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DISSOLUTION PROFILES OF FLUID BED COATED SMALL DIAMETER PARACETAMOL PELLETS USING APPARATUSES 1 AND 3

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Abstract

The purpose of this study was to coat pellets containing paracetamol in a fluid bed in order to obtain more favorable dissolution characteristics for these pellets, using both apparatus 1 (basket) and apparatus 3 (Bio-Dis®), in order to formulate orally disintegrating tablets (ODT). Accordingly, pellets were produced via the extrusion-spheronization process, and subsequently dried in a fluid bed. Then, coating formulations containing different proportions of PVP VA64 / PEG 4000 were applied in the fluid bed. The percentage data for paracetamol dissolved over time was subjected to statistical evaluation by hierarchical cluster analysis. The results indicated that the presence of PEG 4000 in the coating formulations was capable of modifying paracetamol delivery from the pellets, a fact that was observed in both the dissolution methods employed (apparatus 1 and apparatus 3). Furthermore, both methods were capable of satisfactorily distinguishing the formulations obtained. However, Bio-Dis® presents the advantage of enabling a dissolution method in which a pH gradient, such as that observed in the mouths and stomachs of human beings, to be reproduced with relative ease.

Keywords: multivariate analysis, orally disintegrating tablets, coating.

1. Introduction

Dissolution tests are commonly used for quality assurance purposes, as well as research and development processes, especially those involving solid oral dosage forms. In order to evaluate drug delivery from immediate-release solid dosage forms, apparatuses 1, 2, 3 and 4 of the United States Pharmacopeia (USP) are generally used. Of these, apparatus 1 (basket) and apparatus 3 (reciprocating cylinder) are particularly useful for evaluating multiparticulate systems. The use of apparatus 3, also known as reciprocating cylinder or Bio-Dis®, is an alternative to apparatus 1, since

in this system dosage forms can be continuously subjected to different pH conditions, and it presents superior hydrodynamics compared to apparatus 1 [1,2].

Multiparticulate systems consist of pellets, granules and mini-tablets, and they have a number of advantages over monolithic systems, such as being free flowing throughout the gastrointestinal (GI) tract, with predictable movement; a reduced risk of localized irritation in the GI tract; being less reliant on the nutritional state of patients, with regards to the absorption of the drug; less risk of adverse effects pertaining to dose dumping; and, reduced inter-individual and intra-individual variability [3,4].

Among these multiparticulate systems, pellets are especially worthy of note, due to their significant potential for application in oral dosage forms, such as orally disintegrating tablets (ODT), where patients do not require water for ingestion, among other advantages [5-9]. ODTs may be prepared by compressing coated pellets, thus enabling the unpleasant taste of some drugs to be masked, considering that this is an important factor with regards to the use of this type of delivery system [10,11].

Therefore, the production of small-diameter pellets that are then coated and later transformed into tablets is an interesting method for obtaining ODTs, and determining the most suitable coating, among other factors, for delivering a drug from a dosage form of this type is of great importance to its success [10,11].

Among the different processes used for coating pellets, fluid bed technology stands out. This involves applying a solution over the pellets, which remain suspended on an air flow. While this coating is being applied, the material is dried as the solvent is removed by means of heating. This process must be carefully monitored to ensure that uniform pellet coating is achieved, otherwise there could be a negative effect on product performance [12-16].

The purpose of this study was to coat pellets containing paracetamol in a fluid bed in order to obtain favorable dissolution characteristics for these pellets, using both apparatus 1 (basket) and apparatus 3 (Bio-Dis®), in the formulation of orally disintegrating tablets (ODT).

2. Material and methods

2.1. Raw material

All raw material used in this study was of pharmaceutical grade and it was employed as received.

The type-101 microcrystalline cellulose, commercially designated Microcel MC101®, and the hydroxyproylmethyl cellulose (HPMC), designated as Methocel K100M®, were kindly donated by Colorcon do Brasil Ltda. The material used for coating the pellets (Kollidon® VA 64 and Kollicoat® SR 30D) was kindly provided by Basf S.A.

