Control of crystal shape in the batch crystallization process

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Sphere crystallization has emerged as one of the areas of intensive research in the pharmaceutical industry. This design technique enables simultaneous crystallization and agglomeration in a single step, which can have a positive effect on downstream processes, such as filtration and drying.

In the batch crystallization process, the effect of the solvent, anti-solvent, and bridging liquid on the granulometric properties and the structure of the anti-arrhythmic drug, dronedarone hydrochloride was examined.

Based on the good solubility of dronedarone hydrochloride in acetonitrile and isopropanol that two solvents were selected for further examination. The metastable zone has been determined and the crystallization of two different systems was performed. In order to achieve spherical crystallization, the water was selected anti-solvent while ethyl acetate, hexane, and heptane were applied as breeding liquids.

The agglomerates were characterized by stereoscopic microscopes while XRD was used to determine crystal polymorphic forms. Although the shape and size of the crystals have been affected by the choice of solvent systems, their structure has not changed. As different shapes of crystals were obtained in different solvent systems, a drug release test in the phosphate buffer was performed. Needle-like crystals show a gradual release of the drug over time, while spherical clusters dissolve abruptly in a short period of time.

INTRODUCTION

To maintain chemical stability throughout transportation, packing, and storage, most active pharmaceutical ingredients (APIs) are synthesized in crystalline form. Crushing, sieving, mixing, and granulation are all energy-intensive procedures that APIs go through prior to final tableting. [1] Some of these procedures are wasteful in terms of energy use, can contaminate products, increase process time and energy consumption, and eventually can result in polymorphic form alterations. Direct tableting, which uses spherical crystal agglomerates to improve manufacturing procedures, has been created for tablet production. Bridging liquid, which is immiscible with the suspending medium, can be used to promote the formation of spherical crystals. [2] Today, spherical crystallization is used in the pharmaceutical, food, chemical, and military industries. [3]

Dronedarone is a class III antiarrhythmic medication that helps patients with paroxysmal or chronic atrial fibrillation regain normal sinus rhythm. The solvent, antisolvent, and bridging

liquid for the recrystallizations of dronedarone hydrochloride are chosen in this study, as well as the method for carrying out the crystallization process. The possibility of generating spherical agglomerates of dronedarone hydrochloride was investigated by modifying the solvent system, bridging agents, and mixing rate. [4]

MATERIALS AND METHODS

Materials

Dronedarone hydrochloride is a derivative of amiodarone used to treat atrial fibrillation. The chemical name of dronedarone hydrochloride is N- (2-butyl-3- (p- (3- (dibutylamino) propoxy) benzoyl) -5-benzofuranyl) methanesulfonamide. The molecular formula is $C_{31}H_{44}N_2O_5S$ and the molecular weight is 556.8 g/mol.

Solubility of dronedarone hydrochloride and mass portion of solvents for spherical agglomeration

Crystal 16 is used to determine the solubility of dronedarone hydrochloride in various solvents.

Ternary phase diagrams for solvent, antisolvent and bridging liquid were constructed in *DynoChem®software* to select a suitable zone for the preparation of spherical agglomerates (Figure 1).

Methodology

A double-walled crystallizer with the Rushton dimension, equipped with 4 baffles and a pitched 4-blade impeller, was used to perform crystallization. The crystallization procedure was carried out in isopropanol or acetonitrile, using water as the antisolvent. The process conditions for the experiments are shown in Table 1. The required amount of dronedarone hydrochloride was added based on the solubility data of dronedarone hydrochloride in isopropanol at 55 °C and acetonitrile at 50 °C and 55 °C. During the process of creating crystals in solutions, when water was added, bridging liquids such as hexane, heptane, or ethyl acetate were added in order to generate spherical crystal agglomerates.

Table 1. The process conditions for the conducted experiments.

