ORIGINAL ARTICLE

Spray drying of nanoparticles to form fast dissolving glipizide

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Poor water solubility of pharmaceutical candidates creates a big barrier to development and clinical applications. In this study, glipizide as a poorly water soluble drug was precipitated as nanoparticles and processed by spray drying to produce fast dissolving powders. Nanosuspensions of glipizide were prepared using the sonoprecipitation technique in the presence of selected stabilizers. Sorbitol, mannitol, and microcrystalline cellulose (Avicel) were involved in the formulations as the carrier of drug nanoparticles for spray drying process. Physicochemical characteristics of nano and microparticles were determined as well as maximum saturation solubility and dissolution profile of processed powders. The screening data introduced the sodium lauryl sulfate as the better nanosuspension stabilizer. Particle size and yield of nanosuspension formulations were in the range of 262.2–498.8 nm and 65.50–95.21%, respectively. The particle sizes of spray dried powders were between 2.27 μm and 29.25 μm and dissolution of the drug from these micropaticles 58.45–81.65% during the first 5 min. Spray drying of glipizide nanosuspension would be a promising approach to enhance drug solubility as well as physicochemical properties.

Key words: *Avicel, glipizide, nanosuspension, spray drying, sugar carrier*

INTRODUCTION

Glipizide, a medium to the long acting anti-diabetic drug, belongs to second generation sulfonylurea and is commonly used in patients with diabetes mellitus Type II. It is practically insoluble in water (1.4 μg/mL) and comes under Group II of biopharmaceutical classification system. Poor water-soluble drugs such as glipizide face problems of low bioavailability as their dissolution are the rate limiting factor and, therefore, it becomes a requirement to improve the solubility for the formulation of dosage forms.[1-3]

During the last two decades, nano-sized particles have been developed to be capable candidates for enhancing the solubility of poorly water soluble drugs. Moreover, nanoparticle formation typically lead to a reduction in fed-fasted variability and also provide some inherent taste masking.[4,5] Due to these benefits, this technology has been quickly adopted by the industry, and a number of oral nanoparticulate products are now commercially available.[6]

The particles can be obtained either by size reduction of larger crystals, forming nanocrystals (top-down approach) or by building up particles obtained from precipitation of dissolved molecules (bottom-up approach).[7,8] Although "top-down" approaches are widely employed, the drawbacks associated with mechanical attritions processes, such as intensive energy use, introduction of impurities, inadequate control of particles size and electrostatic effects, promote greater interest toward "bottom-up" creation of nanoparticles.[9] Developing sonoprecipitation is believed to be one of the most effective bottom-up approaches to produce nanosuspensions as a colloidal dispersion of nanoparticles in an outer liquid phase.[10] The functioning principle of this technique is mainly based on the creation of bubbles (cavitations) followed by collapse which releases shock waves for nucleation. Ultrasonic waves were found to cause faster and more uniform nucleation, as well as the reduction of agglomeration.

Stability issues associated with nanosuspensions have been widely investigated and can be categorized as physical and chemical instabilities. Drug particles can either settle down or cream up in the formulation

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medium depending on their density. Another concern is agglomeration that achieve by the large surface area of nanoparticles and high total surface energy.[11]

A preferred approach to enhance the stability of nanosuspensions is the production of dried powders for reconstitution. In this manner, spray drying as a single step manufacturing process can be successfully applied to transform liquid nanosuspension to a dry powder with the appropriate size.[12] In addition to optimizing the process variables of spray drying, using proper excipients such as sugar-based excipients is considered as a rational approach to improve products' physical properties, as well as stability profiles.[13]

The present work is aimed toward enhancing the solubility and dissolution of glipizide by the formation of nanoparticle containing powders. In order to organize nanoparticles in solid dosage forms or dry powder formulations, nanosuspensions of glipizide were co-spray dried in the presence of different types and ratios of sugar-based carriers.

