European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 441–446

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Investigation of preparation parameters of nanosuspension by top-down media milling to improve the dissolution of poorly water-soluble glyburide

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ARTICLE INFO

Article history:
Received 24 January 2011
Accepted in revised form 16 March 2011
Available online 23 March 2011

Keywords:
Bead mill
Zeta potential
Nanosuspension
Mean particle size *d*(90)
X-ray powder diffraction
Unmilled drug

ABSTRACT

The objective of this study was to identify and optimize formulation and process variables affecting characteristic and scale-up of nanosuspension manufacturing process on bead mill considering industrial perspective. Formulation factors evaluated were ratio of polymer to drug and ratio of surfactant to drug, whereas process parameters were milling time and milling speed. Responses measured in this study include zeta potential and mean particle size *d*(90). The test revealed that ratio of polymer to drug and milling speed have significant effect on zeta potential whereas milling time and milling speed have significant effect on the particle size distribution of nanosuspension. The X-ray powder diffraction pattern of drug milled at high and low speed reveals no form conversion when compared with unmilled drug. The formulated nanosuspension has shown a faster dissolution profile (98.97% in 10 min), relative to that of raw glyburide (18.17% in 10 min), mainly due to the formation of nanosized particles. The ANOVA test revealed that there was no significant difference in the dissolution profiles of fresh and aged nanosuspension. These results indicate the suitability of formulation procedure for preparation of nanosized poorly water-soluble drug with significantly improved in vitro dissolution rate and thus possibly enhance fast onset of therapeutic drug effect.

1. Introduction

Nanosuspensions are liquid dispersion consisting of solid drug nanoparticles, which are stabilized by polymer and/or surfactant. Nanosizing has been proven to be an effective tool for an active moiety considered as "brick dust candidate". There are two main approaches for formulating a nanosuspension i.e., top-down and bottom up technology. The bottom up technology involves dissolving drug in a solvent, to which a nonsolvent is then added to precipitate the crystals .The top-down approach relies on mechanical attrition to render large crystalline particles into nanoparticles. The 'Top-Down Technologies' include media milling (Nanocrystals®), high-pressure homogenization in water (Dissocubes®), high-pressure homogenization in nonaqueous media (Nanopure®) and combination of precipitation and high-pressure homogenization (Nanoedege®). Table 1 lists some of the FDA approved products relying on nanotechnology. Nanosuspensions for oral route are mainly characterized by mean particle size *d*(90), zeta potential, crystalline status, dissolution velocity, and saturation solubility. A particle of less than 400 nm is considered to be acceptable for a nanosuspension to be administered intravenously [1]. For a physically stable nanosuspension solely stabilized by electrostatic repulsion, a zeta potential of ±30 mV is required as a minimum. In the case of a combined electrostatic and steric stabilization, a rough guide line of ±20 mV is sufficient [2]. The crystalline structure of nanosuspension is important for drugs existing in different polymorphic forms. This is mainly confirmed by DSC, X-RD, or wide angle X-ray analysis (WAXS). Dissolution velocity and saturation solubility are generally performed using official pharmacopoeial methods. The stability and robustness of a nanosuspension are mainly governed by various formulation and process variables. Selection of proper steric and electrostatic stabilizer and its optimum quantity plays a major role in formulating a nanosuspension. Commonly used steric stabilizer includes hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), povidone (PVP K-30), and pluronics (F68 and F127) whereas electrostatic

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doi:10.1016/j.ejpb.2011.03.014

Table 1
FDA approved products based on nanoparticles technology.

Product, active ingredient, Company	Manufacturing approach
Rapamune®, Sirolimus, Wyeth	Top-down, media milling
Emend®, Aprepitant, Merck	Top-down, media milling
Tricor®, Fenofibrate, Abbott	Top-down, media milling
Megace®, ES, Megestrol acetate Par Pharmaceuticals	Top-down, media milling
Triglide®, Fenofibrate Skye Pharma	Top-down, high-pressure homogenization