2.2. Pellet Preparation

A single batch of pellets weighing about 500 g was prepared with the following composition: 70% paracetamol; 30% microcrystalline cellulose type 101; 215.36 g of HPMC (in a 2% water solution).

After being weighed, the paracetamol and the microcrystalline cellulose were mixed in an industrial mixer (± 20 rpm) for about 10 minutes. Then the previously-prepared HPMC solution was added, little by little, and the homogenization process was continued until the mass reached a point suitable for extrusion, which was ascertained visually. The material was then placed in an APEX® Multiplex DUA-11 (New Jersey, USA) radial-type extruder, set to ± 3 rpm and coupled with a 0.5 mm mesh. The extruded material was then transferred to a CALEVA® Model 250 spheronizer (Dorset, UK), equipped with a “cross-hatch” plate, rotating at 1,000 rpm for about 4

minutes. Subsequently, the pellets were dried in a HÜTTLIN® Mycrolab fluid bed (Steinen, Germany) for 40 minutes, with an intake air temperature of 55°C and a flow rate of 12 m^3 per hour.

2.3. Coating

After production, the pellets were divided into sub-batches of 80 g each and these were then subjected to the fluid bed coating process in the Hüttlin® Mycrolab fluid bed (Steinen, Germany), configured to operate in "bottom spray" mode, according to the parameters detailed in Table 1.

Table 1 – Fluid bed coating application parameters

PARAMETER	CONDITION EMPLOYED
Air flow	6 m^3/ hour
Air intake temperature	60 ºC
Microclimate pressure	0.4 bar
Spray pressure	0.7 bar
Filter pressure	3 bar
Peristaltic pump speed	5 rpm

The coating material (Table 2) was prepared in the following manner: after the components were dissolved in water, Kollicoat® SR 30D was added to the solution, and the mixture was shaken until it was completely homogenized. After coating, the pellets were left in the fluid bed for about 15 minutes, under the same conditions, however without the polymer being applied, in order to dry the material.

Table 2 - Coating formulations applied to the pellets (quantities in grams)

Composition	R1	R2	R3	R4	R5
Kollicoat® SR 30D	10	10	10	10	10
Kollidon® VA 64	0.5	1.0	1.5	2.0	3.0
Polyethylene Glycol (PEG) 4000	2.5	2.0	1.5	1.0	---
Propylene glycol	0.15	0.15	0.15	0.15	0.15
Talc	1.9	1.9	1.9	1.9	1.9

Water q.s.	31.25	31.25	31.25	31.25	31.25

2.4. Characterization of coated pellets

2.4.1. Dissolution profile

In order to assess drug delivery from coated pellets, we executed two dissolution tests: one in apparatus 1 (basket) and the other in apparatus 3 (Bio-Dis®); both are described below in the following sections.

2.4.1.1. Dissolution profile (apparatus 1 - basket)

A dissolution profile for the formulations in a phosphate buffer (pH 5.8) was traced, as specified by USP 32 [17] for paracetamol tablets, using a VanKel VK7010 (Cary, USA) Dissolution Test Station coupled to a Varian Cary 50 UV-Vis Spectrophotometer (Cary, USA). In the manner described in the United States Pharmacopeia [17], 900 mL of medium was employed, at a temperature of 37°C, a stirring speed of 75 rpm and collection times programmed at 2, 5, 10, 15, 20 and 45 minutes.

2.4.1.2. Dissolution profile (apparatus 3 - Bio-Dis®)

Apparatus 3 (Varian Inc., Cary, USA) was configured to operate at a temperature of 37°C with 250 mL of the dissolution medium, coupled to a Varian VK 8000 Dissolution Sampling Station (Cary, USA), programmed to collect 5 mL of medium at pre-established time intervals. Two media were used: a pH 7.2 phosphate buffer - used in the first row of the vessels as an initial dissolution medium, with collection times programmed at 2 and 5 minutes and the device operating at 4 oscillations per minute (OPM); and hydrochloric acid 0.1N (HCl 0.1N) - used in the second row of vessels, as a stage following the phosphate buffer medium, with collection times programmed at 10, 15, 20, 30 and 45 minutes. For this medium, the stirring speed was set at 10 oscillations per minute.