Samples	Initial mass ratio (g/100 $ml_{solvent}$)	S/AS/BL	Mass portion (%) S/AS/BL	Temperature (°C)	Mixing rate (rpm)
A1	5,125	ACN/W/HEX	85.1/14.2/0.75	50	12.8
A2	3,880	ACN/W/HEX	79.0/19.32/1.7	50	12.8
I1	3,300	IP/W/EA	83.33/8.82/7.84	55	5.8
I2	3,300	IP/W/EA	76.19/4.71/19.14	55	5.0
I3	3,300	IP/W/EA	81.09/11.15/7.76	55	7.5
I4	3,300	IP/W/HEP	81.17/11.05/7.79	55	8.3

Characterization of crystals

After the crystallization process, the shape and size of the dried crystals were observed using an *Olympus SZX 16 stereomicroscope*. Using a *Shimadzu XRD-6300*, the structure of the produced crystals was analyzed by X-ray analysis.

Dronedarone hydrochloride dissolution test

The Tester *RC -6D from Zhengzhou Nanbei Instrument* was used to test the dissolution of dronedarone hydrochloride samples. The dissolution medium was 1000 mL of phosphate buffer, pH 4.5. The stirrer speed was 75 rpm and the buffer temperature was 37±0.5 °C. Sample solutions were withdrawn at predetermined time intervals (10, 15, 20, 30, 45, 60, 90, and 120 min),and then filtered with a *CHROMAFIL® Xtra PET -45/25 filter*. The amount of dissolved dronedaronehydrochloride in the sample solutions was analyzed with a *Shimadzu UV/Vis spectrophotometer UV-1280* at 289.8 nm.

RESULTS AND DISCUSSION

Table 2. Solubility of dronedarone hydrochloride in different solvents.

Solvent	Mass ratio ($g_{DRNDHCl}/100g_{soventl}$)
Methanol	>50
Dichlormetan	>50
Acetonitrile	0.75
2-propanol	0.65
Water	<0.1
Hexane	<0.1
Heptane	<0.1
Ethyl acetate	<0.1
Isooctane	<0.1

After evaluating the solubility of dronedarone hydrochloride in several solvents (Table 2), acetonitrile and 2-propanol were chosen as solvents for recrystallization. [5] Due to their high solubility, methanol and dichloromethane were eliminated for future research. Water was chosen as the antisolvent, whereas heptane, hexane, and ethyl acetate were chosen as the bridge liquids. In order to identify the region optimal for providing spherical crystallization, it was important to understand the equilibrium between the solvents used. Figure 1 shows ternary diagrams for chosen systems with research points indicated. All experiments were performed within the heterogynous region, with up to 20% mass proportions of water and bridging liquids (up to 25 mass%). In order for the system to crystallize, the weight of the solvent required to reach at least 75%. The concentration of dronedarone hydrochloride and hydrodynamic conditions influence the quantity and size of spherical crystals.