stabilizer includes polysorbate (Tween-80), sodium lauryl sulfate (SLS). A suitable working polymer to drug ratio (steric stabilizer) is from 0.05:1 to 0.5:1 [3]. At high stabilizer concentrations, well above of the plateau of the adsorption isotherm, electrostatic stabilizers can cause a decrease in the diffuse layer leading to a decreased zeta potential and decreased physical stability. Electrolytes are present in the gastrointestinal tract, and the contact of the nanocrystals with these electrolytes cannot be avoided. Electrostatic stabilization is reduced in its efficiency in an electrolyte containing environment. Therefore, it is important to find the optimal concentration for a stabilizer. Processing factors for formulating a stable nanosuspension vary based on the equipment selected for manufacturing. As seen from Table 1, majority of products existing in market are based on media milling technique due to its many advantages over high-pressure homogenization. Therefore, scale-up of a nanosuspension using bead mill with varying operating capacity from 250 mL to 4 L and more requires a better understanding of formulation and process variables. A major emphasis should be given to increase the solid content (API) in nanosuspension, which will decrease the processing time and in turn also decrease the drying time while converting it to a solid dosage form.

Apart from this, several research articles are available for better understanding of nanocrystals formulated by other than media milling technology. But most of the products existing in market are developed based on the media milling technique [4].

High-pressure homogenization relies on the forcing of a suspension through a small gap which makes miniaturization of this technology less straightforward. Media milling, on the other hand, can be performed by agitation of devices containing the starting suspension and milling media. Furthermore, nanosuspension production by media milling is characterized by its ease of scale-up [5], making results generated on nanosuspensions in downscaled designs valuable and was therefore selected for this study.

Glyburide is used as a model drug for this study. The aim of our research work was therefore to investigate the feasibility of preparation of a glyburide nanosuspension using media milling technique, in order to achieve fast dissolution, which would presumably yield quick onset of the peak plasma concentration. The second aim of this work was the study of the effects of different preparation conditions, added stabilizers, and drying methods on formulated nanosuspensions with glyburide and to investigate the possibility to change its physico-chemical properties and improve its dissolution rate.

2. Materials and methods

2.1. Materials

Glyburide USP used in this study was manufactured by Dr. Reddys Laboratories Limited, Hyderabad, India. Hydroxypropyl methylcellulose 6cps (HPMC) was purchased from Samsung fine chemicals Co., Ltd., Korea, and sodium lauryl sulfate (SLS) was purchased from Stepan Co., USA. Purified water USP was used in this study. Lutrol F68 (Poloxamer 188) and polyvinylpyrrolidone (PVP) K-25 were from BASF (Ludwigshafen, Germany); Tween-80 (polysorbate 80) was supplied by Rankem, India. Other laboratory chemicals used, such as sodium hydroxide and potassium dihydrogen phosphate, were purchased from Sigma–Aldrich (Steinheim, Germany) and were of analytical grade.

2.2. Solubility testing of raw glyburide

The solubility of glyburide in water and in aqueous solutions of different stabilizers was determined by addition of excess of the drug to the solvent, after which the mixture was stirred on a magnetic stirrer at 25 °C for 24 h, then filtered (cutoff 0.45 μm, Minisart SRP 25, Sartorius, Germany), and the content of dissolved drug was analyzed spectrophotometrically at 230 nm (Shimadzu, UV-1800, Double beam UV–Visible spectrophotometer, Japan). Each sample was analyzed in triplicate.

2.3. Preparation of nanosuspension by top-down, media milling

Nanosuspension preparation involves two main steps: the first one is uniform dispersion of drug and stabilizers in dispersion media and second one is particle size reduction in milling chamber. Glyburide, HPMC 6cps, and SLS were dispensed (Table 2) and added sequentially to purified water under stirring using Heidolph mixer (Model: RZR2051 Control, Rose Scientific Ltd., Alberta, Canada) operated at 500 rpm to form a uniform dispersion. This suspension was loaded in milling chamber of bead mill (Model: Lab Star 1, Netzsch Mill, Germany) for particle size reduction. The milling operation was performed with the suspension fed at a rate of 100 mL/min. The operating parameters for bead mill are as follows: fed rate, 100 mL/min; milling speed, 2800 rpm; milling time, 6.5 h; product temperature, 18–20 °C; and milling media, 0.2-mm yttrium-stabilized zirconium beads. The milling operation was performed in a recirculation mode.

