

Effect of Solvent on Crystal Habit and Dissolution Behavior of Tolbutamide by Initial Solvent Screening

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ABSTRACT

By an initial solvent screening of 18 solvents, 14 pure good solvents were selected for the crystallization of tolbutamide. Solid generation by the solvent-change method was carried out using the pure good solvents. Crystals were generated in only 10 of the 14 solvents. Different crystal forms of tolbutamide were obtained. Crystals were subjected to evaluation tests such as differential scanning calorimetry, optical microscopy, and in vitro dissolution. All crystals were determined as isomorphic by differential scanning calorimetry. Dissolution rate was influenced by crystal form. Thus, the choice of suitable crystal habit and proper selection of solvent is important in manufacturing the drug tolbutamide.

INTRODUCTION

Solubility, crystallinity, and the crystal properties of an active pharmaceutical ingredient (API) play a critical role in the value chain of pharmaceutical development, manufacturing, and formulation. Because these properties are all solvent dependent, solvent screening is of fundamental and foremost importance to the pharmaceutical industry (1). The solubility of an API in solvents and solvent mixtures has a considerable influence on the choice of solvents and the course of operation in solvent-based processes such as chemical reactions, extraction, crystallization, filter-cake washing, and wet granulation (2). Most pharmaceutical manufacturing processes include a series of crystallization processes to achieve high purity and to produce the desired final crystal form. Use of different solvents and processing conditions during crystallization may alter the crystal habit of the purified drug, leading to variation in raw material characteristics such as melting point, solubility, true density, dissolution profile, flowability, compressibility, and tabletability (3–9).

The amount of drug dissolved with time depends on the size and number of crystal faces exposed to the dissolution medium. Therefore, habit modification seems to provide an alternative means of modifying the dissolution behavior of drugs (8, 10, 11). Use of different solvents alters crystal habit, which may alter dissolution rate. Selection of a proper solvent for crystallization may give optimized crystal properties. Consequently, initial solvent screening is important in choosing a proper solvent for crystallization. This article promotes a solvent-screening strategy that is tailor-made for the processes of drug development and design of API solids.

Tolbutamide (1-butyl-3-(p-tolysulfonyl) urea) (TBM), shown in Figure 1, was selected for our solvent-screening

strategies because of the lack of extensive solvent studies on its solubility, crystallinity, and crystal habit. Tolbutamide is used as an oral hypoglycemic agent. The drug is practically insoluble in water, and its dissolution is supposed to be the rate-limiting step for its absorption from the gastrointestinal tract (12). Several studies on commercial brands of tolbutamide dosage forms have shown marked variations in dissolution rate and bioavailability (13–15). Reported methods for the enhancement of the dissolution rate of TBM include crystallization of tolbutamide from acetonitrile by a temperature-cooling method (16), spherical agglomerates prepared by spray-drying an ethanol solution of TBM with colloidal silica (17), complex formation with β -cyclodextrin (18), and tolbutamide-urea and tolbutamide-mannitol systems (19).

The aim of this initial solvent-screening study was to produce different crystal forms of TBM by crystallizing it from different solvents and study the dissolution behavior of its different crystal forms.

MATERIALS AND METHODS

Solvents

Table 1 lists the solvents used in the study and their properties. All solvents were purchased from s.d. fine-chem Ltd., except for ethanol (95.2% v/v), which was purchased from Baroda Chemical Industries Ltd. Double-distilled water was used throughout the study.

Active Pharmaceutical Ingredient

Tolbutamide ($C_{12}H_{18}N_2O_3S$, mp = 126–130 °C, MW = 270.349) was supplied as a gift sample by Sanofi Aventis Pharma Limited at Ankleshwar.

Solubility Studies

Approximately 10 mg of the API was weighed in a 5-mL vial. Drops of solvent were titrated carefully with a

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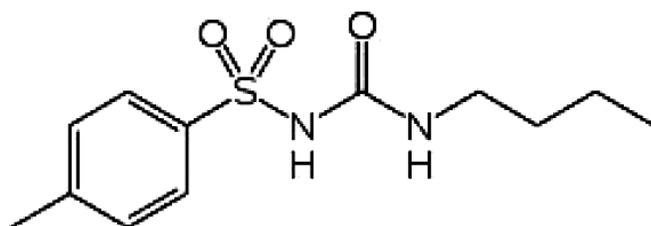


Figure 1. Chemical structure of tolbutamide.

micropipette into the vial with intermittent shaking until all API solids were just dissolved. The solubility of the API at room temperature was calculated as the weight of the API in a vial divided by the total volume of solvent added to the vial.

