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Research Article

Formulation and Physical characterization of microcrystals for dissolution rate enhancement of Tolbutamide

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ABSTRACT

Tolbutamide (TBM) is a first-generation sulphonylurea, used for treatment of non-insulin dependent diabetes mellitus. Tolbutamide is practically insoluble in water and its dissolution is the rate-limiting step for its absorption, which leads variable bioavailability. The aim of this investigation was to enhance the dissolution rate of Tolbutamide by formation of microcrystals using solvent change method. The in situ micronization process was carried out using solvent change method in the presence of Polyvinylpyrrolidone (PVP) as stabilizing agents that limits the size of the particles generated. TBM was dissolved in methanol and the stabilizing agent in water (as non-solvent). The non-solvent was poured rapidly into the drug solution under stirring by a magnetic stirrer, and the resultant was oven-dried. Microcrystals were characterized by optical microscopy, SEM, FTIR, DSC, XRD and in vitro powder dissolution study. TBM microcrystals showed narrow particle size and change in crystalline shape from rod-shape to. FTIR and DSC results showed no interaction between the drug and the stabilizer. XRD diffractograms of microcrystals showed smaller peak height than untreated TBM indicates that crystal habit modification occurred in the microcrystals without any polymorphic changes. Negative Gibb's free energy change represented spontaneous solubility of microcrystals. Dissolution efficiency of TBM microcrystals at 15 min. ($DE_{15\%}$) was increased about 9 times. Microcrystals were found to have good flow property.

Keywords: Microcrystal; Solvent Change Method; Dissolution Efficiency; Tolbutamide

1. INTRODUCTION

More than 40% of active substances during formulation development by the pharmaceutical industry are poorly water soluble (M. Martinez et al., 2002). Poor water solubility, which is associated with poor dissolution characteristics. Dissolution rate in the gastrointestinal tract is the rate limiting factor for the absorption of these drugs, and so they suffer from poor oral bioavailability (G.L. Amidon et al., 1995). For BCS class II-drugs, the dissolution rate is the limiting factor for the drug absorption rate (R. Löbenberg et al., 2000). An enhancement in the dissolution rate of these drugs can increase the blood-levels to a clinically suitable level.

Several techniques are commonly used to improve dissolution and bioavailability of poorly water-soluble drugs, such as size reduction (Perrut et al., 2005), the use of surfactants (Raghavan et al., 2001), the formation of solid dispersions (Leuner and Dressman, 2000), complexation with cyclodextrins, and the transformation of crystalline drug to amorphous state (Goddeeris et al., 2008).

In addition to the general solubility enhancement techniques described above, drug particle size reduction has often been used, in regards to the Noyes–Whitney and Ostwald–Freundlich equations, to enhance dissolution of poorly water-soluble compounds (Mosharraf and Nyatrom et al., 1995). Many approaches have been attempted to produce microparticles, including milling (Muller et al., 1996), supercritical fluid technique (Steckel et al., 1997) and solvent change method (N. Rasenack et al., 2003). Physical methods such as milling and grinding are successful in particle size reduction; however the particle size uniformity is not achieved and extremely inefficient due to high energy input (E.L. Parrott et al., 1990). Disruptions in the crystal lattice can cause physical or chemical instability. Micronized powders with a higher energetic surface show poor flow property and broad size distribution (Muller et al., 1996). Supercritical fluid technique is believed to be attractive methods for the size reduction, providing particles with narrow size distribution. However, they also have the limitations of low yield and high equipment cost (Wang et al., 2007).

Therefore, in recent years, solvent change method (antisolvent precipitation method) has been used for microcrystallization of drugs in the presence of excipients

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for increasing the dissolution rate of poorly water soluble drugs (N. Rasenack et al., 2003). Particle size reduction is achieved because adsorption of excipients onto the particle surface that inhibits particle growth (Lechuga-Ballesteros et al., 1995a). Crystal morphology may be altered by preferential adsorption of stabilizing agent onto specific faces of the growing crystal (Lechuga-Ballesteros et al., 1995b). Powder wettability can be increased through adsorption of hydrophilic stabilizing agent. Thus it is clear that precipitation in the presence of stabilizing agent can have a positive effect on dissolution rate. This technique is a rapid, easy to handle, needs only common equipment and direct process (N. Rasenack et al., 2002), which can be performed with ease.

Tolbutamide is widely used as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (type II). It has a low solubility in water and gastric fluids, which determines a low dissolution rate and hence inter individual variability on its bioavailability (Miralles et al., 1982). The aim of this study is to prepare and characterize tolbutamide microcrystals and optimize the solvent ratio and stabilizing agent concentration.

