PARAMETRIC STUDY OF COATING BY COOLING CRYSTALLIZATION

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RÉSUMÉ

The purpose of this work, the parametric study of the operating conditions that can affect the new technology of coating of ibuprofen naked tablets manufactured by compression by surose solution using cooling crystallization. Seeding crystallization was used in this new process, tablets of ibuprofen were used as heterogeneous seeds (core materials) were coated with sucrose was used as coating material. The growth rate on the surface of the naked tablets and surface morphologies were investigated under various experimental conditions. These experimental conditions are: The viscosity of the coating solution, surface properties of the naked ibuprofen tablets (surface tension and contact angle). The optimal conditions were found to achieve compact and uniform coating.

Mots Clés: *Crystallization, Coating, Ibuprofen naked tablets, Parametric study.*

NOMENCLATURE

Symboles :

K_g crystal growth coefficient
g : Order of crystal growth rate, K
ΔC supersaturation.
ΔT degree of subcooling, K
ΔL thickness, m
Δt retention time, min

Lettres grecques :

σ surface tension, mN /m
θ contact angle, deg

Indices / Exposants :

MSZW metastable zone width

1. INTRODUCTION

Most tablets today are coated after being pressed. This process is necessary for various reasons. It can strengthen the tablet, control its release, improve its taste, making its handling and packaging easier and protect it from moisture and light. Sugar coating, one of the earliest methods, is still widely used in the confectionery industry, pharmaceutical, as well as food markets [1-3]. Until now, the sugar coating process with spray atomizers has been the most frequently employed to produce coatings in the pharmaceutical industry [4]. However, even if the sugar coatings were popular for a long time, they are still not optimized and present several drawbacks such as cracking and splitting on the surface of the coating, fast dissolution rates and non-uniformities in the coatings [5]. One of the first studies devoted to use the coating process by crystallization on pharmaceuticals has been made by Kim and Ulrich [5-6]. They used isomaltulose or ascorbic acid as coating materials and hemi-spherical pastilles from bisacodyl ($C_{22}H_{19}NO_4$), produced by a melt solidification process, as heterogeneous seeds. A

homogeneous crystalline-formed coating was obtained by this process. The coated seed was very uniform and the surface was consistent crystalline [7]. The focus of this work is the parametric study of new coating technology by cooling crystallization applied on the naked tablets of ibuprofen.the optimal operating condition affect the surface nucleation, growth rate and crystal morphology were investigated experimentally. These experimental conditions are: The viscosity of the coating solution, surface properties of the naked ibuprofen tablets (surface tension and contact angle).

2. METHODE EXPERIMENTALE

Sucrose $C_{12}H_{22}O_{11}$ dissolved in distilled water was used as coating material. Ibuprofen uncoated tablets (200 mg, average diameter 10 mm, average weight 328 mg ±5 %) manufactured by NADPHARMADIC PRODUCTION were used as heterogeneous seeds (core material). The viscosity of sucrose was measured versus temperature for different saturation concentrations ranging from 67.83 to 76.72 wt%. Then for a particular saturation concentration 72.36 wt% at 50 °C, the viscosity was determined versus temperature for a different degree of subcooling by means of a HAAKE Viscotester VT550 device.

The surface tension of the coating materials was measured for different supersaturated sucrose solutions at a degree of sub-cooling (ΔT=10 K) using a digital tensiometer (K10ST KRUSS GmbH).

To examine the effect of surface properties (surface tension and contact angle on the coating process, hence on the surface nucleation, growth rate and crystal morphology, another type of heterogeneous seeds (glass beads) were used. The drop method, an optical technique, in which a droplet of supersaturated coating material with known surface tension (σ) is placed on the surface in this case of the naked ibuprofen tablet is shown in Fig. 1. The contact angle θ is obtained by drawing a tangent along the droplet edge where the solid, liquid, gaseous phases meet by using a camera.

