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A new method for the preparation of pure topiramate with a micron particle size

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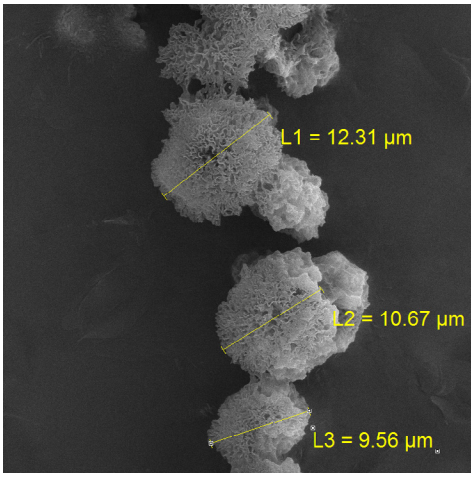
HIGHLIGHTS

- A micron-sized topiramate sample was synthesized by using of Triton X-10.
- The purification and reduction of the size of topiramate were performed in one step.
- The kinetic solubility of topiramate was improved by size reduction.

GRAPHICAL ABSTRACT



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ABSTRACT

Crude topiramate was prepared from the reaction between diacetonefructopyranose, sulfuric diamide, and 2-picoline. During a controlled processing the presence of Triton-X-100, crude topiramate in a methanol-water solvent, was converted to pure micron size topiramate particles. The factors affecting the purification and micronization of topiramate, such as solvent and anti-solvent type and concentration ratio, temperature, and mixing speed, were investigated. A mechanism for the preparation of topiramate was proposed based on the results of changes in the concentration of the raw materials and an investigation of the intermediates. In addition, the solubility rate of topiramate with different particle sizes has been determined.

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1. Introduction

Dissolution of drug is an important rule of drug absorption and bioavailability [1-3]. The relationship between particle size, bioavailability, and dissolution is well documented. Bioavailability is often directly dependent on the particle size for solid delivery systems because it controls dissolution solubility characteristics. It is well know that a fine particle size has more solubility. At present, most new drugs and 40% of drugs currently used in industry have poor solubility [1].

Several techniques have been used to overcome the solubility problems of poorly soluble drugs [4-10]. These techniques include amorphous formulations, salt/pro-drug formation, co-solvents, and complexation. In recent years, the use of micronized particles has been reported in pharmaceutical applications to increase the solubility rate of poorly soluble drugs [11-14]. Bottom up and top down are the two technologies resulting in micronized drugs or nanoparticles. In bottom up technology, the micronized or nano drug is precipitated by an anti-solvent method. The drug is dissolved in a solvent in the presence of a surfactant, and then precipitated by the addition of an anti-solvent as a micronized form [15-17]. In top down technology the particle is crushed by mailing or a high pressure homogenizer [18]. In these technologies the particle size is reduced by pressure, scrubbing, and abrasion which maybe damage the drug [19]. The particle size range for direct-compression tablets is a very important factor. In direct-compression tablets, the drug should have suitable properties of compaction behavior and powder flow [20]. Although particle size reduction increases solubility, it also increases the density of matter and the accumulation of particles. It should be kept in mind that the accumulation and particle density does not neutralize the positive effect of increased solubility [21]. Therefore, the use of micronized materials is more useful than nano-scale materials in the formulation of tablets [21].

Topiramate is a sulfamate-substitute of the natural occurring monosaccharide D-fructose with anticonvulsant or antiepileptic properties. It is designated chemically as 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranosesulfamate (Figure 1). It is a white or almost white crystalline powder with a bitter taste. Topitamate was invented by Maryanoff [22]. The solubility of topiramate is low in water (9.8 mg/mL) [23]. Topiramate is known as an anticonvulsant or antiepileptic drug [24]. It is also used to prevent migraine headaches [25]. Topiramate can also help people lose weight [26]. Topiramate is efficacious in the treatment of alcohol use disorders and is an alternative treatment to FDA-approved medications [27].

The preparation of active pharmaceutical intermediates (APIs) in various shapes and sizes is always considered. Topiramate is a new drug whose use is expanding, so far a grinding method has been used to prepare its various sizes. Usually grinding of materials is associated with weight loss of the product, destruction of the chemical structure due to heat and pressure, and consumption of energy [19]. In this work, we investigated the preparation of micronized topiramate using the sedimentation method.

2. Materials and Methods

2.1. Materials

Diacetonefructopyranose (99.21%) was purchased from Grindlays Pharmaceuticals Pvt. Ltd., India. Sulfuric diamide, 2-picoline, toluene, ammonia, and hydrochloric acid 37% were obtained from Aldrich. All compounds were used as received without further purification. Topiramate was synthesized in the lab.