2. MATERIALS AND METHODS

2.1. Materials

Tolbutamide ((1-butyl-3-(p-tolysulfonyl) urea (TBM), $C_{12}H_{18}N_2O_3S$, Melting point [mp] = 126° C to 130° C, MW = 270.349) was provided as a gift sample by Sanofi Aventis Pharma Limited, Ankleshwar. PVP K_{30} LR was purchased from S d fine – chem limited, Mumbai. Potassium phosphate monobasic AR was purchased from Astron Chemicals (India) Pvt. Ltd, Ahmedabad. Sodium hydroxide (pellets) and methanol (CH_3OH, HPLC–Spectro grade, bp = 64.7° C, MW = 32.04) were purchased from S d Fine – Chem limited, Mumbai. Double distilled water was used throughout the study.

2.2. Optimization of solvent change precipitation procedure

The solvent change precipitation [SC] was conducted by instantaneously mixing two liquids in the presence of a stabilizing agent. The organic phase (solvent phase) was a methanolic solution of tolbutamide at (8.8 gm/50ml), a PVP K_{30} LR was selected as a stabilizing agent in the aqueous phase (N. Rasenack et al., 2003).

The non-solvent (aqueous phase) was poured rapidly from a beaker into the methanolic drug solution under stirring using a magnetic stirrer. The process was carried out at room temperature. The effect of experimental variables on the yield of the precipitates was accounted (D. Douroumis et al., 2006). Four different solvent ratios (1:2, 1:4, 1:8 and 1:16 of methanol to water) were tried to select the most appropriate ratio to achieve the smallest particles and the maximum yield of the particles. For this experiment, a high concentration of stabilizing agent (0.5%) was selected in order to avoid the stabilizing agent concentration being a limiting factor. A second experiment was carried out using the selected solvent ratio and five different concentrations of PVP (0, 0.01, 0.05, 0.1, 0.2 and 0.5%) in order to estimate the minimum concentration of PVP necessary to obtain the smallest stable drug particle size (Marcilio S.S. Cunha-Filho et al., 2008).

2.3. Crystallization procedure

First, an organic solution of the drug was prepared by dissolving 8.8 gm of the drug in 50 ml of methanol. Then 200 ml of an aqueous solution containing 0.1% w/v PVP was added rapidly under stirring to the drug solution. This caused super saturation with respect to the drug and subsequent nucleation and crystal growth. The mixture was stirred for 60 min. The crystals were collected by filtration using whatman filter paper (grade 1, 90 mm diameter) followed by three consecutive washings with 10 ml of cold water to remove any non adsorbed excipient and dried in an oven at 45^0 C for 2 hr.

2.4. Characterization of crystals

2.4.1. Particle size analysis

The size distribution of microcrystals and untreated TBM powder was measured with an optical microscope.

2.4.2. Solubility study

Excess amount of TBM microcrystals and pure TBM drug powder were dispersed in 20 mL distilled water. The dispersion was shaken at 100 rpm at 37^0 C for 24 hrs using thermostatic cabinet (Remi, RIS-24BL, Mumbai). The dispersion was filtered through a whatman filter paper (grade 1, 90 mm diameter). The filtered sample solutions analyzed using a UV–visible spectrophotometer (shimadzu 1650PC) at 226 nm after appropriate dilution. The mean results of triplicate measurements and the standard deviation are reported. The Gibbs-free energy of change (ΔG°_{tr}°) of tolbutamide occurred during formation of microcrystals from untreated TBM powder was calculated using equation 1.

$$\Delta G^{0}_{tr} = -2.303RTLog\frac{S_0}{S_S} \quad \text{.....(1)}$$

Where S_0/S_s, is the ratio of the molar solubility of TBM microcrystals in distilled water to that of the untreated TBM powder. R is gas constant (8.31 J K^{-1} mol^{-1}) and T is temperature in degrees Kelvin (310.15^0 K).

2.4.3. Scanning electron microscopy (SEM)

Scanning electron micrographs of TBM microcrystals and untreated TBM drug powder were taken using a scanning electron microscope (Philips, Philips XL 30 ESEM). Samples were fixed on an aluminum stub with conductive double-sided adhesive tape and coated

with gold in an argon atmosphere (50 Pa) at 50mA for 50 sec.

2.4.4. Fourier transform infrared spectroscopy

The FTIR spectra were recorded on a FT-IR spectrophotometer (Perkin-Elmer, Spectrum GX FTIR, USA), in the wavelength region of 4000 – 400 cm^{-1}. A blend of drug particles and KBr (about 1% w/w) was compressed into 12 mm discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded.

2.4.5. Differential scanning calorimetry (DSC)

A differential scanning calorimeter (Perkin Elmer, DSC-pyris-1, USA) was used to monitor the thermal events during heating. The DSC was calibrated by the melting points of indium (156.6±0.2^0 C) and zinc (419.5±0.3^0 C) standards. Samples weighing 2–3 mg were placed in open aluminium pans and heated from 55 to 250^0 C at a rate of 10^0 C per min. Nitrogen gas was purged at a flux rate of 50 ml/min. The onsets of the melting points and enthalpies of fusion were calculated by the software (Pyris, Perkin-Elmer).