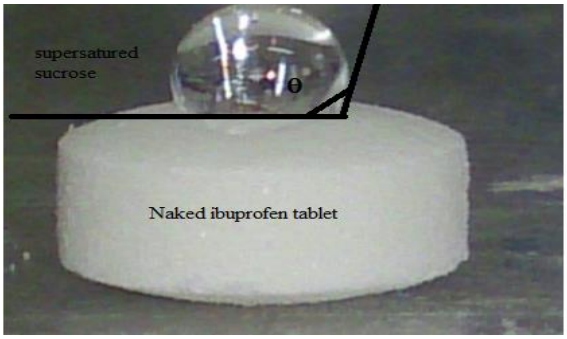


Figure. 1 Contact angle between supersaturated sucrose solution and the used seed material.

The experimental apparatus is described in Fig. 2. It consists of 100 mL double jacketed crystallizer,a programmed thermostatic bath, a stirrer and a sieve for the separation of coated tablets out of the mother liquid.

The coating solution was prepared in the crystallizer; the homogeneous solution was cooled down using a programmed thermostat until reaching the desired temperature. Then, the heterogeneous seeds (uncoated ibuprofen tablet) were added to the supersaturated sucrose solution at optimal range of viscosity. Then, the sucrose nuclei were generated and grown on the surface of ibuprofen naked tablets. At the end of the coating process, the ibuprofen coated tablets were separated with a sieve from the mother liquid. Furthermore, an optical microscope (OM) images were used to investigate the coating layer thickness and the surface morphology of the coatings against the retention time, the external surface of coated tablet was observed by means of the SEM technology.

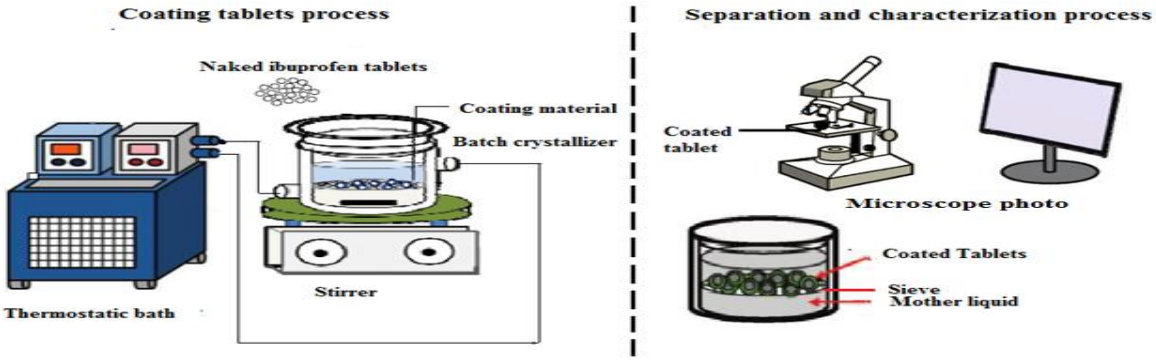


Figure. 2 Schematic diagram of experimental setup

3. RESULTATS

3. 1. Parametric study of process operating conditions

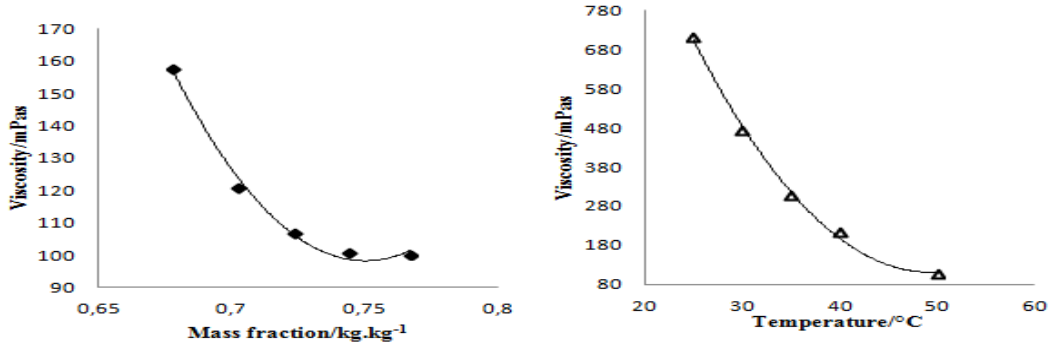
3. 1. 1. Effect of the viscosity of coating material

Figure.3 shows the viscosity of the sucrose-water system as function of temperature. Due to the Newtonian nature of the sucrose solution, the measurements were made at a constant shear rate ($100\ min^{-1}$).