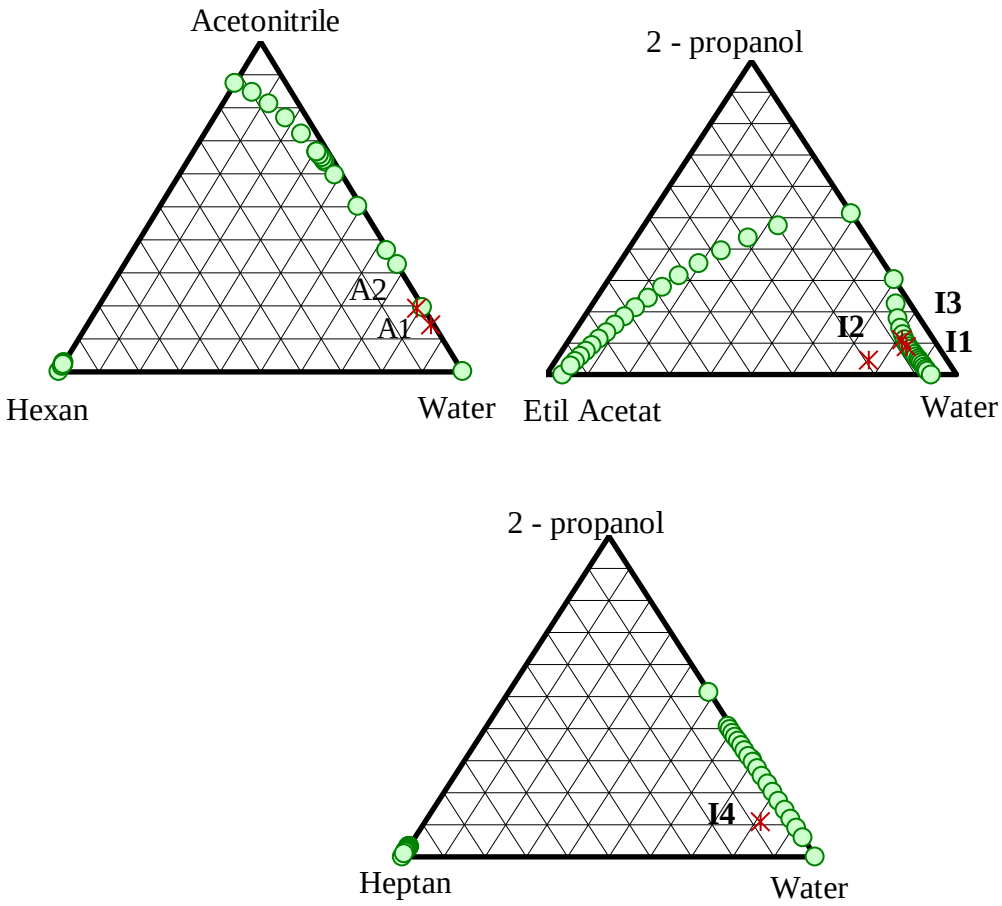

Figure 1. Ternary phase diagram of a) acetonitrile-water-hexane; b) 2-propanol-water-ethyl acetate; c) 2-propanol-water-heptane.

Stereomicrographs of crystals obtained from various solvent-antisolvent-bridging liquid systems are shown in Figure 2. Crystals obtained from acetonitrile are only partially aggregated. By comparing samples A1 and A2, it can be noticed that sample A2 contains more agglomerated crystals. In experiment A2, the initial concentration of dronedarone hydrochloride is lower, but the amount of bridging liquid (hexane) is higher, resulting in a higher proportion of agglomerates. Isopropanol-water-ethyl acetate system produced spherical agglomerates with varying diameters. Most of the spherical agglomerates are very fragile, and they fall apart when you touch them. The amount of agglomerated crystals in this system is reduced with the addition of the greatest quantity of bridging liquid. The isopropanol-water-heptane system produced elongated crystals (I4) with no spherical agglomerates. Because this sample was shaped differently than the others, its internal structure was investigated, and its solubility was compared to that of the spherical shape (A2).