2.4.6. X-ray diffractometry

Powder X-ray diffraction (PXRD) patterns were collected in transmission using an X-ray diffractometer with a rotating anode (Philips, X-pert-MPD) with Cu Kα1 radiation (monochromator: graphite) generated at 200 mA and 40 kV. Powder was packed into the rotating sample holder between two films (PETP).

2.4.7. In vitro Dissolution study: Powder Dissolution

Powder dissolution study was carried out by using a USP apparatus II (Electrolab, TDT-08L) in 900 ml of phosphate buffer pH 7.4 at a temperature of 37±1^{0}C at 75 rpm. A powdered sample (100 mg) was introduced directly into the dissolution medium. At regular time intervals, suitable amount of sample was withdrawn and same amount replaced by fresh medium. Samples were suitably diluted and filtered through syringe filter (Axiva SFCA25X, 0.45µm). Drug amount released was analyzed spectrophotometrically (shimadzu 1650PC) at wavelength of 226nm. All studies were carried out in triplicates. Dissolution efficiency (DE %) was calculated t according to equation 2.

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\% \quad \text{.....(2)}$$

2.4.8. Flow property study

The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using density apparatus (Serwell, Bangalore, India). The Carr's index (%) and the Hausner's ratio were calculated by using LBD and TBD. The angle of repose of untreated TBM powder and the microcrystals were assessed by fixed funnel method.

2.4.9. Statistical analysis

Paired t-test and one-way ANOVA were employed to analyze the results (Microsoft Excel and Statplus software). Difference below the probability level 0.05 was considered significant. Difference below the probability level 0.001 was considered highly significant.

3. RESULTS AND DISCUSSION

3.1. Optimization of solvent to antisolvent ratio

The mean particle size of untreated TBM powder was 95.25 µm while particles precipitated in the presence of 0.5 % of PVP was less than 25 µm (Table 1.). No important disparity was achieved in particle size values and cumulative drug release among the different methanol/water ratio. This was might be because of the fact that constant concentration (0.5 %) of PVP was used in optimization of methanol/ water ratios. Statistical analysis of the particle size of TBM microcrystals produced by using various methanol/water ratios by a one-way ANOVA test showed that methanol/water ratio had not significant effect ($p > 0.05$) on the particle size of the TBM microcrystals. Methanol/water ratios had highly significant effect ($p > 0.001$) on % crystal yield of the TBM microcrystals. So, selection of optimum methanol/water ratio was based on the % crystal yield of microcrystals at various ratios. Maximum crystal yield and small particle size obtained at a solvent ratio 1:4 (Table 1.). Therefore, 1:4 was optimum methanol/water ratio for crystallization of tolbutamide. A lower % crystal yield in case of ratios of 1:2, 1:8 and

Table 1: Mean particle size, % crystal yield and % cumulative drug release of micronized TBM prepared using different methanol/water ratios.

Solvent : Anti-solvent Ratio (v/v)	% Crystal Yield	Mean Particle Size (µm)	% Cumulative Drug Release (average ± SD)		
			$Q_{5\%}$	$Q_{30\%}$	$Q_{60\%}$
1:2	55.4#	22.5	56.40 ± 1.6	76.97 ± 0.89	84.09 ± 0.49
1:4	67.4#	21.25	61.35 ± 0.34	80.73 ± 1.19	87.35 ± 1.19
1:8	54#	23.25	58.05 ± 0.9	76.41 ± 1.17	84.87 ± 0.28
1:16	51.6#	24.25	57.83 ± 0.9	75.83 ± 1.2	84.34 ± 0.88

Significant difference ($p > 0.05$) upon application of one-way ANOVA.

Q = Cumulative drug release; SD = Standard Deviation

1:16 because of methanol/water ratio of 1:2 entails a little efficient polarity change because aqueous phase was insufficient to bring out complete crystallization from organic solvent, whereas a1:8 or 1:16 ratio means the use of a high aqueous phase volume that solubilizes a tolbutamide fraction (marcilio s.s et al., 2008).

3.2. Optimization of concentration of PVP

Table 2 that presents the mean diameter of TBM particles precipitated using different concentrations of PVP after 60 min. The minimum concentration of PVP required to obtain small and stable size particles of TBM was 0.1%, below this concentration the particle growth occurs. Results of statistical analysis showed that concentration of PVP had highly significant effect ($p > 0.001$) on the particle size of the TBM microcrystals as compared to untreated TBM powder. TBM particles produced by crystallization without PVP have a bigger size and broader particle size distribution, whereas the system with the stabilizer PVP stops the molecular association and the crystal growth instantaneously at the moment of solvent change, which is in agreement with other authors' reports (N. Rasenack et al., 2003).