MATERIAL AND METHOD

Material

Glipizide, mannitol, sorbitol, and microcrystalline cellulose (Avicel) were purchased from Sigma-Aldrich Corporation, USA. Organic solvents, triethylamine, phosphoric acid, sodium hydroxide and polyvinylpyrrolidone (PVP) were obtained from Merck, Germany. Hydroxyl propyl methyl cellulose (HPMC) was supplied by Shin-etsu, Japan and sodium lauryl sulfate (SLS) were purchased from BASF, Germany.

Glipizide nanosuspension

Glipizide nanosuspensions were prepared by the sonoprecipitation method in the presence of different ratios of surfactants according to the Table 1. First, 25 mg of glipizide was dispersed in 25 mL of purified water containing the proper amount of surfactant and was dissolved by gradually addition of NaOH 1N under stirring (500 rpm) to increase pH up to 10. Nanosuspension was prepared using a probe sonicator (Heilscher, Germany) which was immersed in a drug solution subjected to the ice bath to prevent the sample temperature increase. The device operates at amplitude 90 and cycle 0.9 for 150 s. Precipitation started with decreasing pH by adding phosphoric acid 85% drop-wise (one drop per 30 s).

After preliminary screening of the efficacy of different stabilizers, the concentration of better surfactant and total mass of formulation were investigated according to Table 2.

Spray drying of nanosuspensions

Freshly prepared glipizide nanosuspensions were spray dried using B-191 mini spray dryer (Büchi labortechnik AG, Switzerland) in the presence of different types and ratios of carriers as shown in Table 3. Carriers were dispersed in distilled water and then glipizide nanosuspension was added to a final volume of 150 mL. The process parameters were set at inlet temperature of 120°C, an aspiration ratio of 88%, air flow rate of 550–600 L/h, and outlet temperatures in the range of 50–60°C. Spray drying process was conducted using a peristaltic pump at flow rates of 2 mL/min. After collecting the powders from receiving chamber and evaluating the yield percentage, they were stored in glass desiccators at room temperature for further investigations.

Physicochemical characterization

Particle size analysis

The mean hydrodynamic diameter (called Z-average) and polydispersity index (PDI) of the nanoparticles were measured by photon correlation spectroscopy (Malvern, UK) at 25°C. All the samples were diluted with double distilled water to create a suitable obscuration before analysis.

The size of spray dried particles was measured by the laser diffraction method (Malvern, UK) at obscurations between 0.18 and 0.20. For each sample, a small amount of powder

Table 1: Preliminary screening of the type and concentration of stabilizers

Formulation	Stabilizer	Concentration (mg/mL)	Size (nm)	PDI	Zeta potential
F_1	SLS	0.5	645±10	0.41±0.02	−44±2
F_2		1	383±5	0.21±0.06	−48.8±1
F_3		2	534±21	0.30±0.09	−49.9±4
F_4	Poloxamer	0.5	1173±3	1±0.03	0.9±0.01
F_5		1	1733±10	0.98±0.1	4.2±0.1
F_6		2	3007±12	0.98±0.6	4.3±0.5
F_7	PVP	0.5	2983±2	0.87±0.1	−0.8±0.1
F_8		1	4984±5	0.94±0.4	−0.5±0.2
F_9		2	4762±41	0.61±0.03	−0.3±0.2
F_{10}	HPMC	0.5	867±5	0.62±0.4	−0.1±0.05
F_{11}		1	910±21	0.21±0.07	−0.3±0.1
F_{12}		2	1024±16	0.54±0.04	−0.7±0.1
F_{13}	Tween80	0.5	911±45	0.70±0.2	−0.4±0.06
F_{14}		1	1098±21	0.66±0.3	−0.1±0.05
F_{15}		2	1033±19	0.40±0.3	−1.1±0.1

SLS: Sodium lauryl sulfate, PVP: Poly vinylpyrrolidone, HPMC: Hydroxyl propyl methyl cellulose, PDI: Polydispersity index

Table 2: Effect of different concentrations of SLS and total mass on the size of nanosuspension