The initial unmilled suspension of Glyburide (referred as SPD-REF-UM) and the nanosuspension were dried using spray dryer (Spray Dryer Model: LU 222, Labultima, Mumbai, India) under following set of conditions: inlet temperature, 85 °C; outlet temperature, 60 °C; feed rate, 2.5 mL/min; and atomization pressure, 2 kg/cm^2. The spray-dried API was collected and used for further studies. This spray-dried nanosuspension is referred as SPD-NS – M in the following text.

2.4. Study of ratio of polymer to drug, ratio of surfactant to drug, milling time, and milling speed

Initial screening trials were carried out for evaluating the formulation and processing aspects of nanosuspension. Various factors like concentration of drug, ratio of polymer to drug, ratio of surfactant to drug, solvent for nanosuspension, milling media, volume of milling media, milling time, and milling speed were identified as critical to give a product in nanorange and with required stability. The results from the initial screening trials suggested that ratio of polymer to drug, ratio of surfactant to drug, milling time,

Table 2
Formula composition of nanosuspension batches.

Ingredients	Quantity/batch (g)
Glyburide	10.0
HPMC 6cps	1.6–8.0
SLS	0.32–0.96
Purified water qs	

qs, Quantity sufficient to 250 g.

and milling speed are the main factors, which affects the particle size and zeta potential of the nanosuspension.

The four factors identified for this study were as follows: ratio of polymer to drug, ratio of surfactant to drug, milling time, and milling speed. The concentration of drug, type of polymer, type of surfactant, milling media, volume of milling media, solvent i.e., purified water was kept same for all the experiments. Table 2 lists out the formula composition of nanosuspension.

2.5. Particle size measurement

The particle size of nanosuspension was measured using Malvern Zetasizer ZS200. Each sample was measured three times. The average values were employed for the calculations of the response surfaces.

2.6. Zeta potential

The zeta potential of nanosuspension was measured using Malvern Zetasizer ZS200 at 25 ± 0.5 °C. Each sample was measured three times. The average values were employed for the calculations of the response surfaces.

2.7. Determination of drug content in powder samples

After milling (SPD-NS – M), some amount of glyburide will be lost. Therefore, glyburide content in the dried sample was determined by dissolving 100 mg of dried sample (e.g., containing glyburide, HPMC, and SLS) in 100 mL of phosphate buffer solution (pH 7.4 ± 0.1), stirring the solution on a magnetic stirrer (400 rpm) at room temperature for 24 h, filtering, and analyzing spectrophotometrically at 230 nm. Each sample was prepared and analyzed in triplicate.

2.8. In vitro dissolution studies of glyburide

The dissolution of powder samples of SPD-REF-UM and SPD-NS – M**,** containing the same amount of drug (5 mg), was determined according to the Eur. Ph. 6th Ed. paddle method (Erweka DT 6, Germany). A concentration of 900 mL of phosphate buffer (0.05 M) solution (pH 7.5 ± 0.1) was used as a dissolution medium at 37 ± 0.5 °C, and the rotation speed of the paddles was 50 rpm. At predetermined time intervals, 5 mL of samples was withdrawn and immediately filtered (cutoff 0.2 μm, Minisart SRP 25, Sartorius, Germany) and the amount of dissolved drug was determined spectrophotometrically. Withdrawn samples were replaced with 5 mL of fresh medium.

2.9. X-ray powder diffraction analysis

Initial unmilled suspension of glyburide and nanosuspension milled at high speed (3500 rpm) and low speed (2500 rpm) were dried using spray dryer (Spray Dryer Model: LU 222, Labultima, Mumbai, India) under following set of conditions: inlet temperature, 85 °C; outlet temperature, 60 °C; feed rate, 2.5 mL/min; atomization pressure, 2 kg/cm^2. The PXRD pattern of samples was recorded using X-ray diffractometer (Bruker axs, D8 Advance) with a Cu line as the source of radiation. Standard runs using a 40-kV voltage, a 40-mA current, and a scanning rate of 0.013° min^{-1} over a 2 μm range of 3–45° were used.