During the crystal precipitation, surface energy of the system increases. Here, PVP adsorbed onto the newly created surface of the precipitated drug in order to lower the interfacial tension. Thereby, the surface energy and consequently the enthalpy of the system are lowered. The formed small particles, which normally would aggregate in order to lower the surface energy, are stabilized sterically against crystal growth by an adsorbed layer of PVP. Micron sized particle formed and simultaneously stabilized in the formed dispersion by PVP.

Higher crystal yield 76.6% was obtained in case of TBM microcrystals prepared using 0.1% PVP. Results of one-way ANOVA showed that 0.05% and 0.5% of PVP had significant effect ($p > 0.05$) and 0.1 % of PVP showed highly significant difference ($p > 0.001$) on % crystal yield of the TBM microcrystals as compared to % crystal yield of TBM crystals prepared using without stabilizing agent.

The tendency of the solid phase to exhibit solubility is best described by the Gibbs free energy change (ΔG°_{tr}). Negative Gibbs free energy values indicate favourable conditions. The ΔG°_{tr} values were all negative at various concentrations, thus indicating that TBM microcrystals had higher aqueous solubility. These values decreased with increasing concentration of PVP up to 0.1 %, thereby demonstrating that drug solubility increased as the concentration of PVP increased up to 0.1 %. After 0.1 % of PVP, ΔG°_{tr} values were increased compared to its lower concentration, which showed that after 0.1 % PVP concentration, drug solubility was decreased.

Higher 58.3% dissolution efficiency after 15 min. obtained in case of 0.1 % PVP as compared to TBM microcrystals prepared using other concentration of PVP. Results of One-way ANOVA test stated that highly significant difference ($p > 0.001$) in drug release was observed for TBM microcrystals prepared using 0.05, 0.1, 0.2 and 0.5 % of PVP as compared to untreated TBM powder.

TBM microcrystals prepared using 0.1% PVP as stabilizing agent showed small particle size, higher crystal yield, high water solubility, great reduction in Gibb's free energy, and higher dissolution efficiency as compared to other TBM microcrystals. Therefore, 0.1% concentration was optimum concentration of PVP for microcrystallization of TBM.

Crystallization was carried out employing the solvent change method using PVP at 0.1% as the stabilizing agent and a solvent methanol/water ratio 1:4. Fluffy powders were obtained.

Table 2 : Percentage (%) crystal yield, Mean Particle size, solubility in distilled water, Gibb's free energy change and dissolution efficiency (DE) after 15 min of dissolution test of untreated TBM powder, TBM crystal prepared without PVP and its microcrystals prepared by solvent change method.

Conc. Of aqueous solution of PVP	% Crystal Yield	Mean Particle Size (µm)	Solubility in water (mg/ml)	Gibbs free energy change (ΔG°_{tr}) ($J\ K^{-1}Mol^{-1}$)	$DE_{15\%}$
0.0 %	69.4	42.5##	0.044 ± 0.001	-965.761	14.58
0.025 %	70.6	23.25##	0.301 ±0.0023	-5893.14	49.59
0.05 %	72.6#	22.5##	0.309 ±0.0018	-5965.04	53.13
0.1 %	76.6##	18.25##	0.339 ± 0.002	-6203.9	58.3
0.2 %	68.8	21##	0.255 ±0.0015	-5464.84	53.68
0.5 %	65.3#	21.25##	0.235 ± 0.002	-5257.52	54.27
Untreated TBM powder		95.25	0.031 ± 0.003		6.70

Significant difference ($p > 0.05$) upon application of one-way ANOVA.
Highly Significant difference ($p > 0.001$) upon application of one-way ANOVA.
DE = Dissolution efficiency