Solvent Miscibility Studies

Of the 18 solvents, approximately 1-mL portions of each solvent comprising a pair were shaken together for about 1 min in a 5-mL vial. If no interfacial meniscus was observed after the contents of the vial were allowed to settle, the solvent pair was considered to be miscible. If a meniscus was observed without apparent change in the

volume of either solvent, the pair was regarded as immiscible.

Crystallization Method

Crystallization of TBM was carried out by using solvent-change method. A suitable amount of the drug was dissolved in 100 mL of each solvent (decided from the solubility values determined at room temperature from experiments in solubility studies). Crystallization was carried out by adding 400 mL of water continuously under stirring conditions. The resulting dispersion stirred for 60 min. Crystals were collected by filtration using Whatman filter paper (no. 1) and dried in an oven at 450 °C for 2 hr. Crystal yield was calculated for each solvent.

The solvents used were methanol, ethanol, IPA, acetonitrile, acetone, chloroform, ethyl acetate, DMA, DMF, MEK, nitrobenzene, xylene, THF, and butan-1-ol.

Crystal Characterization

Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (Perkin Elmer, 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 °C) and zinc (419.5 ± 0.3 °C) standards. Samples weighing 2–3 mg were placed in open

Table 1. Solvent Properties

Solvent	Formula	Grade	BP (°C)	MW
acetone	CH ₃ COCH ₃	HPLC–Spectro	56	58.08
acetonitrile	CH ₃ CN	HPLC	81.6	41.05
butan-1-ol	CH ₃ (CH ₂) ₃ OH	HPLC	117.7	74.12
chloroform	CHCl ₃	HPLC–Spectro	60.5–61.5	119.38
N,N-dimethylaniline (DMA)	C ₆ H ₅ N(CH ₃) ₂	AR	193	121.18
N,N-dimethylformamide (DMF)	HCON(CH ₃) ₂	HPLC	153	73.10
ethanol 95.2 %v/v	CH ₃ CH ₂ OH	Rectified Spirit	78	46.7
ethyl acetate	CH ₃ COOC ₂ H ₅	HPLC	76.5–77.5	88.11
n-heptane	CH ₃ (CH ₂) ₅ CH ₃	LR	98	100.21
isopropyl alcohol (IPA)	(CH ₃) ₂ CHOH	HPLC	82.4	60.1
nitrobenzene	C ₆ H ₅ NO ₂	AR	210–211	123.11
methanol	CH ₃ OH	HPLC–Spectro	64.7	32.04
methyl tert-butyl ether (MTBE)	(CH ₃) ₃ COCH ₃	HPLC	55.2	88.15
methyl ethyl ketone (MEK)	C ₂ H ₅ COCH ₃	HPLC	81.6	72.11
tetrahydrofuran (THF)	C ₄ H ₈ O	HPLC–Spectro	65–67	72.11
xylene	C ₆ H ₄ (CH ₃) ₂	AR	137–144	106.17
p-xylene	C ₆ H ₄ (CH ₃) ₂	AR	138	106.17

Table 2. Average Solubility of Tolbutamide in Various Solvents

Solvent Used	Average Solubility (mg/mL ± SD)
Methanol	177.59 ± 4.77
Ethanol	120.52 ± 2.90
IPA	62.66 ± 3.93
Butane-1-ol	52.65 ± 1.38
Acetone	252.35 ± 9.84
Chloroform	314.61 ± 3.42
Ethyl acetate	133.95 ± 2.76
Acetonitrile	100.02 ± 2.01
Nitro benzene	107.96 ± 2.95
THF	219.20 ± 2.63
N,N-dimethyl aniline	41.67 ± 0.52
DMF	248.16 ± 9.29
MEK	190.06 ± 7.39
Xylene	7.66 ± 0.55
Methyl tert-butyl ether	ND
n-heptane	ND
p-xylene	ND
Water	ND

ND = Not Detected

aluminum pans and heated from 55 to 25 °C at a rate of 10 °C/min. Nitrogen was used as a purge gas at a flux rate of 50 mL/min. The onsets of the melting points and enthalpies of fusion were calculated using Pyris software (Perkin-Elmer).

Particle Morphology and Particle Size Determination

A compound microscope (Zeiss) equipped with a CCD camera (Pixel view station V5.14C TV) was used to record images of the crystal forms. Particle size was determined using the optical microscope.