Formulation	Drug content (mg)	SLS content (mg)	Total mass (mg)	Size (nm)
S_1	25	19	44	485±12
S_2		25	50	381±21
S_3		31	56	262±32
S_4	50	38	88	413±5
S_5		50	100	337±10
S_6		62	112	308±13
S_7	75	57	132	499±8
S_8		75	150	480±12
S_9		93	168	458±19

SLS: Sodium lauryl sulfate

Table 3: Different formulations of spray dried glipizide nanosuspension

Run	Carrier ratio (%)		
	Sorbitol	Mannitol	Avicel
R_1	100	0	0
R_2	75	25	0
R_3	50	50	0
R_4	25	75	0
R_5	0	100	0
R_6	0	75	25
R_7	0	50	50
R_8	0	25	75
R_9	0	0	100
R_{10}	25	0	75
R_{11}	50	0	50
R_{12}	75	0	25

(about 5 mg) was dispersed in 5 mL suitable non-solvent such as propanol, dichloromethane, and acetonitrile with the aid of the water bath sonicator (Starsonic 60, Italy) for 3 min. All measurements were carried out in triplicate.

Scanning electron microscopy

Morphological properties of glipizide nanosuspension and selected spray-dried formulations were studied using a scanning electron microscope (SEM, Hitachi model S-4160, Japan). Samples were spread on a stub and dried at 25°C and then sputtered with gold using a sputter coater (BAL-TEC, Switzerland).

Differential scanning calorimetry

A differential scanning calorimeter (DSC, Mettler Toledo, Switzerland) was used to obtain DSC thermal profile of unprocessed glipizide, lyophilized SLS containing nanosuspension powder and selected spray dried powders. All samples were weighed (4–9 mg) and placed in sealed aluminum pans and heated from 10 to 400°C at 100°C/min under nitrogen purge.

Dissolution studies

The drug release of each formulation was studied in phosphate buffer solution (PBS) at pH 7.4 as dissolution medium. About 10 mg of each spray dried formulation was dispersed in a screw-capped glass vial (100 mL) containing 50 mL of medium by shaking at 200 rpm and 37 ± 0.5°C in shaker incubator (Labotec, Germany). At predetermined time intervals (5, 10 and 15), about 1 mL of the dispersion was taken away and replaced with 1 mL of the fresh medium. The samples were filtered through 0.22 μm syringe filters. A reverse phase chromatography method was used for evaluation of the amount of dissolved glipizide using isocratic HPLC system (Waters, USA) and C_{18} column packing L_5 (5 μm, 15 cm). The mobile phase consisted of acetonitrile, distilled water, and triethylamine 0.01% (45:54:1, pH 3.5) at a flow rate of 1 mL/min with ultraviolet detection at 275 nm. The retention time was 7.2 min.

Statistical analysis

All experiments were performed in triplicate. The results were expressed as the mean ± standard deviation. Statistical significance of the results was determined using one-way analysis of variance (ANOVA), employing a confidence interval of 95%.

RESULTS AND DISCUSSIONS

Preliminary screening on the type and concentration of stabilizers

Sonoprecipitation technique was adopted to prepare nanosuspension of glipizide. To reduce agglomeration induced by the high surface energy of nanosized particles, different types, and concentrations of stabilizers were used in the formulation of nanosuspensions. As shown in Table 1, particle size in the formulations stabilized by SLS was significantly ($P < 0.05$) smaller than formulations containing poloxamer, PVP, HPMC, and tween80. It could be attributed to the higher viscosity of polymeric solutions due to the trap of water between opened chains of the polymers.[14] These viscous solutions need more energy for breaking up to small particles than solution containing small molecules of surfactants.