Contrary to other sugar solutions, for which viscosity increases with increasing solubility, for sucrose, the viscosity of saturated solutions decreases when the solubility increases, as may be observed in Figure. 3(a). Furthermore, as seen in Figure.3 (b), sucrose viscosity increases with increasing degree of sub-cooling. Bensouissi et al. [8] have shown that such difference may results from the difference in sucrose conformation in concentrated solutions and also from their interactions with water. Moreover, low sucrose solubility implies a high saturated viscosity which inhibits the diffusivity in solution.When the viscosity reaches a limit value of 473.23 mPas of supersaturated sucrose, the growth rate is inhibited. The factor that tends to inhibit the crystallization rate is the viscosity [9]. The higher the viscosity the lower is the crystallization rate. Other factors such as a temperature and concentration play an important role during the coating by crystallization, too.

Increasing of supersaturation means an increase in crystal growth rate, but at the same time an increase in viscosity means a decrease in growth rate. Working at low viscosity and high temperature would lead to dissolution of the naked ibuprofen. The naked ibuprofen tablets (heterogeneous seeds) would be dissolved before the crystallization phenomenon takes place due to the viscosity, retention time and interfacial tension.

Ibuprofen naked tablets coating by crystallization is possible for a viscosity of the solution ranging from 101.11 to 473.23 mPas. At viscosity values less than 101.11 mPas the naked tablets were dissolved.

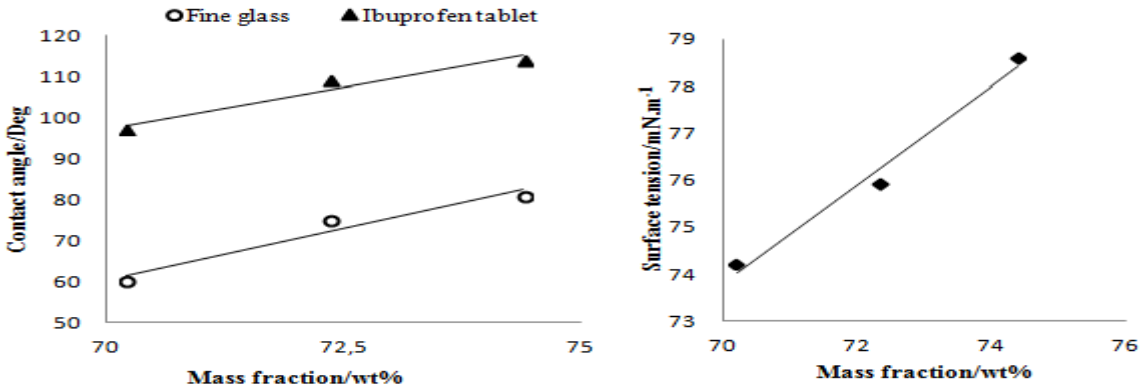


(a) (b)

Figure. 3 Viscosity of sucrose solutions versus temperature under experimental conditions: Shear rate 100 min^{-1}, cooling rate 0.1 K/min.
(a): Viscosity of saturated sucrose solutions versus different saturation concentrations.
(b): Viscosity of supersaturated sucrose solution versus temperature for different degree of subcooling starting from saturation concentration at 50 °C.

3. 1. 2. Effect of surface characteristics

Surface nucleation, growth rate and surface morphology are essential elements for homogeneous and crystalline coating by cooling crystallization. The surface nucleation depends on various parameters such as: The surface tension of the supersaturated sucrose surface characteristics of the used seeds (contact angle).



(a) (b)

Figure. 4 Contact angle and surface tension as function of different supersaturated sucrose concentration, (a): Contact angle at different surface characteristics, (b): Surface tension of supersaturated sucrose at a degree of sub-cooling 10 K.