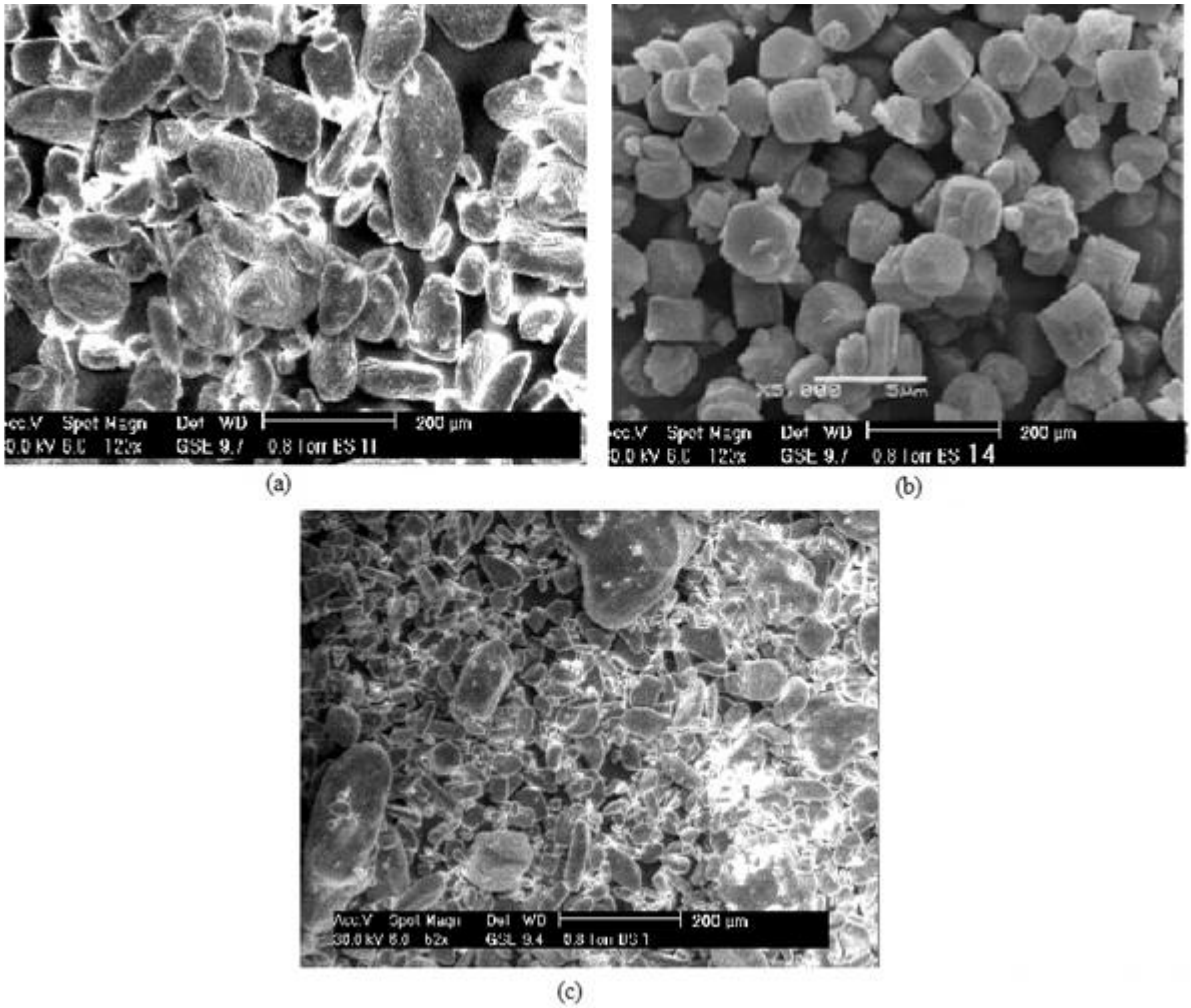

Figure 1: Scanning electron micrographs of: (a) Pure TBM drug powder, (b) tolbutamide crystals without PVP (c) TBM microcrystals prepared using 0.1% PVP

3.3. Scanning electron microscopy (SEM)

Face specific adsorption of stabilizing agent alters the growth rates of the faces where adsorption takes place and thus changes the morphology of the crystal (Lechuga-Ballesteros et al., 1995a). Modification of crystal habit can improve the dissolution rate by promoting growth of more hydrophilic faces, or inhibiting growth of more hydrophobic faces (H.M. Burt et al., 1980). Scanning electron micrographs of Pure TBM drug powder, TBM crystals prepared without stabilizing agent and TBM microcrystals shown in figure 1. Pure TBM powder showed large rod like shaped crystal habit, while TBM crystals without stabilizing agent plate shaped. Microcrystals prepared using 0.1 % PVP showed small platy crystals.

3.4. Fourier transforms infrared spectroscopy

Figure 2 showed that FTIR spectras of the pure TBM powder, microcrystals and TBM crystals without PVP were identical and the main absorption bands of tolbutamide appeared in all the spectra. Absorption band for N-H stretching of urea group of tolbutamide appeared around 3330 cm^{-1}. Similarly, the S=O stretching of sulphonamide group of tolbutamide located at 1335 cm^{-1} and 1159 cm^{-1} was not shifted in microcrystals (P. Chakravarty et al., 2005). The absorption band for C=O stretching of urea group of tolbutamide located at 1702 cm^{-1} and 1662 cm^{-1} in pure TBM drug powder, and these were not shifted in the microcrystals spectra. The FTIR spectra of all the tested samples showed the prominent characterizing peaks of pure tolbutamide which confirmed that no chemical modification of

Table 3: DSC results of Pure TBM drug powder, TBM crystals without PVP and its microcrystals prepared using PVP.