Furthermore, according to Table 1, it was found that SLS in the concentration of 1 mg/mL was more effective to control the size and PDI of particles. The mean particle size of this formulation was 383 ± 5 nm with PDI of 0.21 ± 0.06. Furthermore, it was observed that the zeta potential of formulations varied between negative to positive levels depending to the applied stabilizer. Zeta potentials in SLS containing formulations were the most negative values. This finding could be justified by the structure of SLS. The lipophilic dodecyl alkyls-CH_3 (CH_2) was oriented outside from the water surface while the hydrophilic-OSO_3 head groups were directed into the aqueous environment. When the concentration of sodium dodecyl sulfate reaches its corresponding critical micellar concentration (CMC) value, the dodecyl sulfate anions start to aggregate into the negatively charged globular micelles.[15]

Nanosuspension characterization

The effects of three levels of SLS amounts (19, 25, and 31 mg) on the particle size of nanosuspensions were studied. A sharp decrease in particle size from 485 ± 12 nm to 262 ± 32 nm [Table 2] was observed as SLS content increased from 19 mg to 31 mg. SLS exerts its stabilizing effect by adsorbing at the droplet interface and consequently, reducing surface tension and promoting mechanical and steric stabilization.

Surfactants by reduction of surface tension allow formation of smaller droplet and, as a result, small mean size of nanoparticles. Moreover, higher surfactant concentrations raise the viscosity of the aqueous phase and enhance hydrodynamic stabilization by preventing coalescence of droplets. Above CMC, the excess surfactant is available for droplet coverage and better hydrodynamic stability results in lower particle size.[16] Further increase in SLS content to 93 mg led to increment in particle size that was related to increase in viscosity[16] and difficulty of droplet breakage by sonication.[17]

Polydispersity index is an important parameter in nanotechnology; as it gives an indication about the width of particle size distribution and the long-term stability. A PDI value of 0.1–0.25 demonstrates a narrow size distribution.[9]

In addition, the effects of total solid mass in these formulations were investigated. As shown in Table 2, the lowest particle size (262.2 ± 32 nm) was observed in the formulation S_3 containing 31 mg SLS. The mean particle size of nanosuspensions increased at higher total mass.

Spray drying

To incorporate nanosuspensions into solid dosage forms such as tablets, capsules, and pellets, transformation of the liquid nanosuspensions into a dry powder is necessary. Technically, it can be achieved using established unit operations such as freeze-drying, spray-drying, pelletization or granulation[6] but, selection of the drying technology is important, because it needs to be ensured that the nanoparticles can be re-dispersed as separated particles and do not aggregate, which would lead to a loss of their special properties.

To embed glipizide nanoparticle in a carrier matrix in microparticlulate structure, the selected nanosuspension formulation was incorporated with appropriate sugar excipients. The effect of the ratio and type of these carriers on the properties of spray dried powder was studied.

Effect of carriers on the particle size

As illustrated in Figure 1, the mean particle size of spray dried powders varied in the range of 2.3–29.2 μm. The increase in the ratio of mannitol in the formulations resulted in the formation of larger microparticles. This finding could be explained by shell formation at increased concentrations; in which, saturation of mannitol at the surface of the drying droplet may be reached earlier, and particle shell formation takes place. A stable shell may then fix the apparent particle diameter at its borders.[18] On the other hand, changing the combination of sorbitol and Avicel in the formulations did not cause a great variation in particle sizes.

Effect of carriers on the yield

The yield of spray drying was in ranges of 11.2–66.1%. As shown in Figure 2, the yield of formulations containing mannitol and sorbitol was relatively low, and an increase in the ratios of these carriers resulted in the reduction of yield. Conversely, higher ratios of Avicel in the formulations improved the yield of the process. Hygroscopicity of sorbitol and thermoplastic nature of mannitol could be responsible for adhesion of powders to the drying chamber, pipings, and cyclone that results in low process yields.[19,20]

Physicochemical characterization

Morphology of processed particles

Surface morphology of nanosuspension and spray dried microparticles were evaluated by SEM Figure 3 represents near spherical shapes of glipizide nanoparticles in the selected nanosuspension. This micrograph confirms the result of photon correlation spectroscopy.