2.2. Instruments

A high-performance liquid chromatography system (2 pumps waters 510, detector IR waters 410), FT-IR

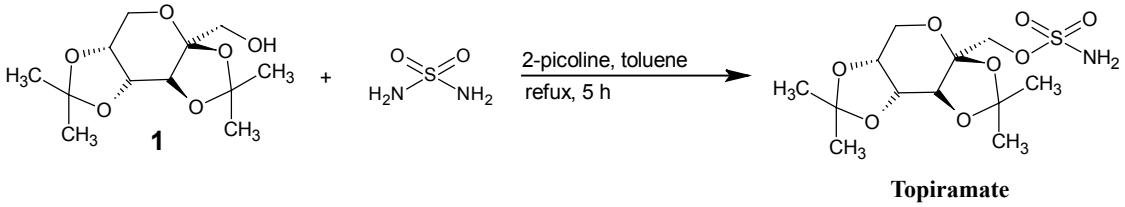

Fig. 1. Preparation of topiramate.

spectrometer (Philips PU 9624), scanning electron microscope (Tescan), and laser scattering particle size analyzer (Mastersize 3000, Malvern) were used to characterize purity and mesh size of the micronized topiramate.

2.3. Preparation of topiramate

In a three necked round bottom flask equipped with a magnetic stirrer, condenser, and thermometer, sulfuric diamide (9.6 gr, 0.1 mole), and 2-picoline (9.3 gr, 0.1 mole) were mixed in toluene (60 ml) and stirred at 50 °C. After 15 minutes, a two-layered mixture was obtained. Diacetonefructopyranose (10 gr, 0.1 mole) was added to the mixture. The reaction mixture was refluxed for 5 h. The reaction was cooled to room temperature. An aqueous solution of sodium hydroxide (4 gr in 60 ml of water) was added to the reaction mixture. The aqueous layer was separated and neutralized with HCl 37% (8.22 ml). The resulting crude product was filtered, washed with water (2×20 ml), and dried in oven at 50 °C for 3 h (24.45 gr, 72%).

2.4. Preparation of micronized topiramate

In a three necked round bottom flask equipped with a magnetic stirrer, condenser, thermometer, and addition valve connected to the peristaltic pump, crude topiramate (10 gr, 0.03 mole) and Triton-X-100 (0.02 gr) were mixed with methanol (10 ml). The mixture was refluxed for 5 min. until a clear mixture was obtained. The clear mixture was cooled to 30 °C and stirred at 600 rpm. Water (20 ml) was added to the mixture at a rate of 1ml/min by the peristaltic pump. Under these conditions, the mixture was stirred for 30 min. The reaction temperature was adjusted to 10 °C for 30 min. and the mixture was stirred for an additional hour. The resulting powder was separated by filtration, washed with water (2×5 ml) and dried at 50 °C under vacuum (50 mmHg) for 3h. The yield and purity of the micronized product (12 μm) were, respectively, 83% and 99.54% (by HPLC). 1H-NMR ($CDCl_3$) δ: 1.34 (s, 3H, isopropylidene CH_3), 1.42 (s, 3H, isopropylidene CH_3), 1.48 (s, 3H, isopropylidene CH_3), 1.55 (s, 3H, isopropylidene CH_3), 3.76-3.80 (d, 1H, j=12.9 Hz, H-6a), 3.87-3.92 (dd, 1H, j=13.0, 1.8 Hz, H 6-b), 4.22-4.24 (d, 1H, j=10.9 Hz, H-1a), 4.25-4.26 (dd, 1H, j=7.9, 1.0 Hz, H-5), 4.29- 4.30 (d, j=2.7 Hz, H-3), 4.31-4.33 (d, 1H, j=10.9 Hz, H-1b), 4.59-4.63 (dd, 1H, j=2.6, 7.9 Hz, H-4), 5.15 (s, 2H, NH_2).

2.5. Kinetic solubility studies

2.5.1. Sample preparation

A synthetic sample of topiramate was milled. Three samples of topiramate with mesh sizes of 841-1000 μm, 297-344 μm, and 149-177 μm were separated by sieves No. 18, 20, 45, 50, 80 and 100. A fourth sample of micronized topiramate with a mesh size about 12 μm was produced at the lab.