	Melting Point (^{0}C)	Peak height (mw)	Area (mj)	Delta H (j/g)
Pure TBM drug powder	130.597	29.6755	458.519	213.563
0.0 %	129.130	15.3550	149.325	61.679
0.1 % PVP	128.305	9.5308	122.416	60.096

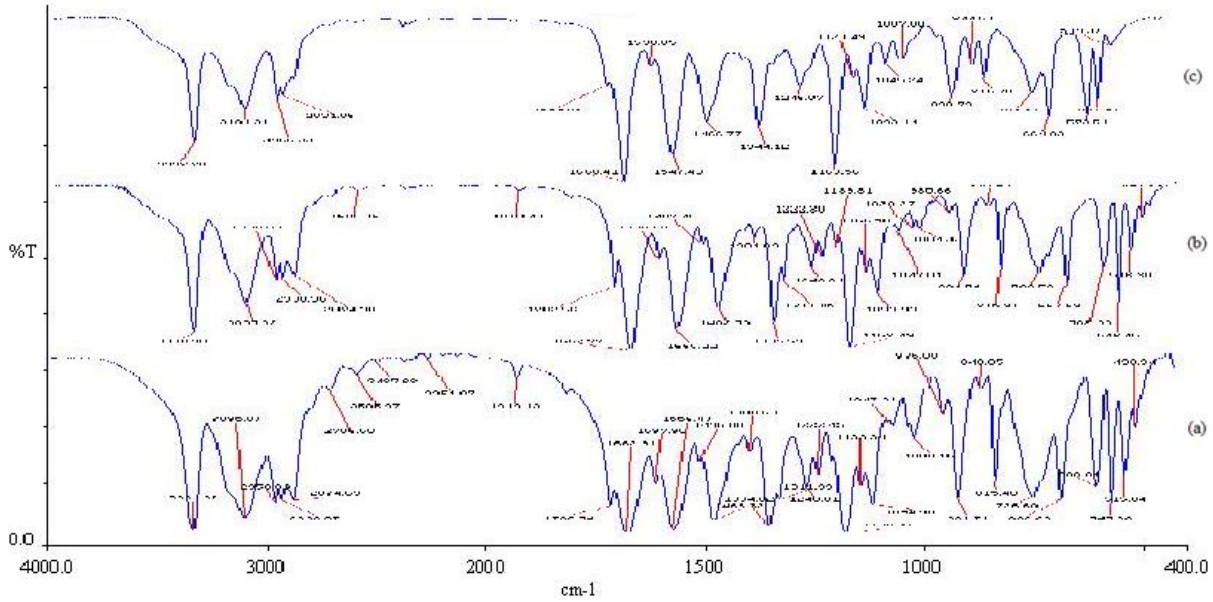

Figure 2: FTIR spectra of: (a) Untreated TBM powder, (b) tolbutamide crystals without PVP (c), and TBM microcrystals prepared using 0.1% PVP

the drug had been taken place. Intensity of IR peaks of TBM microcrystals were decreased as compared to untreated TBM powder, implying that the change in crystal habit and particle size reduction in microcrystals is responsible for these changes (J. Varshosaz et al., 2008).

3.5. Differential Scanning Calorimetry (DSC)

DSC thermographs of pure TBM drug powder, TBM crystal prepared without HPMC and its microcrystals prepared using 0.1% PVP showed a sharp endothermic peak (Tm) at 130.59^{0}C corresponding to melting point of tolbutamide Form I (Kimura K. et al., 1999). Melting endotherm not appreciably change in TBM crystals prepared without PVP and in presence of PVP. This observation also confirmed the absence of chemical interaction of drug with PVP during crystallization process, further supporting the results of FTIR spectroscopy. The DSC results of pure TBM drug powder, TBM crystal prepared without PVP and its microcrystals prepared using 0.1% PVP were shown in the figure 3 and their value obtained in DSC thermograph shown in Table 3. Tm of the drug in all cases was almost the same but with a slight reduction that did not seem to be significant.

3.7. In vitro Dissolution study: Powder Dissolution

The micronized TBM powders showed a dramatic enhancement in dissolution rate as illustrated in Figure 5. $DE_{15\%}$ of the studied microcrystals in comparison with the pure TBM powder was presented in Table 2. Statistical analysis was performed on dissolution data using a one-way ANOVA test. Results suggested that dissolution profile of microcrystals was significantly differ ($p \pm 0.05$) from untreated TBM powder. TBM crystals prepared without stabilizing agent did not show significant improvement in drug release when compared with pure TBM drug powder.

