The compressibility index and the Hausner Ratio (HR) for unprocessed drug and for precipitated drug particles were calculated and are presented in the Table 7. The values obtained for the compressibility index indicate that, even though both powders are classified to have poor flow, the flow properties of precipitated drug particles were somewhat better than those of unprocessed drug. The values obtained for the HR indicate that the flow properties of processed drug particles (HR between 1.25-1.50) could be improved by the addition of glidants while those for unprocessed drug cannot (HR > 1.50). The flow properties of the precipitated drug particles were not much improved probably due to, firstly, the decrease in the particle size which resulted in an increase in the specific surface area and the cohesive forces between the particles and, secondly, due to the shape of the particles which was elongated as indicated by SEM images.

The drug loading (LD) % obtained using the LAS precipitation method was calculated and it was high (the average of 7 different batches was 90.47 ± 7.61, n = 7).

2.3. In vitro dissolution studies

The dissolution of gliclazide both unprocessed and from precipitated drug particles into 900 ml 0.1N HCL at 37 °C and 100 rpm was evaluated and the results are presented in Fig. 7. The %

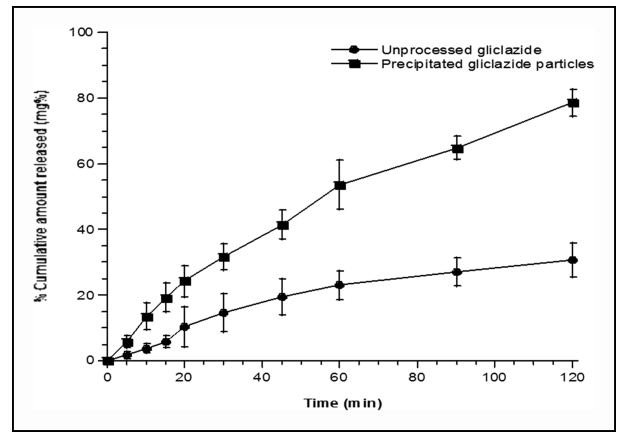


Fig. 7: Cumulative amount (%) released from unprocessed gliclazide (n = 4) and precipitated gliclazide particles (n = 6) into 900 ml 0.1N HCl at 37 °C and 100 rpm.

cumulative amount released from precipitated drug particles was 2.55 times that released from unprocessed drug probably due to the reduction in crystal size (crystallinity) and having a narrower size distribution.

2.4. Conclusions

The LAS precipitation technique was efficient, reproducible, and resulted in the precipitation of particles highly loaded with drug. It is clear that the stabilizers (HPMC 4000 and SDS), used at proper concentrations, inhibited the growth of drug crystals. By choosing the suitable process parameters, significant reduction in particle size, PSD, and crystallinity was achieved and accordingly the dissolution rate was enhanced several folds.

3. Experimental

3.1. Precipitation of drug particles

A solution of 15 mg/ml gliclazide in acetone was added to water containing 0.312 mM SDS and 0.200% w/v HPMC 4000, using a stainless steel nozzle (0.01-in. i.d.) at a flow rate of 20 mL/min. A Heidolph peristaltic pump 5201 (Germany) was used to pump the solution at the specified flow rate. The temperature of the water was kept at 1 °C using Lab Companion RW-0525G Refrigerated Bath Circulator (USA). The ratio of the antisolvent to solvent was 5:1. The Sonics Vibracell^{TM} ultrasound (VC 505) horn was immersed in water at a depth (below the water level) of 1.5 in. The tip (1 in. i.d.) of the ultrasound horn was directed over the nozzle such that the flow of the solution was dispersed instantaneously into antisolvent by the vibrating (75% of 500 watt) surface of the tip. The solution was insonated for 15 min. The suspension was filtered using 0.2 micrometer filter paper (Sartorius), the precipitated drug particles were left to dry at room temperature, collected, and used for further studies.

3.2. Optimization of process variables

Effects of polymer concentration (0.0125, 0.025, 0.05, 0.1, 0.2, and 0.4 mg/ml), surfactant concentration (0.078, 0.156, 0.312, 1.56, and 6.24 mM), drug concentration (2.5, 5, 10, 15, 20, 30, and 35 mg/ml), time of insonation (2.5, 5.0, 7.5, 10.0, 12.5 and 15.0 min), antisolvent-to-solvent ratio (5:1, 10:1, 15:1, 20:1), and amplitude (25, 50, 75, and 100% of 500 watt) on particle size and PSD were studied. This was done by precipitating drug particles as in Section 3.1 except that the specified parameter was varied and its effect studied at different levels with keeping the other parameters fixed. For example, when the effect of polymer concentration was studied, it was varied (0.0125, 0.025, 0.05, 0.1, 0.2, and 0.4 mg/ml) while keeping the surfactant concentration fixed at 0.312 mM, drug concentration at 15 mg/ml, time of insonation at 15 min, anti-solvent-solvent ratio at 5:1, and amplitude at 75% of 500 Watt.

