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Influence of the type of enteric coating suspension, coating layer and process conditions on dissolution profile and stability of coated pellets of diclofenac sodium

Roberta Albanez [a,*], Marcello Nitz [a], Osvaldir Pereira Taranto [b]

[a] Mauá Institute of Technology (IMT), São Caetano do Sul, São Paulo, Brazil
[b] School of Chemical Engineering, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

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ABSTRACT

In this work, diclofenac sodium pellets were produced through an extrusion/spheronization process and subsequently coated in a fluidized bed coater column with a Wurster insert. The aim of this work was to study the coating of pellets with two commercial aqueous enteric polymer suspensions, Advantia® Performance and Acryl-Eze® MP. The coating process was studied with a 2^3 experimental design. The variables were as follows: inlet air temperature, suspension flow rate and coating polymer. The response variables were as follows: the process efficiency, which generated results above 78.2%, and the agglomeration fraction, which generated results below 8%. The polymer coating type was the variable that influenced the response variables the most. The minimum masses gain needed to achieve enteric release were also determined: Acryl-Eze® MP: 9.7% and Advantia® Performance: 8.6%. The coated pellets were tested for drug content, dissolution and stability. Neither the drug content nor the release profiles were significantly affected by storage at 40 °C and 75%. The suspensions were tested for rheology, contact angle and static wettability to investigate the characteristics of the polymer.

1. Introduction

Oral solid forms of medication are broadly accepted and most commonly administered because tablets and capsules are a unit dosing form that enables a simple and precise administration of a single dose. Multiple-unit dosing forms, such as pellets, exhibit well-known biopharmaceutical advantages compared to larger single-unit forms [1]. Dispersing these pellets throughout the gastrointestinal tract decreases the risk of irritation and dose dumping, resulting in more reproducible drug absorption. In addition, their spherical shape is ideal for film coating [2,3].

Coating a solid dosing form in a polymeric film may generate a product that exhibits a controlled release of active components, protection from external conditions, masks the taste and odor and provides physical and chemical protection to the specified component [4]. Two major types of controlled release profile have been reported: sustained, which reduces the dosing frequency compared to the conventional form, and delayed release, where the drug is released sometime other than immediately after administration, as observed in enteric-release forms. pH-sensitive enteric coatings are commonly used to deliver drugs to the small intestine [5].

Many commercial aqueous coating suspensions are available: Aquacoat®, Eudragit®, Kollicoat®, Advantia®, Acryl-Eze® and Surrelease®. The suspension blend is chosen based on the desired release profile. The aqueous dispersions are advantageous for toxicological and environmental, but have critical issues related to fluid-bed coating, film formation and stability [2,6].

Three elementary configurations are commonly used when coating pellets with a film: top-spray, bottom spray (appropriate for Wurster insert) and Tangential spray. The fluid bed coater with the Wurster insert is the most suitable apparatus for coating small particles with a film [7]. This configuration is characterized by a bottom-spray nozzle and a Wurster tube, which is centered above a perforated distributor plate. The particles are circulated through the equipment and sprayed with a suspended coating [8,9].

Film coating is a complex process because too many variables are involved, and varying these parameters is generally restricted. The objective of this process is to apply spray droplets uniformly and to dry them at the proper rate, avoiding agglomeration and elutriation. Therefore, the development of these products and processes is always very complex [10].

The process variables that influence the coating efficiency include the following: the type of fluid bed equipment, the inlet air temperature and humidity, the air pressure used for atomization, the spraying nozzle position, the size distribution of the beads, the flow rates of the air and coating suspension, the type of coating suspension and the subsequent

* Corresponding author at: Mauá Institute of Technology, Praça Mauá, 1, 09580-900, São Caetano do Sul, SP, Brazil. Tel.: +55 11 42393008.
E-mail address: roberta.albanez@maua.br (R. Albanez).

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curing process [7,11,12]. In this work, a fluidized bed coater column with a Wurster insert was used. This type of bed is one of the best systems for coating particles. One of the major advantages of this system is that it avoids dead zones [13].

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) in the aryl-acetic acid class used to treat degenerative joint diseases, such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis; it also has both analgesic and antipyretic properties. The use of NSAIDs is limited by the relatively high incidence of their gastrointestinal side effects: indigestion, hemorrhage, mucosal erosion and ulceration [14]. However, these side effects are not the only reasons to justify the use of enteric release formulations. Palomo et al. [15] showed that exposure to acidic conditions considerably reduces the water solubility of these compounds, which significantly affects the drug release rate. De Castro et al. [16] and Albanez et al. [10] showed that pre-treating sodium diclofenac with 0.1 N HCl affects its dissolution rate in pH 6.8 buffer. Therefore, the salt must be protected from the gastric juices to avoid losses in bioavailability.

After considering all of the advantages of multi-particulate systems and the need to protect diclofenac sodium from acidic media, the purpose of this work was to study the coating process of diclofenac sodium pellets with two commercial aqueous enteric polymer suspensions, specifically Advantia® Performance and Acryl-Eze® MP. These two suspensions are dispersible in water, which saves preparation time. The influences of the inlet air temperature, the flow rate of the suspension and the type of coating suspension on the coating process were evaluated, and the polymer layer required to provide stable enteric release according to the United States Pharmacopeia [17] standards was found for each type of coating suspension.