Scanning electron microscope images of microparticles indicate typical morphologies as expected for powders generated by spray drying.[21] Application of sorbitol as the main carrier in R_1 resulted in the formation of smooth surfaces particles with some degree of concavity [Figure 4a]. R_5 as a mannitol-based formulation showed agglomerated near spherical particles [Figure 4b]. Smooth surfaces of particles cause more interaction between particles as observed in other investigation.[19]

Avicel-based formulation (R_9) produced separated particles with corrugated surfaces [Figure 4c]. These corrugation on the particles prevents them from adhering tightly to each other.[22] Evaluation of Figure 4d and f reveals that the presence of Avicel in the formulations containing mannitol/sorbitol could be helpful to produce separated particles rather than agglomerations. Whereas, fused and aggregated particles were harvested for R_3 as the combination of mannitol and sorbitol [Figure 4e].

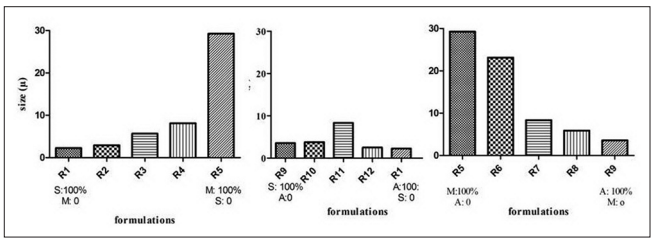

Figure 1: Effect of the carriers on particle size of spray dried powders. A: Avicel, M: Mannitol and S: Sorbitol

Thermal analysis of processed particles

Differential scanning calorimeter analysis was performed to assess the solid state of glipizide in the nano and microparticles. Figure 5 presents thermograms of unprocessed glipizide, SLS and lyophilized nanosuspension powder. The DSC profile of pure glipizide exhibits a single endothermic peak at an onset temperature of 216°C. This peak was appeared in lower intensity in nanosuspension thermogram. This fact could be justified by the lower crystalline structure of glipizide in nanosuspension[23] and partial crystallization of drug due to the SLS properties that facilitate surface-mediated nucleation of drug crystals.[24]

Unprocessed mannitol and sorbitol showed endothermic peaks at 164°C and 95°C, respectively [Figure 5]. In the spray dried samples of R_1, R_9, R_7, and R_3, the endothermic peaks of carriers and nanosuspension were disappeared completely that indicates amorphous particles[25] and absence of crystalline structure.[26]

Effect of carriers on drug dissolution

The dissolution profiles of spray dried powders and unprocessed glipizide are presented in Figure 6. The unprocessed glipizide was practically insoluble in the medium. Cumulative release after 15 min in formulations containing sorbitol or mannitol as a carrier was relatively low (58.4% and 81.6%, respectively) in comparison to the Avicel-based formulations; Where, increasing the ratio of Avicel to these carriers improved the maximum dissolved drug up to 100% in R_9.

When the ratio of Avicel in formulations raised the amorphous fraction in the particles increased or even completely amorphous particles were formed.[27] These amorphous particles dissolve faster than the crystalline particles.[28] Furthermore, Avicel has a tendency to develop static charges with increased moisture content, and it has a fast wicking rate of water and a small elastic deformation. Both these properties facilitate its disintegration effects.[29,30] Hence, Avicel carrier acts as a dissolution enhancer.[31]

CONCLUSION

Spray drying of glipizide nanosuspension would be a promising approach to enhance drug solubility as well as physicochemical properties. The ratio and type of the

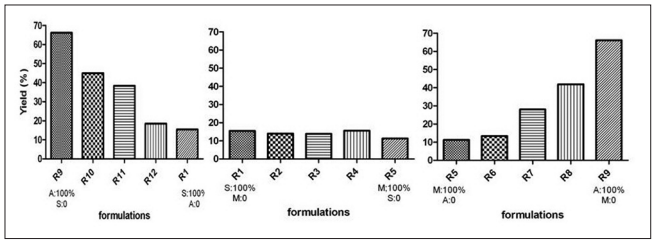

Figure 2: Effect of type and ratio of carriers on the yield of spray drying process; A: Avicel, M: Mannitol and S: Sorbitol