After being weighed (about 100 mg of each formulation), the pellets were transferred to the cylinders of the device (fitted with a 1.25/177 µ "Poly screen") and then the test was initiated. The samples were quantified in a Beckman Couter DU 640 spectrophotometer with a 0.5 cm cuvette at 242.5 nm.

2.4.2. Statistical evaluation of the dissolution profiles

Data pertaining to the percentage of paracetamol dissolved per unit of time during the dissolution tests were subjected to multivariate hierarchical cluster analysis using the Statistica® 10.0 (StatSoft) software. The Euclidean distance was used to evaluate similarity between clusters and Ward's method was used as a clustering strategy.

3. Results

The five coated pellet formulations (R1, R2, R3, R4, R5) and the uncoated formulation (SR) were subjected to the dissolution test using apparatuses 1 (basket) and 3 (Bio-Dis®), in accordance with the United States Pharmacopeia, and their profiles are presented in Figures 1 and 2.

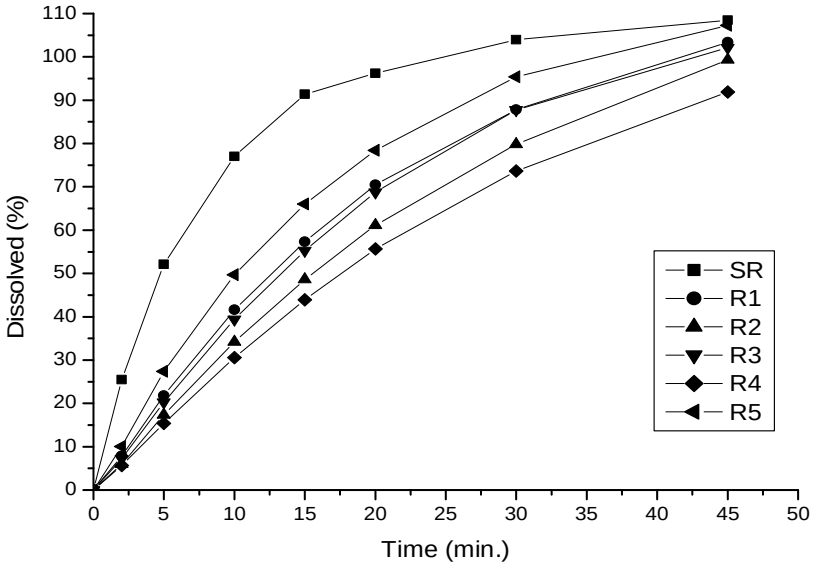

Figure 1 - Dissolution profiles obtained in apparatus 1 (basket) for the uncoated formulation (SR) and formulations R1, R2, R3, R4 and R5. Medium: pH 5.8 phosphate buffer (n=5)