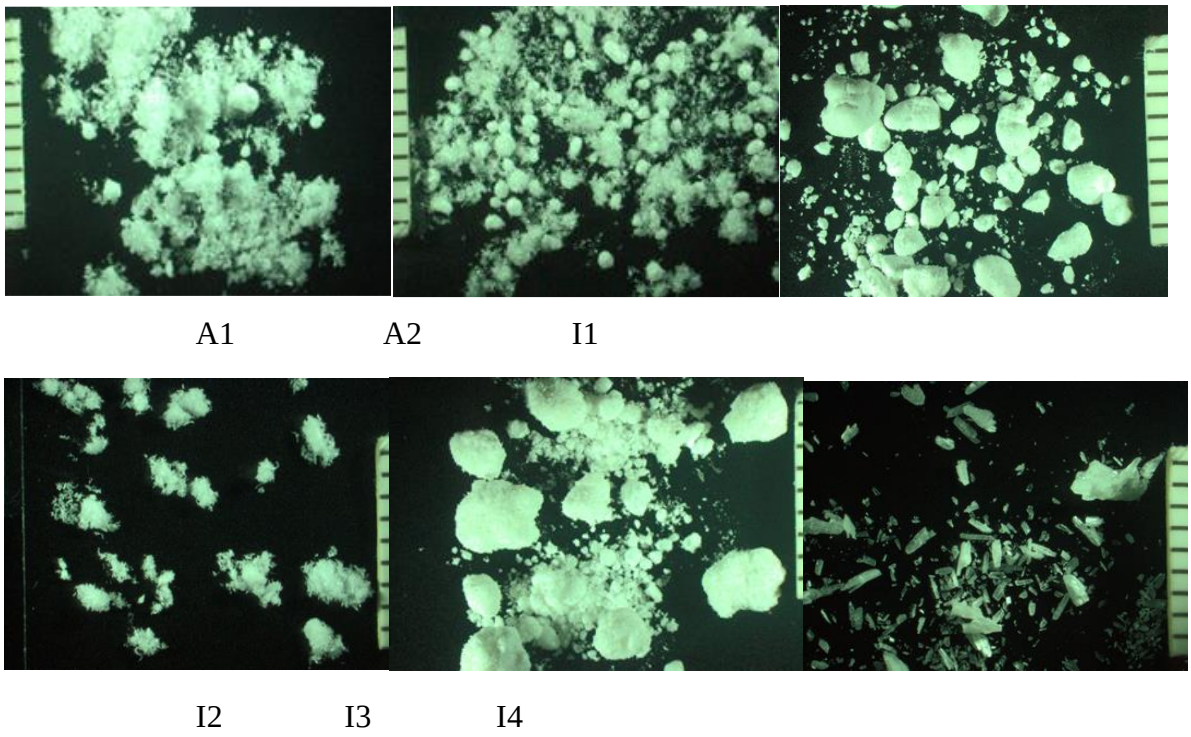

Figure 2. Stereomicrographs of crystals obtained in different solvent systems under stereomicroscope

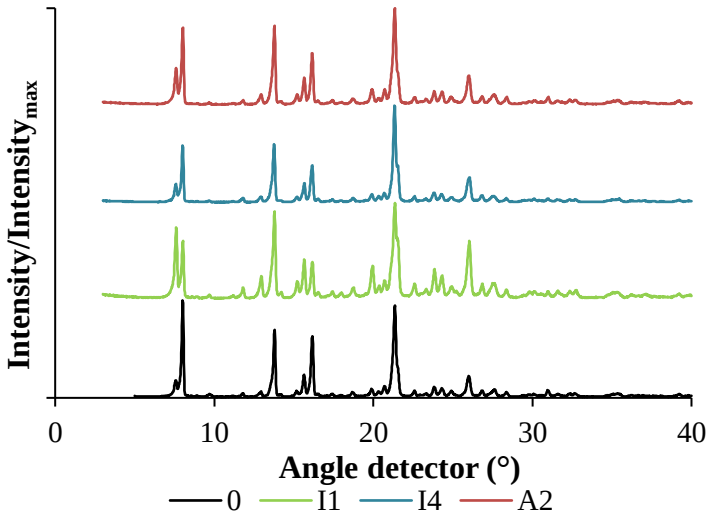

Figure 3. XRD spectra of dronedarone hydrochloride obtained in different solvent systems.

Figure 3 shows the X-ray diffraction data of the material before crystallization (0), as well as samples I1, I4, and A2. The change in the solvent system has no effect on the crystal's internal structure. Dronedarone hydrochloride is known to exist in three polymorphic forms: A, B, and C, with B being the most stable. [6] The X-ray peaks (7.62; 8.02; 13.78; 15.66; 16, 18; 19,98; 21,34; 26,02; Figure 3) indicate that this is not a stable structure B. The obtained pictograms can be compared to the structure described in the patent. [7]