Figure. 6(a-1) and (b-1) show the microscope images which gives the crystal morphology of the coated seeds is growing against the retention time.
Figure. 6 shows less nuclei on the smooth surface of glass beads, but a high number of nuclei agglomerate on the rough surface of naked ibuprofen tablets, under the chosen conditions which means that the surface nucleation could be improved by the larger contact angle and rougher surface of the seed particles.
From these results, it can be concluded that, the contact angle (surface characteristics of seeds, surface tension) has a big effect on the surface morphology and the growth rate.

Growth rate G is the evolution of the coating thickness, L on the used heterogeneous seeds by elapsed time Δt.

$$G = \frac{\Delta L}{\Delta t} = K_g \Delta C^g \qquad \text{(Eq.1)}$$

Here the increasing of the thickness ΔL is measured by microscope images.
In Figure. 6 the effects of the surface characteristics are shown with respect to the growth rate. The contact angle increases as the surface of used seeds gets rougher. The crystal growth rates obtained on the surface of the ibuprofen tablets with a high contact angle are relatively higher than on the surface of the glass beads the lower contact angle.

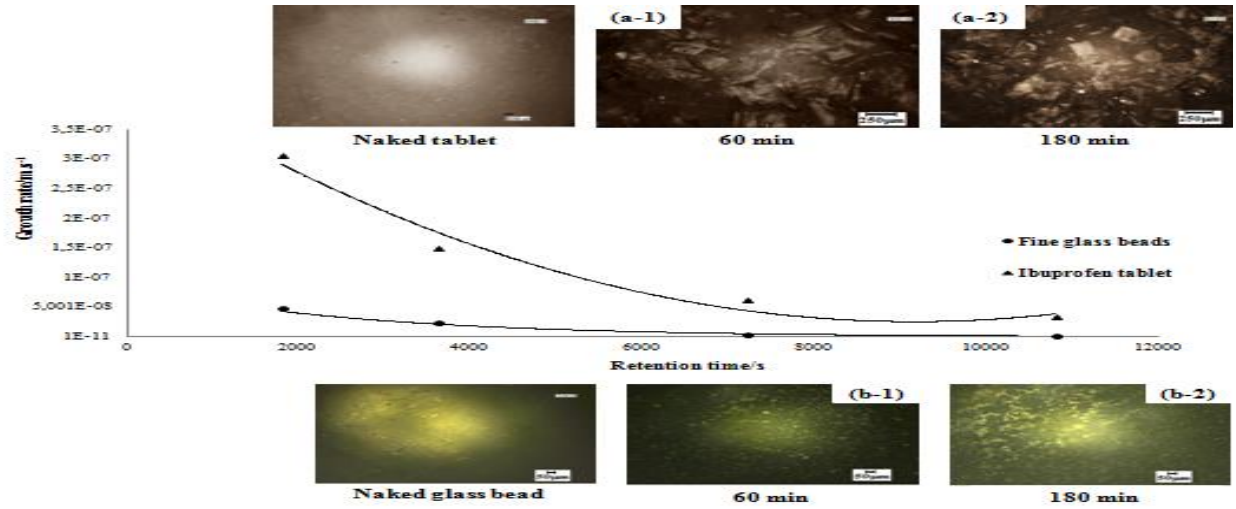


Figure. 5 Growth rates and surface morphologies of seed particles and their coating, (a- coated ibuprofen tablet), (b- coated glass beads), at optimal operating conditions: Concentration of coating material 72,36 wt%, degree of sub-cooling 10 K, agitation speed 200 rpm, retention time 180 min, spatial resolution (100).

3. 2. 5. Kinetic crystal growth on ibuprofen tablet surface

Figure. 6 shows the relationship between the growth rate and the supersaturation on the surface of naked tablets. The solute excess, expressed by supersaturation ΔC in the liquid can be deposited on the surface of naked tablets and can be represented by the amount of dry sucrose on this surface (coated sample).