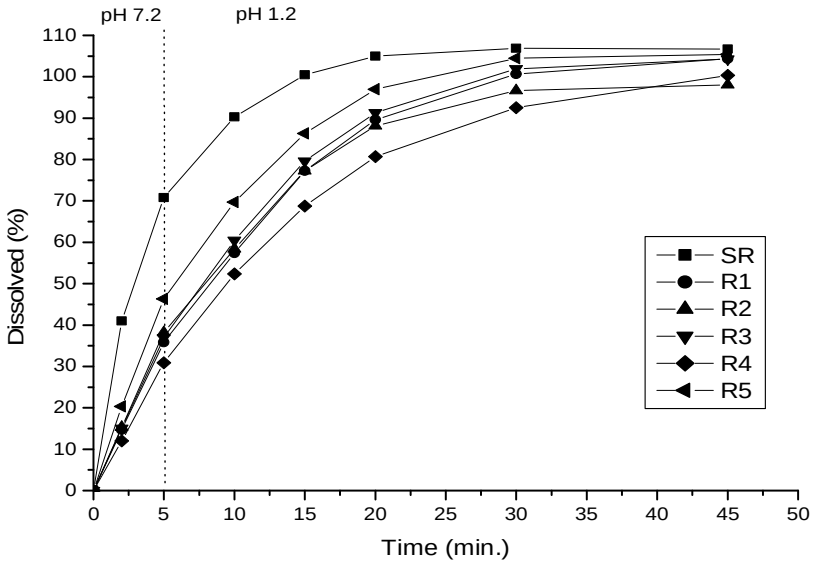

Figure 2 - Dissolution profiles obtained in apparatus 3 for the uncoated formulation (SR) and formulations R1, R2, R3, R4 and R5. Media: pH 7.2 phosphate buffer for the first 5 minutes and HCl 0.1 N, 5 minutes into the test (n=3)

Through the cluster analysis, the existence of two groups with distinct characteristics can initially be considered: the SR formulation and the others (Figures 3 and 4), regardless of the type of dissolution test executed.

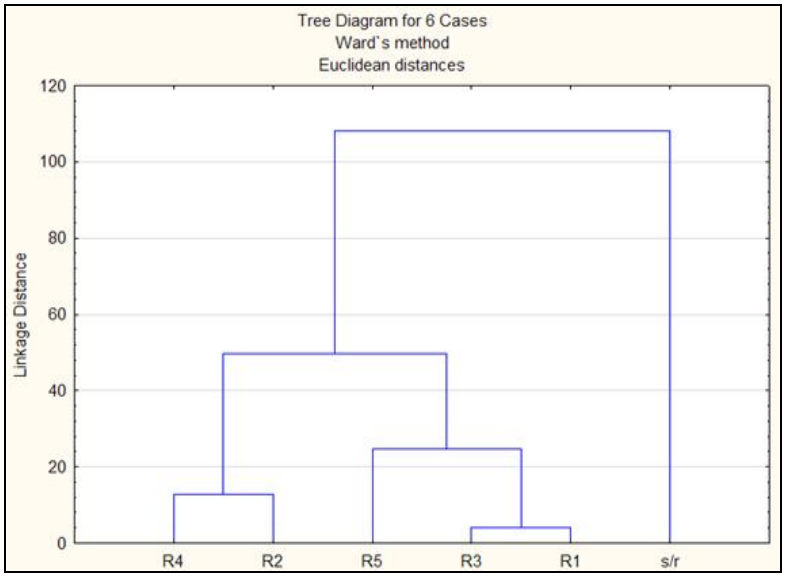

Figure 3 - Hierarchical cluster analysis of the percentage data for the dissolved drug using apparatus 1

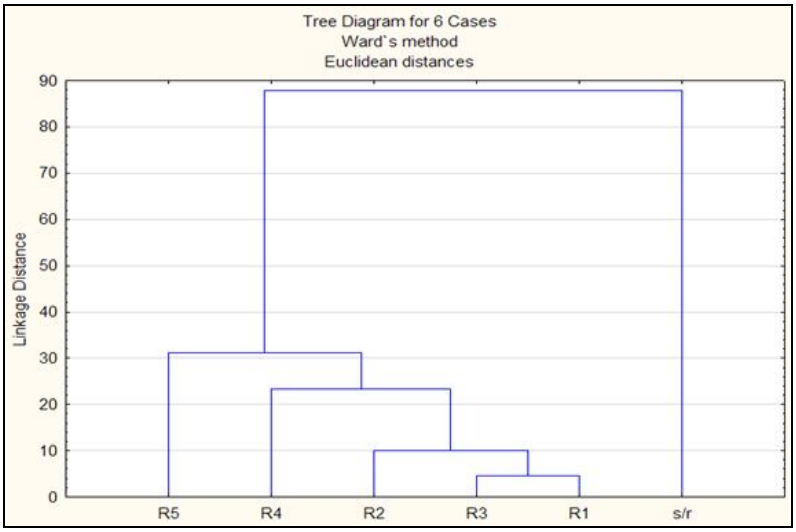

Figure 4 - Hierarchical cluster analysis of the percentage data for the dissolved drug using apparatus 3

Specifically for the dissolution test executed in apparatus 1, the cluster analysis (Figure 3) also enables the existence of four clusters to be ascertained: the SR; R1 and R3; R5; R2 and R4 formulations.