Samples A2 and I4 were chosen for the dissolution test because they were produced with different solvents, bridging liquids, and crystal shapes. A UV/Vis spectrophotometer was used to determine the concentration of sample solutions that were withdrawn from solution at a predetermined period (Figure 4). Figure 4 illustrates a dissolution profile that differs between various samples. The sample I4, which is less desirable due to its elongated crystals, exhibits a

slow release over time (about 45 minutes for 80 % of the active pharmaceutical ingredient). In the case of the A2 pattern, when the substance was put into the phosphate buffer, it was released in a short period (10 minutes for 80% of the API). It is assumed that agglomerates, which are composed of small crystals, decompose and dissolve rapidly on immersion in phosphate buffer due to their size. In addition, these crystals are the result of recrystallization in various systems, which can also affect the dissolution rate of the active ingredient.

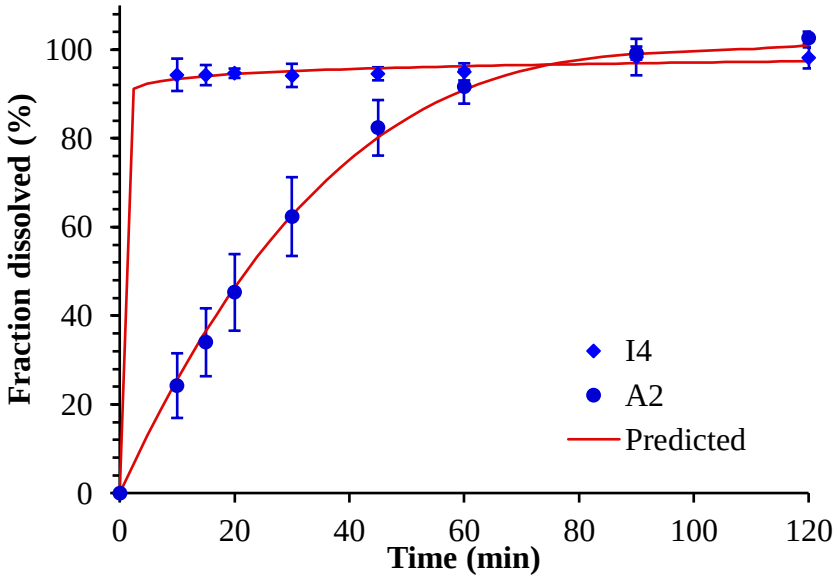

Figure 4. In vitro powder dissolution profile for samples A2 and I4.

Table 3 displays the parameters and correlation of the model used to explain the dissolution profile of the tested samples. While the two-parameter Korsmeyer-Peppas model accurately predicts the release of sample I4, the one-parameter Hixson-Crowell model predicts the gradual dissolution of sample A2.

Table 3. Parameters of fitted models for dissolution data

Korsmeyer-Peppas Model for I4 sample $FD = k_{KP} \cdot t^n$				**Hixson-Crowell Model for A2 sample** $FD = 100 \cdot \left[1 - \left(1 - k_{HC} \cdot t\right)^3\right]$			
Parameter	**Mean**	**SD**	**RSD(%)**	**Parameter**	**Mean**	**SD**	**RSD(%)**
k_{KP}	89.867	2.177	2.423	k_{HC}	0.009	0.002	18.839
N	0.017	0.000	2.124				

CONCLUSION

The effect of the system (solvent, anti-solvent, bridging agent) on the granulometric characteristics and structure of the dronedarone hydrochloride crystals created was studied.
As a result of the solubility of dronedarone hydrochloride, isopropanol and acetonitrile were chosen as solvents.
Water was chosen as the anti-solvent for spherical crystallization, while ethyl acetate, hexane, and heptane were chosen as the bridging agents.
The change in the solvent system has no effect on the structure of the crystals formed.

The micrographs show that the acetonitrile-water-hexane system produces a more favorable crystal shape and has a higher tendency to form agglomerate.
The profile of dissolution reveals the ability to distinguish across various morphologies.

Acknowledgments

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