2.10. Aging studies

The nanosuspension was stored at 25 °C and 75% relative humidity for up to 6 months. The stored nanosuspension was evaluated using dissolution test. The dissolution data (in pH 7.5 phosphate buffer) of aged nanosuspension were compared with those of freshly prepared nanosuspension.

2.11. Statistical analysis

All the data were statistically analyzed by analysis of variance or Tukey's multiple comparison test. Results are quoted as significant where $P < 0.05$.

3. Results and discussions

3.1. Solubility testing of raw glyburide

Table 3 shows that glyburide has shown maximum solubility in 0.5% sodium lauryl sulfate.

3.2. Effect of ratio of polymer to drug, ratio of surfactant to drug, milling time and milling speed on zeta potential and particle size distribution

For zeta potential (E), the ratio of polymer to drug (A) and milling speed (D) were identified as significant model terms, whereas for particle size distribution (F), milling time (C) and milling speed (D) were identified as significant model terms. Zeta potential is the potential at the hydrodynamic shear plane and can be determined from particle mobility under an electric field. The mobility will depend on surface charge and electrolyte concentration. As can be seen from Table 4, the zeta potential values increase at low level of ratio of polymer to drug where the level of ratio of surfactant (B) to drug is high. At low level of ratio of polymer to drug, the particle surface of drug is not covered so densely with HPMC, due to which SLS has more access to the surface of drug if the concentration of HPMC is lower. Adsorption of SLS onto the particle surface leads to high zeta potential value. The zeta potential value of nanosuspension decreases at high level of ratio of polymer to drug, irrespective of ratio of surfactant to drug. If the surface of the particles is covered with HPMC, there will be less electrostatic interaction with SLS than if the negatively charged glyburide surface is exposed, this is why the zeta potential goes down. Consequently, the measured zeta potential is lower. In such cases, zeta potentials

Table 3
Solubilities of glyburide in different solvents.

Solvent	Glyburide solubility (μg/ml) (Mean ± SD) (n = 3) [a]
Water	4.4 ± 0.70
0.5% Tween-80	9.0 ± 0.14
0.5% Poloxamer 188	6.3 ± 0.16
0.5% PVP K-25	4.0 ± 0.90
0.5% Tween-80–PVP K-25 (1:1)	7.6 ± 0.30
0.5% Tween-80–Poloxamer 188 (1:1)	8.2 ± 0.14
0.1% Sodium lauryl sulfate (SLS)	8.32 ± 0.65
0.25% Sodium lauryl sulfate (SLS)	12.48 ± 0.53
0.5% Sodium lauryl sulfate (SLS)	16 .0 ± 0.38
0.75% Sodium lauryl sulfate (SLS)	20.10 ± 0.18
1.0% Sodium lauryl sulfate (SLS)	24.56 ± 0.35
0.1% HPMC	6.12 ± 0.45
0.25% HPMC	8.62 ± 0.22
0.5% HPMC	10.36 ± 0.54
0.75% HPMC	12.42 ± 0.55
1.0% HPMC	15.12 ± 0.88
2.0% HPMC	16.23 ± 0.29
4.0% HPMC	17.98 ± 0.58
6.0% HPMC	21.23 ± 0.38
8.0% HPMC	23.41 ± 0.46

[a] Number of replicates of UV measurements (n) = 3.

Table 4
Effect of ratio of polymer to drug, ratio of surfactant to drug, milling time and milling speed on zeta potential and mean particle size *d*(90).