In Figure 4, which contains the cluster analysis executed with the percentage data of the dissolved drug using apparatus 3, there was no significant change in the clusters. The existence of five clusters can be considered: SR; R1 and R3; R2; R4; R5, considering that R1 and R3 remained within the same cluster, as also observed in apparatus 1 (Figure 3).

4. Discussion

In general, the coating operation was satisfactory, except for formulation R5, where the pellets had a tendency to adhere to the inside wall of the fluid bed, thus requiring constant supervision and stoppages in the application of the polymer in order to ensure maintenance of the other parameters and to dry the pellets so that the process could be continued.

This occurrence seems to be linked to the presence of a larger quantity of Kollidon VA 64® in the coating formulation. The adhesive properties of this substance, which make it interesting for this application, also tended to make the pellets stick together and to the walls of device, thus causing some difficulty in the coating operation.

When a portion of the polyvinylpyrrolidone was replaced with PEG 4000, a polymer with much lower adhesive properties, the coating operation was much more effective, with a consequent gain in productivity.

On the other hand, Kollicoat SR 30D® has the capacity to act as a barrier, preventing total and immediate delivery of the drug and it can also be used as a coating to mask the unpleasant taste of certain drugs [18]. In this specific case, the addition of pore-forming agents in the structure of the coating film is necessary, such as the Kollidon VA 64® and PEG 4000 polymers used here, in order to ensure drug delivery in a timely fashion.

Thus, when the results obtained in apparatuses 1 and 3 (Figures 1 and 2) were evaluated, it was ascertained that the pellet coating was efficient in reducing drug delivery in the initial minutes of dissolution, thus resulting in a significant improvement with regards to this aspect, compared to the uncoated pellets.

By means of the cluster analysis, a very significant similarity can be observed between the R1 and R3 dissolution profiles. Furthermore, the R5 formulation was separated from the others, as it presented a dissolution profile with less drug retention, since more of the drug was released, which seem to reinforce the role of polyvinylpyrrolidone in this type of coating, considering that this formulation contains only this polymer as a pore-forming agent on the surface of the pellets (Figures 1 and 3). However, as previously discussed, the coating operation was excessively complicated in this case.

The replacement of part of the Kollidon VA 64® with PEG 4000 had an impact on the dissolution profile of the pellets, such that each PVP-PEG mixture presented a unique profile. Thus, the lowest rate of delivery occurred at the proportion of 2:1 (PVP-PEG), designated by R4, and the fastest dissolution was registered for the 0.5:2.5 (R1) proportion, very similar to the rate of delivery recorded by the 1.5:1.5 (R3) mixture.

Further with regards to the dissolution profile, when comparing the results obtained in both methods, it was ascertained that with Bio-Dis®, the formulations attained higher dissolved percentage values compared to the basket (apparatus 1). This is probably due to the fact that the shaking regime of the Bio-Dis® (operating at 4 OPM for the first 5 minutes and 10 OPM subsequently) is more efficient, thus enabling these values to be attained.

However, considering the cluster analysis, apparatus 1 presents itself as the most discerning method, because, even though it did not provide the pH alterations that the dosage form can be subjected to throughout the GI tract, it was capable of discerning differences between the types of coatings used.

Thus, pellet coating with Kollicoat SR 30D® proved capable of enabling a slight delay in drug delivery, which can be useful for masking the unpleasant taste of paracetamol in the mouth. On the other hand, the dissolution of the drug in HCl is not compromised, which indicates the potential of the latter in the formulation of ODTs.

With regards to the dissolution tests in apparatus 1 (basket) and apparatus 3 (Bio-Dis®), it is possible to state that both were capable of satisfactorily distinguishing between the formulations obtained. However, Bio-Dis® presents the advantage of enabling a dissolution method in which a

pH gradient, such as that observed in the mouths and in the stomachs of human beings, can be reproduced with relative ease.

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