In Vitro Dissolution Study: Powder Dissolution

The powder dissolution study was carried out using USP Apparatus 2 in 900 mL of pH 7.4 phosphate buffer at 37 ± 1 °C and 75 rpm. A powdered sample (100 mg) was introduced directly into the dissolution medium. At regular time intervals, a suitable amount of sample was withdrawn, and the same volume was replaced by fresh medium. Samples were suitably diluted and filtered through syringe filters (Axiva SFCA25X, 0.45 µm). The amount of drug released was analyzed spectrophotometrically (Shimadzu 1650PC) at a wavelength of 226 nm. All studies were carried out in triplicate.

Table 3. Solvent Miscibility Table: Cosolvent and Antisolvent Systems of Tolbutamide

RESULTS AND DISCUSSION

The solubility of TBM in various solvents at room temperature is shown in Table 2. Based on the solubility study, tolbutamide dissolved well in 14 of the solvents (labeled as “good solvents”): methanol, ethanol, IPA, acetonitrile, acetone, chloroform, ethyl acetate, DMA, DMF, MEK, nitrobenzene, xylene, THF, and butan-1-ol. The crystals only slightly dissolved in four of the solvents (labeled as “bad solvents”) with a solubility less than 1 mg/mL at 25 °C. The bad solvents for tolbutamide were p-xylene, methyl tert-butyl ether, n-heptane, and water.

Table 3 depicts form space for pure good solvent (yellow box), pure bad solvent (red box), good cosolvent (blue box), antisolvent (green box), bad cosolvent (gray box), and immiscible pairs (white box). The results of the solvent miscibility studies of the solvent pairs of the 18 kinds of solvent show that 13 immiscible pairs (26 gray boxes ÷ 2, because of the symmetry in Table 3) can be possible.

The pure-solvent systems are represented as the 18 diagonal boxes. The “form space” of the pure-solvent systems for our initial solvent screening was limited to the number of good pure solvents represented by the yellow boxes. Therefore, the form space for the initial solvent screening of tolbutamide was 14. If the good cosolvent systems (i.e., the binary mixtures of good solvents) were taken into account, the form space of the good cosolvent systems was 90 (180 blue boxes ÷ 2). In addition, if the antisolvent systems (i.e., binary mixtures of a good and a bad solvent) were also considered, the form space of the antisolvent systems was 47 (94 green boxes ÷ 2). So, the total form space for tolbutamide was 14 + 90 + 47 = 151.

The total form space should expand dramatically if various solvent compositions of binary mixtures and ternary solvent systems are also taken into account (20).

Solid generation by the solvent-change method can be applied in the yellow and blue regions. In the present study, no attempts were made for solid generation in the regions of immiscible solvent pairs (gray boxes), bad solvents (red boxes), and bad cosolvents (white boxes) (i.e., binary mixtures of any two bad solvents) in the solvent miscibility table.

In the initial solvent screening of tolbutamide, solids were generated in only 10 out of 14 pure good solvents. Figure 2 depicts DSC thermograms of all white solids generated in each of the 10 solvents. All crystals showed a sharp endotherm in the range of 128–130 °C, which is the melting point of Form I crystals (21). This result clearly verifies that tolbutamide powders that solidified from all 10 solvents were the thermodynamically stable, Form I crystals at room temperature. All crystals prepared were isomorphic.

The images of the crystal habits of tolbutamide crystals produced from pure solvents are represented in Figure 3. Pure TBM drug powder and crystals obtained from butan-1-one show rod-like crystals. Crystals that were obtained from methanol and ethanol show a plate-like crystal habit. Needle-like crystals were produced from solvents like IPA, butan-1-ol, chloroform, and acetone. In crystallization from acetonitrile, only spherical agglomerates were observed. A more cubic crystal habit was obtained using ethyl acetate as crystallizing solvent. In tetrahydrofuran, prismatic crystals were obtained. The present investigation clearly indicates that the crystallizing solvent influences the crystal habit. This might be due to the solute-solvent interaction at various crystal-solution interfaces, which leads to altered