Run	Ratio of polymer (HPMC) to drug (g)	Ratio of surfactant (SLS) to drug (g)	Milling time (h)	Milling speed (rpm)	Zeta potential (mV)	MPS *d*(90) nm
1	4.8	0.64	4.5	2950	−21.7	292
2	4.8	0.96	6.0	2950	−22.4	237
3	1.6	0.64	3.0	2950	−33.2	268
4	8.0	0.64	4.5	2500	−12.1	330
5	1.6	0.64	4.5	2500	−25.5	451
6	4.8	0.64	4.5	2950	−13.7	330
7	4.8	0.64	3.0	3400	−5.46	255
8	4.8	0.64	6.0	3400	−22.4	223
9	1.6	0.96	4.5	2950	−25.0	320
10	1.6	0.64	4.5	3400	−28.4	251
11	8.0	0.96	4.5	2950	−16.6	318
12	4.8	0.96	4.5	2500	−23.9	302
13	4.8	0.96	3.0	2950	−18.7	258
14	8.0	0.64	6.0	2950	−19.5	295
15	8.0	0.32	4.5	2950	−16.0	366
16	8.0	0.64	3.0	2950	−17.2	425
17	4.8	0.64	3.0	2500	−11.6	432
18	8.0	0.64	4.5	3400	−17.0	232
19	4.8	0.32	4.5	2500	−17.9	355
20	1.6	0.32	4.5	2950	−27.5	362
21	4.8	0.32	4.5	3400	−24.0	240
22	4.8	0.96	4.5	3400	−24.3	251
23	4.8	0.32	6.0	2950	−23.5	235
24	4.8	0.32	3.0	2950	−21.4	280
25	4.8	0.64	6.0	2500	−15.3	254
26	1.6	0.64	6.0	2950	−29.3	215

g, gram; h, hours; rpm, rotation per minute; nm, nanometer; mV, mill volts; MPS *d*(90), mean particle size *d*(90).

of about 20 mV are still sufficient to fully stabilize the system in combination with steric stabilization.

Table 4 shows the effect of ratio of polymer to drug and milling speed on zeta potential value. It was observed from the table that zeta potential value increases at high milling speed and lower polymer concentration. The probable reason for this may be that due to high milling speed the adsorption of steric and electrostatic stabilizer is more, which increases the particle mobility and zeta potential value. The zeta potential values increase at low level of ratio of polymer to drug where the level of milling time is high (Table 4). The mean particle size *d*(90) of nanosuspension decreases as the milling time and milling speed increase (Table 4). The minimum value of mean particle size *d*(90) is 213.0 nm at the higher milling time and milling speed. The probable reason for this may be high energy and shear forces generated as a result of the impaction of the milling media with the drug which provides the energy input to break the microparticulate drug into nanosized particles.

As can be seen from Table 4, the mean particle size *d*(90) of nanosuspension decreases at the lower polymer concentration. The probable reason for this may be at lower polymer concentration collision of drug particles due to high impaction of milling media is increased, which in turn decreases the mean particle size *d*(90) of nanosuspension. Moreover, at higher polymer concentration, the viscosity of polymer increases drastically, and this alters or hinders the processing of nanosuspension on bead mill. Issues such as increase in product temperature and increase in pressure on the bead mill were also observed during manufacturing nanosuspension with high polymer to drug ratio and high milling speed. These state that nanosuspension with high polymer to drug ratio to be milled at higher milling speed is unsuitable for manufacturing and scale-up. But an attempt was carried out to overcome this issue by operating the bead mill at lower speed for initial 10 min and further increasing the speed slowly. The milling time also shows a prominent effect on the mean particle size *d*(90) of nanosuspension even at high polymer concentration (Table 4).

3.3. Optimization of formulation and processing parameters

Optimization of nanosuspension was performed to find the levels of ratio of polymer to drug (A), ratio of surfactant to drug (B), milling time (C), and milling speed (D), which gives zeta potential from −20 to −25 mV range and mean particle size *d*(90)of 350–400 nm. Under this study, the predicted zeta potential and mean particle size *d*(90) were obtained in required range at A, B, C, and D values of 3.9 (g), 0.40(g), 3.8 (h), and 2563.0 (rpm), respectively, for a batch size of 250 g (Table 5). By using these values of factors, three different batches of nanosuspensions were prepared. The values of observed zeta potential and mean particle size *d*(90) were in very close agreement to the predicted one.

3.4. In vitro dissolution studies of glyburide

In order to ascertain whether the goal of improving the rate of dissolution of glyburide is achieved, the results of in vitro dissolution of different glyburide samples are shown in Fig. 1. The rate of dissolution of unmilled glyburide (SPD-REF-UM) was very low: Only 18.17% of the drug was dissolved in the first 10 min; only 63.18% of the glyburide was dissolved after 60 min. The formulation of glyburide nanosuspension (SPD-NS – M) significantly improved the dissolution rate, since almost 100% of the drug was dissolved in the first 10 mins. The surface-active agents may have contributed to the increase in dissolution rate due to the improved wettability and solubility of the drug.