2.5.2. Solubility measurements

An excess of each of the topiramate samples (micronized, 841-1000 μm, 297-344 μm, and 149-177 μm) was poured into 100 ml glass vials containing 50 ml of water. The vials were capped and sealed with parafilm®. They were then placed on the shaker platform and continuously agitated at 100 rpm in a water bath maintained at 25 °C. They were sampled at intervals of 15 min. The samples were centrifuged and the concentration of clear solutions was determined by HPLC.

3. Results and discussion

3.1. Preparation of topiramate

In this work, we tried to provide a micronized crystalline topiramate in order to increase topiramate solubility. Topiramate was prepared from the reaction of **1** (Figure 1), 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose (diacetone fructopyranose), with sulfuric diamide and 2-picoline in toluene.

Purification of topiramate is normally performed in different solvents or mixed solvents such as hexane/2-propanol [22], ethanol/water [22], 2-propanol [28], acetone/water [29], and ethylacetate/hexane [30]. Due to the cheapness of alcohols, we used a mixture of alcohols and water to purify the topiramate. There was no significant difference between methanol and ethanol in the experiments. Therefore, a mixture of one volume of methanol and two volumes of water relative to the weight of crude topiramate was used as solvent for purification of the topiramate. It should be noted that

increasing the amount of methanol (as solvent) will reduce efficiency; and although increasing the amount of water (as anti-solvent) can increase efficiency, the purity of the product is reduced (Table 1).

Temperature is an important factor in the crystallization of topiramate. When the crude topiramate is dissolved in hot methanol and water and the mixture is slowly cooled down, a crystalline product with a coarse mesh is prepared [21]. Change in other parameters, such as stirring speed and anti-solvent addition rate, did not play a role in reducing particle size. According to reports [29], the use of surfactants affects the size of crystals formed. In this study, different amounts of a non-ionic surfactant, Triton-X-100, were used to produced micronized scale particles. The lowest amount of Triton-X-100 was 0.2% wt to crude topiramate. No uniformity was observed in particle size in amounts less than 0.2%. Mixing speed was the last factor to be investigated. The optimum mixing speed was found to be 600 rpm. The resulting micronized powder passed all the tests of USP 38 and had an average mesh size of 12 µm according to the results of SEM (Figure 2) and the laser scattering particle size analyzer.

3.2. Mechanism of reaction

Molar equivalent amounts of diacetonefructopyranose, sulfuric diamide, and 2-picoline were dissolved in toluene and refluxed. After an hour, the reaction stopped and the product was separated. The yield of reaction was 30%. The reaction was then repeated with half the amount of diacetonefructopyranose. This reaction efficiency was 30% and there was no change in the yield of product. In two other similar reactions, reducing sulfuric diamide and 2-picoline by half their initial values, the reaction efficiency was also halved. These

Table 1. Amount of methanol and water used for purification of topiramate.

Entry	Crude topiramate/methanol/water (w / v / v)	Yield (%)	Purity[1] (%)
1	1 / 1 / 1	82	99.94
2	1 / 1.5 / 2	71	99.77
3	1 / 2 / 2	65	99.95
4	1 /1 / 1.5	87	99.61
5	1 / 1 / 2	83	99.54

[1] Based on HPLC.

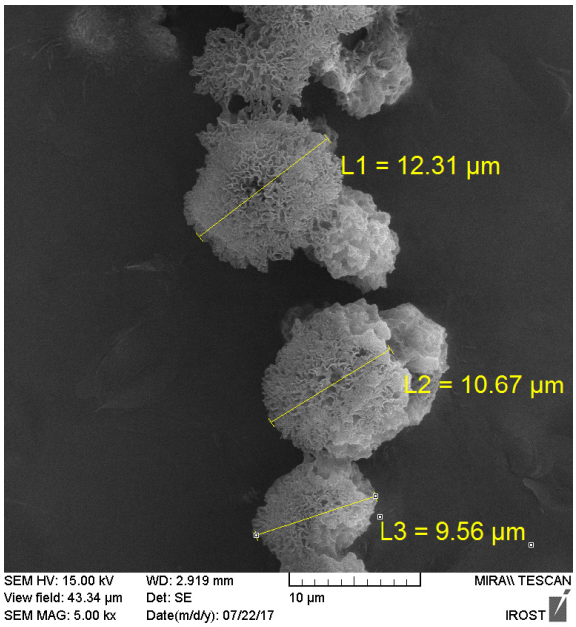

Fig. 2. The SEM image of micronized topiramate.

experiments showed that the concentration of sulfuric diamide and 2-picoline effect the efficiency of the reaction. The proposed mechanism for topiramate synthesis is shown in Figure 3. This suggests that initially an active intermediate **2** is generated by a reaction between sulfuric diamide and 2-picoline. This active intermediate **2** is attacked by diacetonefructopyranose and intermediate **3** is produced and 2-picoline is released. In the final step, intermediate **3** is fragmented into topiramate and ammonia. Thin layer chromatography (TLC) studies did not show any stable intermediate during the reaction.