2. Material and methods

2.1. Chemicals

The diclofenac sodium used was manufactured by Suzhow Ausum Fine Chemical (Suzhow, China). Microcrystalline cellulose (MCC) 101 is the primary diluent used when manufacturing pellets; this material was obtained from Mingtai Chemical (Taoyuan Hsien, Taiwan). Hypromellose, Methocel E5LV was supplied by Colorcon (Dartford, Kent, UK) and was used as a binder. This material was used as the granulation liquid and was added in a 0.5% w/w aqueous solution. Polyethylene glycol (PEG) 4000 is also a binder; it was manufactured by Oxiteno (São Paulo, Brazil). Mannitol, which was obtained from Qingdao Bright Moon (Shandong, China), was also used as a binder. Croscarmellose sodium, which was manufactured by Amishi Drugs and Chemicals (Ahmedabad, Gujarat, India), was used as a disintegrant. Silica Aerosil 200 (Degussa, Frankfurt, Germany) was used as an anti-adherent during the spheronization step. Analytical reagents were supplied by Synth (Diadema, São Paulo, Brazil). The coating polymers used in this work were Acryl-Eze® MP, which was kindly supplied by Colorcon (Dartford, Kent, UK), and Advantia® Performance, which was supplied by Ashland (Ashland, KY, USA).

2.2. Methods

2.2.1. Pellet preparation

The diclofenac sodium pellets were prepared using an extrusion–spheronization process. Microcrystalline cellulose (MCC) 101 (42.1%), diclofenac sodium (27.0%), mannitol (12.9%), polyethylene glycol (PEG) 4000 (12.6%) and croscarmellose sodium (5.2%) were blended in a planetary mixer (Ciranda Chrome Automatic, Arno, São Paulo, Brazil) with an aqueous 0.5% w/w methocel solution (0.14%). Each wet granulation was passed through a gravity feed lab-scale radial extruder (EX50, Zelus, São Paulo, Brazil) with a 1.0 mm screen at 50 rpm. Six-hundred-gram batches were spheronized at 900 rpm for at least 2 min in a model ES50 spheronizer (Zelus, São Paulo, Brazil).

Table 1
Size distribution of pellets used in the coating experiments.

Size range (mm)	Mass (g)	%
0.85 < d < 1.00	55	16
1.00 < d < 1.18	218	62
1.18 < d < 1.40	77	22
Total	350	100

The pellets were then dried in a hot air oven at 50 °C for 36 h. The formulation was based on the study reported in Ref. [10].

2.2.2. Film coating

The coating experiments proceeded in a fluid bed coater column with a Wurster insert (model R-060, by Zelus, São Paulo, Brazil). The Wurster column consists of a concentric cylindrical insert inside an outer cylindrical chamber (bed) with a gap between the insert and bottom (distributer) plate. Hot air is injected in the bottom of the bed, and during the coating process, the pellets are pneumatically transported through the insert. The pellets dry as they pass into a fountain zone, where they lose their momentum and fall into the annulus. Afterwards, the particles flow downward in the annulus in a plug flow manner and re-enter the insert. This cycle repeats until the desired amount of coating is deposited on the pellets [18].

During all of the tests, the airflow rate was $4.9 \cdot 10^{-3}$ g/min, and the initial mass of the pellets was 350 g with the size distribution shown in Table 1. A double-fluid atomizing nozzle with a 0.7-mm orifice was used. The absolute atomizing air pressure was 2.5 bar. The coating suspension was stirred continuously during the coating experiments while being fed with a peristaltic pump (Provitec, DM7900, São Paulo, Brazil).

The airflow rate value was 1.5 times the minimum fluidization flow rate, which was verified previously through a fluid dynamic study of a fluidized bed with a Wurster insert.

A 2^3 experimental design [19] was developed to determine the influences of the inlet air temperature T (°C), suspension flow rate (g/min) and coating polymer P (Acryl-Eze® MP and Advantia® Performance) on the coating process. The variables and the levels used during the experimental design are listed in Table 2. The experiments were performed in a random order.

The 8 possible combinations of the variables were tested in duplicate. The response variables were the coating efficiency and the agglomeration index. The coating efficiency (η%) was calculated by dividing the actual mass gain by the theoretical mass gain. The actual mass gain (φ%) was determined by weighing the dried pellets before and after coating; the theoretical mass gain is the mass that would have been achieved if all of the solid material in the suspension had adhered to the surface. The agglomeration index (m_{agg}%) is the mass of the agglomerates relative to the total mass of pellets. The statistical analyses were performed using the Statistica 8.0 software (StatSoft).

Additional coating experiments were performed to find the minimum amount of each enteric suspension needed to provide the desired enteric release profile. Three-hundred and fifty grams of pellets with the size distribution shown in Table 2 were placed in the fluid bed. The suspension airflow rate was $4.9 \cdot 10^{-3}$ g/min. The inlet air temperature was 55 °C. The amount of suspension sprayed at 5.7 g/min could

Table 2
The variables and the respective levels used in the experimental design.

Variables	Level	
	Lower (−)	Higher (+)
Temperature, T (°C)	55	65
Flow rate (g/min)	2.5	5.7
Coating polymer, P	A	B

Coating polymer: A = Acryl-Eze® MP and B = Advantia® Performance.