The growth rate increased with increasing supersaturation on the surface of the used tablets.

The ln–ln plot of equation 2 giving crystal growth rate versus supersaturation can be expressed by:

$$ln\ G = g ln\ \Delta C + ln\ Kg \qquad \text{(Eq.2)}$$

The graphical representation of equation 2 gives the power of supersaturation $g = 1.0634$ as the slope and the coefficient of crystal growth $Kg = 1.05\ .10^{-4}$ as the intercept. Then, the crystal growth rate expression against supersaturation is given according to the following equation:

$$G = (1.05 \times 10^{-4})\ \Delta C^{1.0634} \qquad \text{(Eq.3)}$$

The supersaturation power on the naked tablets surface obtained in this case is much smaller compared to the supersaturation power of crystals growing freely in bulk liquid of crystallizers which is about 5.7 [7]. The reason is that a high number of nuclei don't occur on the seed particle surface, but rather stay in the bulk.

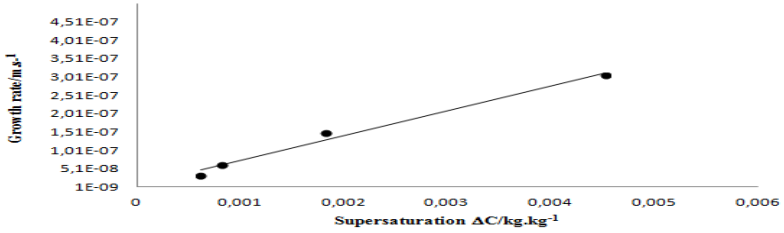


Figure. 6 Growth rate versus sucrose supersaturation on the ibuprofen naked tablet surface

A SEM image of the external surface morphology of a formed coating shown in Figure. 7(a), was uniform and very compact. In Figure. 7(b), one can see the clear distinction between the naked tablet and the newly formed coating layer. The crystalline layer is grown in one direction without any splitting or cracking. The surface morphology shown in Figure. 7(c) was consistant crystalline.

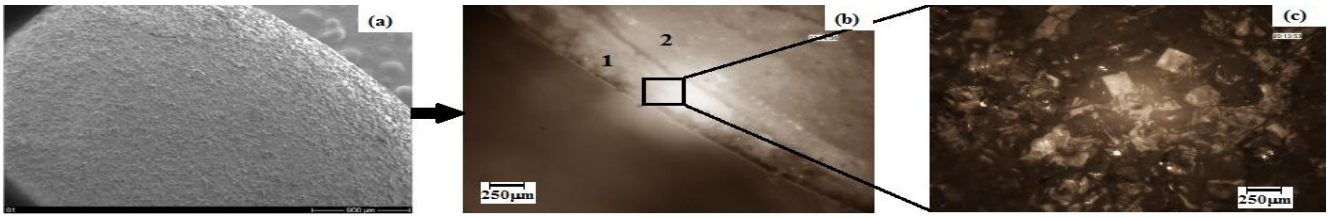


Figure. 7 (a): SEM image of the external surface morphology of a final coated ibuprofen tablet spatial resolution (100). (b): Microscope image of a coated ibuprofen cross section, (b1): Thickness of coating, (b2): Cross section of naked ibuprofen, (c): Microscope image of crystal morphology of coated surface.

4. CONCLUSIONS

A new coating technology was applied on "ibuprofen naked ibuprofen tablets" under various experimental conditions. The feasibility study was proven by a uniform and crystalline coating without cracks on the surfaceof the naked ibuprofen tablets. The viscosity of the coating material was examined. It was found, that at a lower viscosity of sucrose, the naked ibuprofen tablets were dissolved.

The process was carried out under several experimental conditions (viscosity of sucrose, surface properties of used seeds, surface tension and contact angle. The crystal growth rate and the surface morphology of coating are influenced by the contact angle related to the surface properties of the used seeds and the concentration of the coating material. The increase of the contact angle leads to the increase of the crystal growth rate and uniform surface morphologies. Finally, the parametric study for this new process was achieved determined experimentally.

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