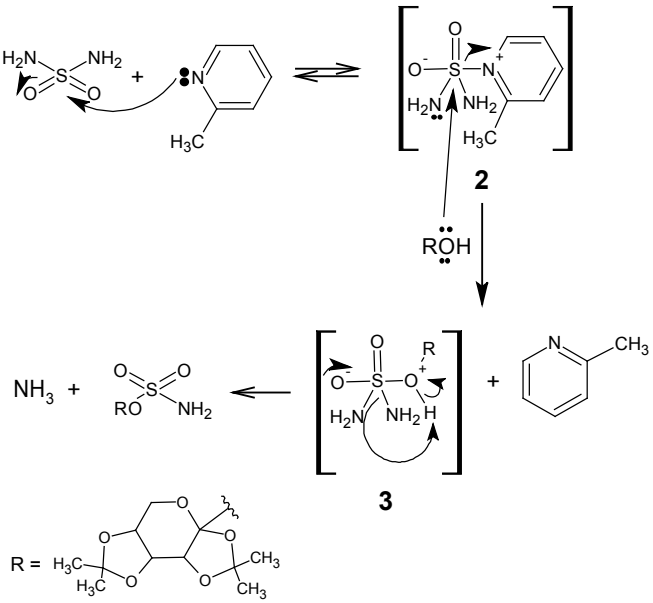

Fig. 3. The Proposed mechanism for topiramate synthesis.

3.3. Solubility of micronized topiramate

A sample of topiramate with an average particle size of 12 microns was generated using crystallization of crude topiramate in a methanol solvent with the aid of a surfactant. Three other samples of topiramate with different particle sizes (841-1000 μm, 297-344 μm, and 149-177 μm) were produced using topiramate screening. The samples were suspended in vials containing water and shaken at 25 °C. The contents of vials were filtered at 15-minute intervals and their concentration was measured by HPLC. As shown in Table 2 and Figure 4, The solubility time of topiramate (mg/ml) with a particle size of 12 μm is 45 minutes, which is half the time required for the solubility of the topiramate with a larger particle size (841-1000, 297-344, and 149-177).

4. Conclusion

Topiramate was prepared from the reaction of diacetonefructopyranose with sulfuric diamide and 2-picoline in toluene. Micronized topiramate was produced by a new non-grinding method. With the process control in this method, the purification and production of micronized particles were performed concurrently. The solubility time of the produced sample is half the time required to dissolve the samples containing larger particles of topiramate. The factors affecting the production of micronized topiramate, such as temperature, stirring speed, and surfactant effect, were investigated. Factors affecting the production of topiramate were also investigated, and based on this evidence a mechanism for this reaction was proposed. Based on the results of the reaction, diacetonefructopyranose does not play a role in the rate determining step. The reaction progress rate is dependent on the concentration of 2-picoline and sulfuric diamide.

Table 2. Topiramate solubility (mg/ml) variation with time for different particle sizes in water at 25 °C.

Time (min)	Mesh size			
	841-1000	297-344	149-177	12
15	1.4	2.1	2.7	4.5
30	2.1	3.0	3.9	9.6
45	3.9	4.3	5.1	9.8
60	5.2	6.1	6.5	9.8
75	6.3	7.6	7.9	9.8
90	8.7	9.4	9.8	9.8
105	9.5	9.8	9.8	9.8
120	9.8	9.8	9.8	9.8

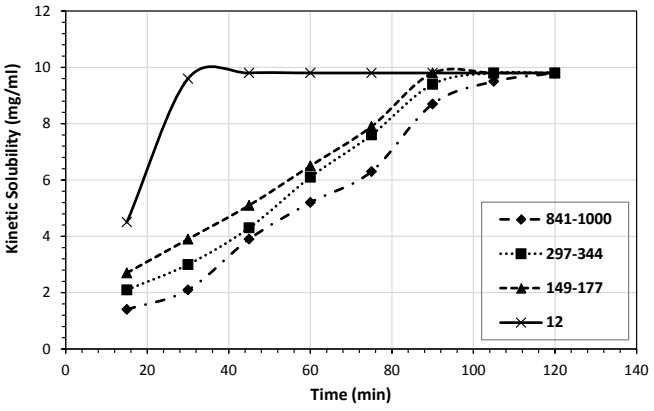

Fig. 4. Kinetic solubility of different particle size topiramate.

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