3.5. Effect of milling speed on the powder X-ray diffraction pattern of API

The powder X-ray diffraction study of spray-dried nanosuspension operated at high milling speed and low milling speed showed

Table 5
Optimized formula composition of nanosuspension batches.

Ingredients	Quantity/batch (g)
Glyburide	10.0
HPMC 6cps	3.9
SLS	0.40
Purified water qs	

qs, quantity sufficient to 250g.

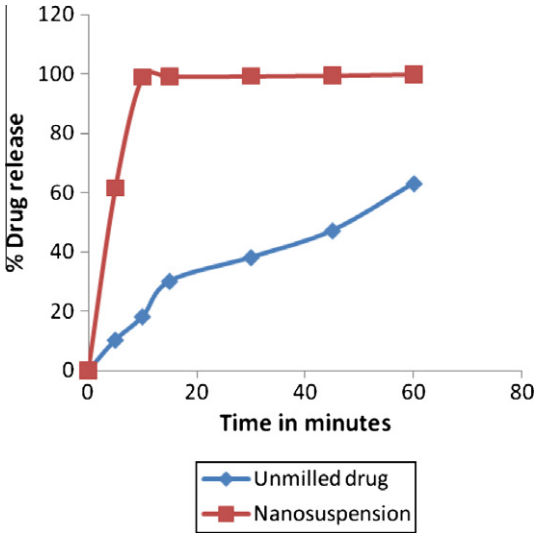

Fig. 1. Mean dissolution profiles of nanosuspension (SPD-NS – M) and unmilled glyburide (SPD-REF-UM). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

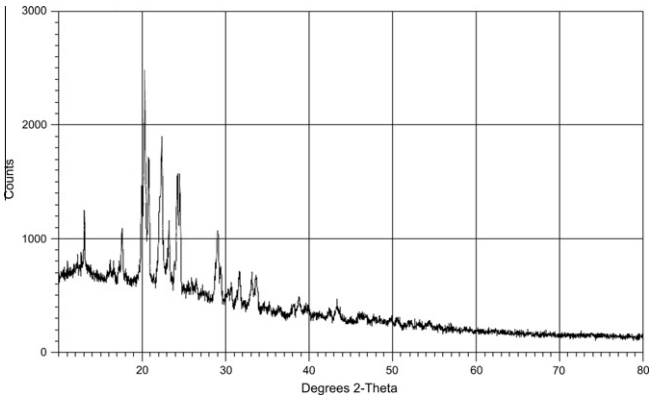

Fig. 2a. X-RD pattern of unmilled drug.

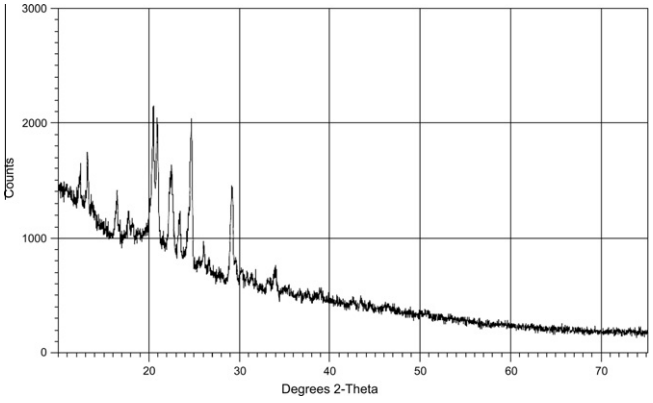

Fig. 2b. X-RD pattern of nanosuspension at low milling speed.