These fixed concentrations/conditions were selected in the middle of the range studied, since an optimum concentration/condition was expected, except for the antisolvent-to-solvent ratio. The increase in antisolvent-to-solution ratio was expected to increase the total volume of the liquid mixture, decrease mixing due to the decrease in the ultrasound energy per unit vol-

ume, and increase the particle size and the PSD. Therefore, the lowest ratio (5:1) was selected and fixed during the optimization of other parameters.
At first it was decided to study the effect of time of insonation up to 30 minutes, therefore, when studying the effect of other parameters, the time was fixed at 15 minutes, but after reconsideration, it was decided that 30 minutes is long for large scale production.

3.3. Characterization of precipitated drug particles

To compare the physicochemical characteristics of the drug before and after processing, drug particles were characterized as described in the following sections:

3.3.1. Particle size and particle size distribution measurements

The suspension of drug particles obtained was analyzed for particle size and PSD using a Microtrac S3500 (USA) Laser diffractometer. It measures volume-weighted particle size distribution over the size range 0.02550 to 2000 μm which typically includes d(10), d(50) and d(90) representing the % of particles below a given size (μm). The suspension was analyzed with dilution. A suspension of unprocessed gliclazide was prepared and analyzed for particle size and PSD in the same way.

3.3.2. Scanning electron microscopy

A field-emission SEM was used to observe the surface morphology of the unprocessed drug and of the precipitated drug particles. Images were obtained using an FEI Company-Inspect F50/FED (Eindhoven, Netherlands) after coating the particles with platinum using Emitech K550 X Sputter Coater (England).

3.3.3. Powder X-ray diffraction

PXRD patterns of unprocessed drug, precipitated drug particles, HPMC 4000, and SDS, were obtained at room temperature using Ultima IV (185 mm) X-ray diffractometer (Rigaku, Japan) operated at a voltage of 40 kV and a current of 40 mA. Samples were analyzed in the 2θ angle range of 3°–50°, scan step size of 0.02° (2θ), and scan step time of 0.5 s.

3.3.4. Differential scanning calorimetry

DSC thermograms of unprocessed drug, precipitated drug particles, HPMC 4000, and SDS, were obtained using DSC 204F1 Phoenix instrument. The powder samples were hermetically sealed in aluminum pans and heated at a constant rate of 20 °C/min, over a temperature range of 30-300 °C. The atmosphere was kept inert by purging nitrogen at the flow rate of 20 ml/min.

3.3.5. Fourier transform infra red spectroscopy

FTIR spectra of unprocessed drug, precipitated drug particles, HPMC 4000, and SDS were obtained on Shimadzu spectrophotometer. The spectra were scan over the wave range of 4650-400 cm^{-1}.

3.3.6. Flow properties

Flow properties of unprocessed drug and of precipitated drug particles were evaluated by calculating the compressibility index and the HR. A known weight of the material was passed through a sieve with apertures equal to 1 mm to break up any agglomerates, then introduced into a graduated cylinder without compacting. The powder was leveled carefully with a spatula and the volume was recorded as bulk volume (V_o). The cylinder was secured in the holder of Jolting volumeter (Stav 2003, UK) and then tapped for 10, 500 and 1250 taps and the corresponding volumes (V_{10}, V_{500}, and V_{1250}) were recorded. If there was no difference between V_{500} and V_{1250}, V_{1250} was considered as the tapped volume. Otherwise the tapping was continued until the difference between two measurements was less or equal to 2% and the tapped volume was recorded. Each experiment was repeated three times. The bulk and tapped densities were calculated and used to determine the compressibility index and the HR using the following equations:

$$\text{Compressibility Index} = 100 \times \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \quad (1)$$

$$\text{Hausner Ratio} = \frac{\rho_{tapped}}{\rho_{bulk}} \quad (2)$$

Where $\rho_{bulk} = Wt/V_{bulk}$ and $\rho_{tapped} = Wt/V_{tapped}$.

3.3.7. Drug loading percentage

A given weight of the precipitated drug particles was dissolved in 0.1 N NaOH. After diluting the sample, the concentration of the drug was determined spectrophotometrically at λ_{max} (225 nm) using a predetermined calibration curve. Solutions of SDS and of HPMC 4000 were scanned against an appropriate blank and they showed no interference at the λ_{max} of the drug (225 nm).
Drug loading (DL) % was calculated using Eq. (3):

$$DL\% = 100 \times \frac{\text{Weight of drug in precipitated drug particles}}{\text{Weight of the precipitated drug particles}} \quad (3)$$

3.4. In vitro dissolution studies

The dissolution of unprocessed drug was studied in an USP dissolution apparatus II. Samples (80 mg unprocessed gliclazide) were placed in a dissolution vessel containing 900 ml of the dissolution medium (0.1N HCL) kept at 37 ± 0.5 °C. The stirring rate was set at 100 rpm. At appropriate time intervals (5, 10, 15, 20, 30, 45, 60, 90 and 120 min), 5 ml samples were withdrawn and filtered using 0.45 μm Millipore syringe filters. Samples were replaced by fresh dissolution medium to maintain a constant volume (sink conditions). After diluting the sample, the concentration of dissolved drug in the medium was determined spectrophotometrically at λ_{max} (225 nm) using a predetermined calibration curve. The dissolution studies were done in triplicates. Dissolution from precipitated drug particles containing 80 mg of gliclazide, was studied in a similar manner and compared to that from the unprocessed drug.

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