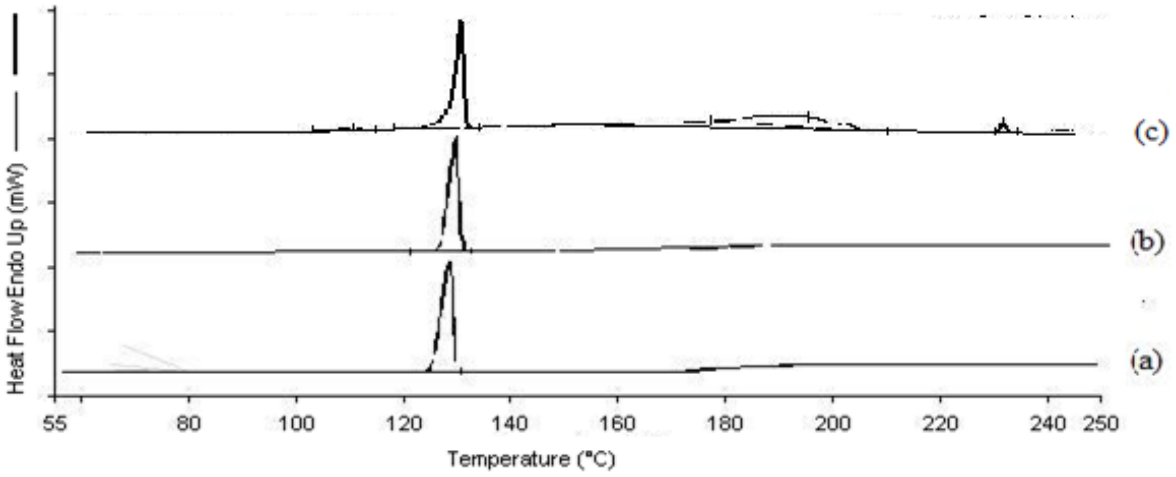

Figure 3: Differential scanning calorimetry (DSC) thermographs of (a) Pure TBM drug powder, (b) tolbutamide crystals without PVP (c) TBM microcrystals prepared using 0.1% PVP

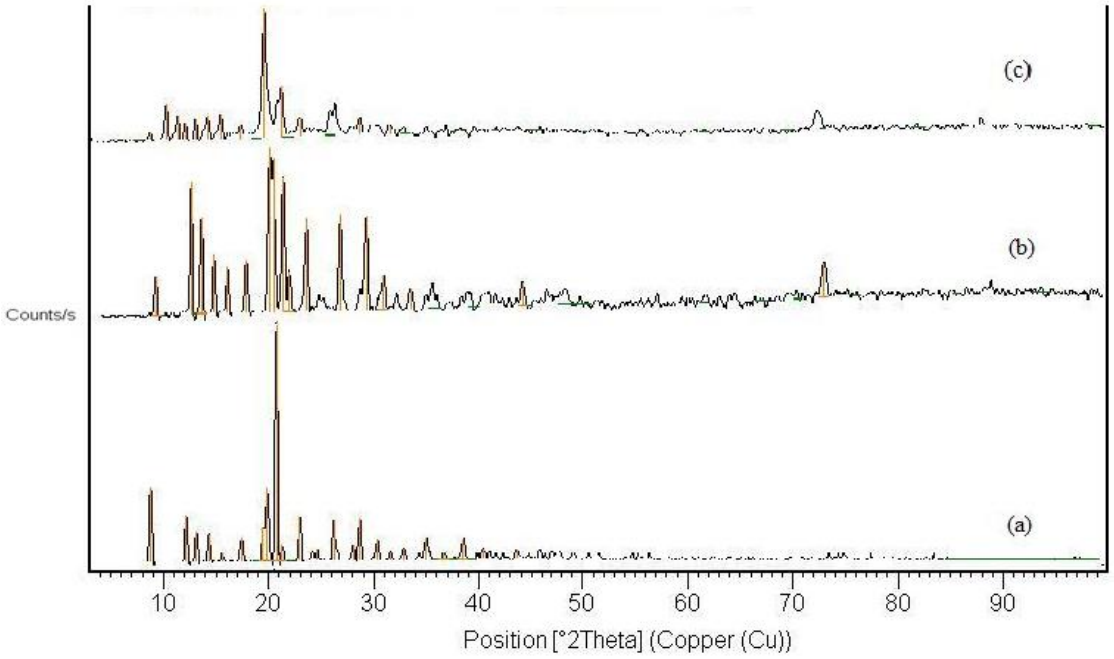

Figure 4: X-ray diffraction patterns of (a) Pure TBM powder, (b) tolbutamide crystals without PVP (c) TBM microcrystals prepared using 0.1% PVP