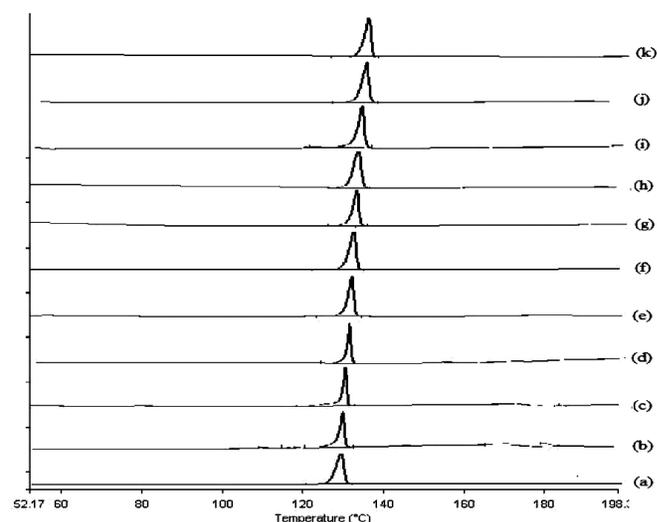


Figure 2. Differential scanning calorimetry curves of (a) pure TBM drug powder and tolbutamide crystals grown from (b) methanol, (c) ethanol, (d) IPA, (e) butan-1-ol, (f) acetone, (g) chloroform, (h) ethyl acetate, (i) acetonitrile, (j) butan-1-one, and (k) tetrahydrofuran.

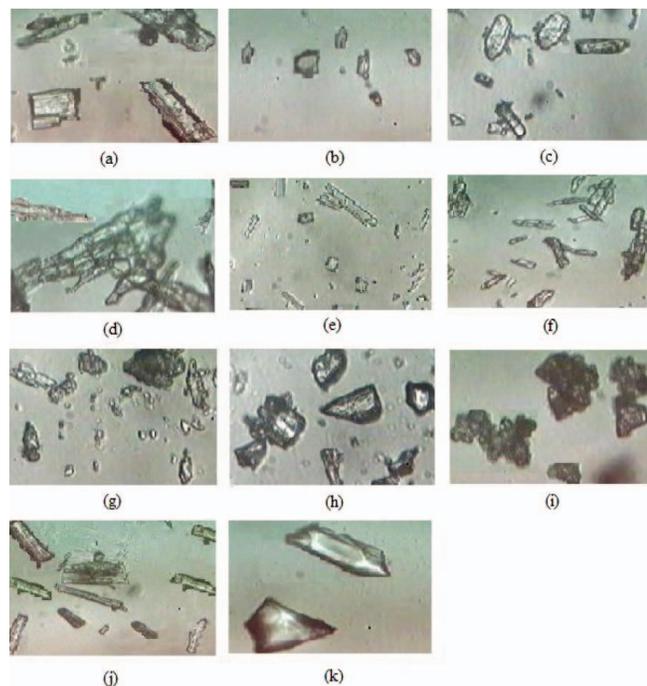


Figure 3. Compound micrographs of crystal habit of (a) pure TBM drug powder and tolbutamide crystals grown from (b) methanol, (c) ethanol, (d) IPA, (e) butan-1-ol, (f) acetone, (g) chloroform, (h) ethyl acetate, (i) acetonitrile, (j) butan-1-one, and (k) tetrahydrofuran.

roundness of the interfaces, changes in crystal growth kinetics, and enhancement (22) or inhibition (23) of growth at certain crystal faces. Polarity of the solvent and the interaction that leads to its preferential adsorption at selected faces of the solute are critical factors in determining the habit of a crystallizing solid.

The particle size, crystal yield, and percent drug release of tolbutamide crystal are shown in Table 4. The mean particle size of pure TBM powder was 95.5 μm . The smallest mean particle size (42.5 μm) with the highest crystal yield (69.4 %) was observed for the tolbutamide crystals prepared from methanol. The TBM crystals showed differences in dissolution profiles depending on the crystallizing solvent (Figure 4). The amount of drug dissolved depends on the size and number of crystal faces exposed to the dissolution medium. Crystallization of tolbutamide from methanol and ethanol produced small, circular, platy crystals that exhibited higher dissolution than rod-like crystals of pure TBM powder. After 60 min, 86.92% and 81.38% drug were dissolved in methanol and ethanol, respectively, while only 67.88% drug was dissolved in pure TBM drug powder. Spherical agglomerates produced from acetonitrile also gave higher dissolution. Needle-like crystals, cubic-shape crystals, and prismatic crystals obtained from acetone, ethyl acetate, and tetrahydrofuran, respectively, showed decreased dissolution relative to pure TBM powder.