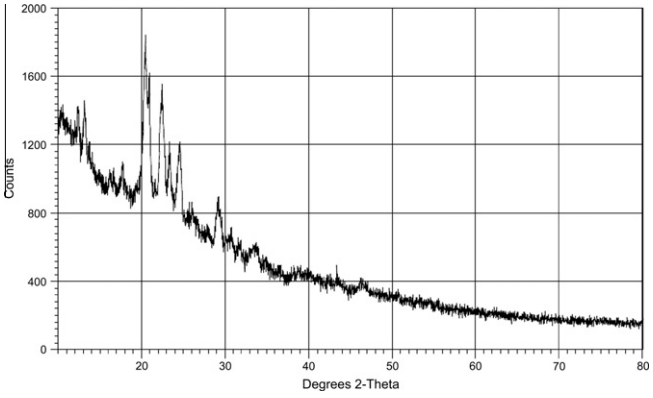

Fig. 2c. X-RD pattern of nanosuspension at high milling speed.

no significant shift in the main peaks when compared with initial unmilled drug. The characteristic peaks for milled drug were observed at same 2θ value as those of unmilled drug. A slight decrease in intensity of peaks was observed with spray-dried nanosuspension operated at higher milling speed. Figs. 2a–c show the X-RD pattern of unmilled drug, spray-dried nanosuspensions at low speed, and spray-dried nanosuspensions at high speed.

3.6. Aging studies

In order to study the effect of aging on dissolution profile of glyburide nanosuspension (SPD-NS – M), the nanosuspension was kept at 25 °C/75% relative humidity for 6 months. Then, dissolution

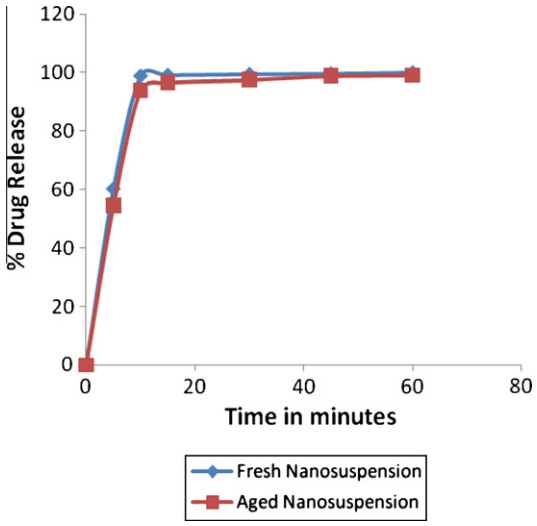

Fig. 3. Mean dissolution profiles of aged and fresh nanosuspensions of glyburide. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

rate was measured. The results revealed that the dissolution rates of nanosuspension were not affected by the humid condition, as there was no significant difference ($P > 0.05$) in dissolution rates of aged nanosuspension compared with the fresh nanosuspension (P value 0.49 which was greater than 0.05). Fig. 3 shows the dissolution profile of fresh and aged liquisolid tablets. Although the aged nanosuspension appears to have lower dissolution rate than the fresh nanosuspension in the graph, similarity factor (F_2) of the two release profiles was 54.18, indicating acceptably similar profiles.

4. Conclusion

Optimization of nanosuspension using media milling approach is a complex process since it involves large number of factors that affects the characteristic of nanosuspension. From this study, it was concluded that polymer concentration (ratio of polymer to drug) and milling speed play a significant role in controlling the zeta potential of nanosuspension. Milling time and milling speed were considered to be significant factors, which affected the mean particle size $d(90)$ of nanosuspension. The study also helped in identifying certain formulation and processing parameters, such as high polymer concentration and high milling speed, which may affects the manufacturing of nanosuspension at higher scale. Zeta potential of the nanosuspension was found to dependent more on the polymer concentration compared with surfactant concentration. The X-ray diffraction study revealed that milling of nanosuspension at high speed and for long period of time did not show any form conversion of drug. The dissolution data revealed that the nanosuspension formed by top-down media milling enhanced the dissolution rate. This suggests that the increased dissolution rate for the nanosuspension is primarily due to the reduction in the particle size. These findings indicate the suitability of formulation procedure for preparation of nanosized poorly water-soluble drug with significantly improved in vitro dissolution rate, and thus possibly enhance fast onset of therapeutic drug effect.

Acknowledgments

We are so much obliged to the Chancellor and Management of Karpagam University, Coimbatore, for providing the facilities to

carry out the aforementioned work. We also thank Dr. Subburaju T., Principal, Karpagam College of Pharmacy, Coimbatore, Dr. Tamizh Mani T., principal, Bharathi College of Pharmacy, Mandya and Indian Institute of Science, Bangalore, to provide the needful support.

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