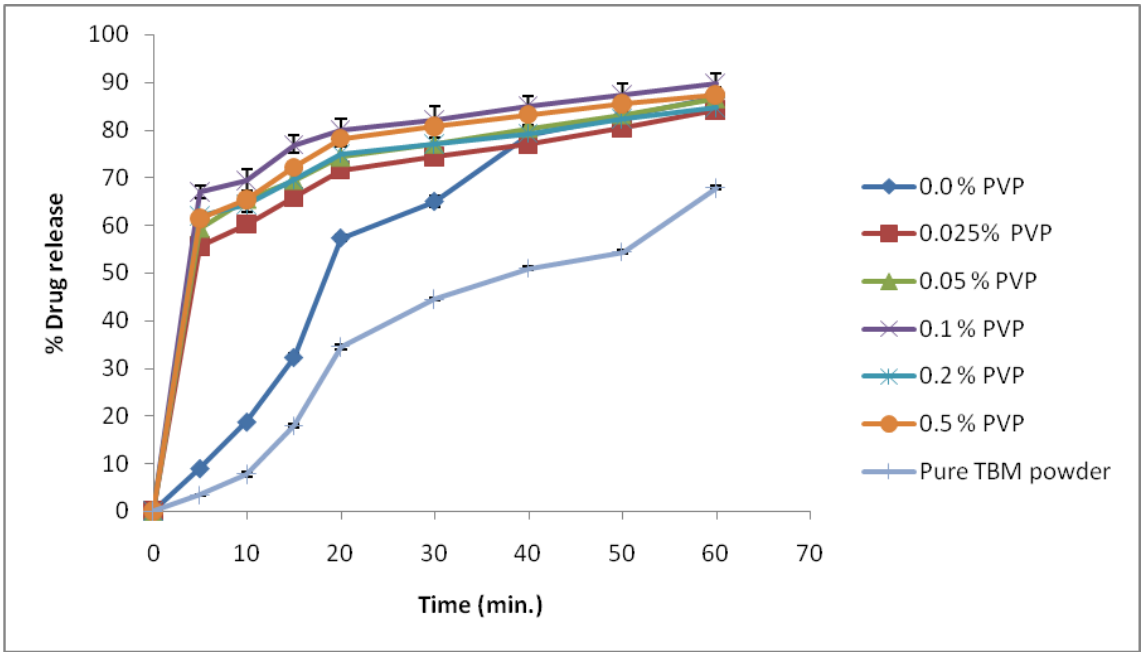

Figure 5: Dissolution profiles of (a) pure TBM powder (b) TBM crystal prepared without PVP (c) TBM crystals prepared using various concentration of PVP

Dissolution enhancement effect of TBM microcrystals explained by the dramatic reduction in the particle size and as a consequence the increment in the surface area, which is additionally hydrophilized by the adsorbed hydrophilic stabilizing agent. Moreover, the natural crystalline growth creates particles with no electrostatic charge and with better wettability properties (marcilio s.s et al., 2008). Formation of partially amorphous tolbutamide occurred during crystallization in presence of stabilizing agent also contributed for dissolution enhancement.

3.8. Flow property study

Bulk density, Tapped density, Angle of repose, % Carr's index and Hausner's ratio for pure TBM powder, TBM crystal prepared without PVP and TBM microcrystals showed in table 4. Pure TBM drug powder exhibited poor flowability and compressibility as indicated by high value of Carr's index (29.49 ± 2.22%), Hausner's ratio (1.42 ± 0.004) and angle of repose (37.70^0 ± 1.1). This could be due to the irregular rod shape, which put hurdles in the uniform flow of powder from the funnel.

Table 4: Bulk density, tapped density, angle of repose, % Carr's index and hausner's ratio for pure TBM powder, TBM crystals without PVP and its microcrystals prepared using PVP.

	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of repose (Average ± SD)	% Carr's index (Average ± SD)	Hausner's ratio (Average ± SD)
Untreated TBM powder	0.58	0.82	37.70^0 ± 1.1	29.49 ± 2.22	1.42 ± 0.004
0.0 %	0.60	0.76	36.21^0 ± 2.15	21.33 ± 2.31	1.27 ± 0.004
0.1 % PVP	0.60	0.69	29.09^0 ± 0.67	13.33 ± 3.06	1.15 ± 0.004

Microcrystals prepared with 0.1 % PVP showed improved flowability as indicated by lower value of Carr's index (13.33 ± 3.06), Hausner's ratio (1.15 ± 0.004) and angle of repose (29.09^0 ± 0.67). Small platy shape microcrystals showed good flowability as compared to rod shaped TBM powder.

4. CONCLUSIONS

TBM microcrystals were prepared by solvent change method using PVP as a hydrophilic stabilizing agent. Solvent ratio (methanol/water) 1:4 and 0.1% PVP were optimum parameters for microcrystallization of TBM. Microcrystals produced using PVP showed narrow particle size distribution and change in the crystal habit from rod type to small plate type. The FTIR, DSC, and XRD results showed no chemical interaction between the drug and the stabilizer, and crystalline habit modification has occurred in the microcrystals without any polymorphic changes. The XRD revealed that crystallinity was reduced significantly in microcrystals. Negative Gibb's free energy change represented higher aqueous solubility of microcrystals. The enhanced dissolution rates attributed to the reduction of the particle size, change in crystal habit, formation of hydrophilic surface and the increased wettability due to adsorption of PVP and reduction in crystallinity of TBM during microcrystallization. In conclusion, the aforementioned technique is a promising tool for effective microcrystal formation during pharmaceutical development in order to increase dissolution rate of poorly water soluble active ingredient.

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