Table 4. Mean Particle Size, Percent Crystal Yield, and Percent Drug Release of Untreated Drug and Tolbutamide Crystals

Solvent Used for Crystallization	Mean particle size (µm)	Percent crystal yield	% Drug Release (Average ± SD)		
			T _{20%}	T _{40%}	T _{60%}
Methanol	42.5	69.4	57.36 ± 0.69	79.10 ± 1.28	86.92 ± 2.01
Ethanol	46.5	64.4	53.68 ± 1.66	72.41 ± 3.68	81.38 ± 0.67
IPA	48.25	58.7	48.51 ± 2.08	65.39 ± 1.7	78.13 ± 1.56
Butant-1-ol	48.5	52.6	46.51 ± 0.16	62.32 ± 1.14	73.00 ± 1.16
Acetone	45	62.6	28.33 ± 0.81	51.64 ± 0.7	57.89 ± 0.49
Chloroform	63.5	62.6	40.04 ± 0.59	57.23 ± 1.38	68.79 ± 1.18
Ethyl acetate	62	56.6	33.77 ± 1.25	49.24 ± 1.71	58.10 ± 0.5
Acetonitrile	46.75	60	43.19 ± 0.59	68.95 ± 0.5	83.08 ± 0.38
Butane-1-one	66	57.8	34.19 ± 1.48	54.32 ± 0.74	66.57 ± 2.82
THF	60.75	67.8	32.86 ± 1.27	50.45 ± 0.17	63.18 ± 2.43
Pure TBM powder	95.5		34.52 ± 0.46	50.99 ± 0.49	67.88 ± 0.48

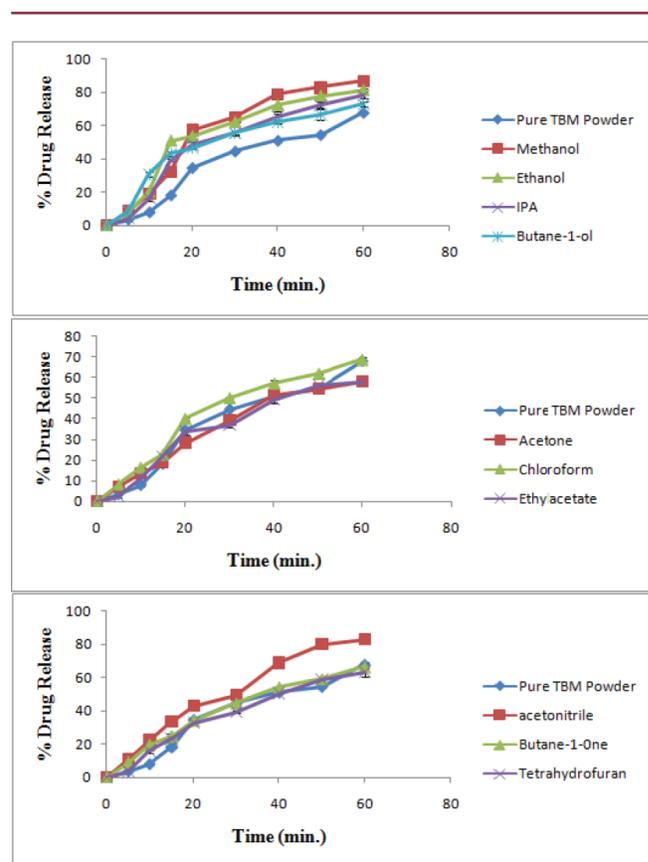


Figure 4. Dissolution profiles of pure TBM powder and TBM crystals from different solvents.

CONCLUSION

The crystal habit of tolbutamide was affected by the type of solvent from which it was crystallized. In this screening, no polymorphic crystals were observed. Only the external shape of the growing tolbutamide crystal was affected by the crystallizing solvent, without change in internal structure. Different crystal habits were prepared using various crystallizing solvents. Dissolution rates of the crystals were also influenced by crystal habit. Crystalline forms prepared by the solvent-change method, in which methanol and ethanol were used as solvents, had the smallest particle size, plate-like shapes, and higher dissolution rates. Those that resulted from acetone, ethyl acetate, and tetrahydrofuran were of larger size with needle, cubic, and prismatic crystal habits, respectively, and had lower dissolution rates. Hence, a critical evaluation of crystal habit and the proper selection of solvent during preformulation will help in maintaining batch-to-batch uniformity of raw materials and ensure reproducibility of dosage-form performance. The initial solvent-screening strategy provided a general method of using miniaturized tools on a routine basis to predict API performance.

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