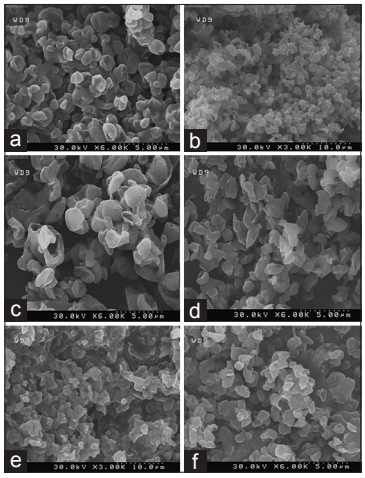

Figure 4: Scanning electron microscope images of spray dried powder contain a: R1, b: R5, c: R9, d: R11, e: R3, f: R7

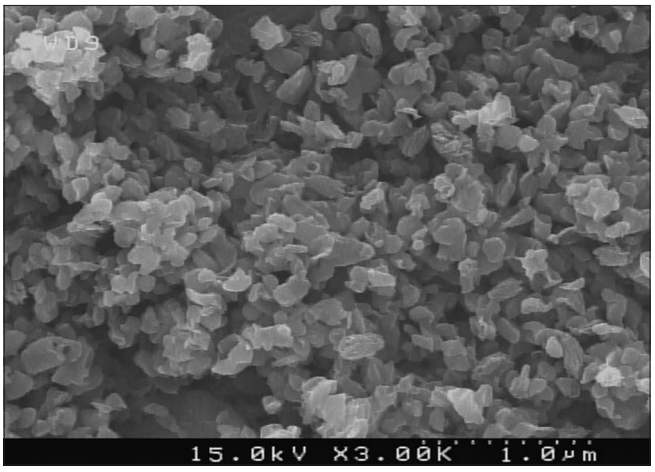

Figure 3: Scanning electron microscope image of selected nanosuspension

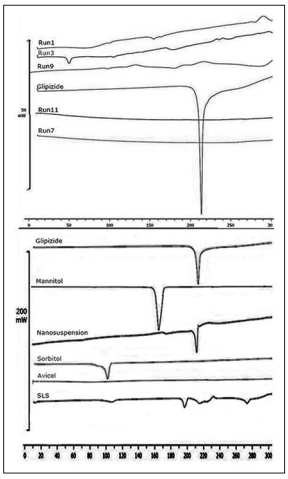

Figure 5: Differential scanning calorimeter thermogram of nanosuspension contains sodium lauryl sulfate, glipizide, and some spray-dried formulations containing sorbitol, mannitol, and Avicel as a carrier(s) and nanosuspension

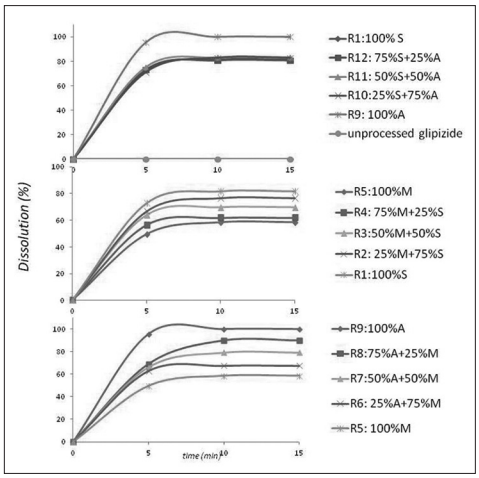

Figure 6: Dissolution profile of glipizide form different microparticles

stabilizer are important parameters that could affect the size and physicochemical properties of nanosuspension. In addition, type and ratio of carriers in the spray drying process showed a great effect on the properties of particles. In this study, Avicel was introduced as a capable carrier to improve the yield of the spray drying procedure, dissolution profile of co-spray dried glipizide nanoparticles, and other properties of produced powder.

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