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Carnauba wax as a promising excipient in melt granulation targeting the preparation of mini-tablets for sustained release of highly soluble drugs

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ABSTRACT

Mini-tablets are a new tendency in solid dosage form design for overcoming therapeutic obstacles such as impaired swallowing and polypharmacy therapy. Among their advantages, these systems offer therapeutic benefits such as dose flexibility and combined drug release patterns. The use of lipids in the formulation has also drawn considerable interest as means to modify the drug release from the dosage form. Therefore, this paper aimed at developing sustained release mini-tablets containing the highly soluble drugs captopril and metformin hydrochloride. Carnauba wax was used as a lipid component in melt granulation, targeting the improvement of the drugs poor flowability and tabletability, as well as to sustain the drug release profiles in association with other excipients. To assist sustaining the drug release, Ethocel™ (EC) and Kollicoat® SR 30D associated with Opadry® II were employed as matrix-forming and reservoir-forming materials, respectively. The neat drugs, granules and the bulk formulations were evaluated for their angle of repose, compressibility index, Hausner ratio and tabletability. Mini-tablets were evaluated for their weight variation, hardness, friability, drug content and *in-vitro* drug release. The results indicated that melt granulation with carnauba wax improved the flow and the tabletability of the drugs, allowing the preparation of mini-tablets with adequate tensile strength under reduced compaction pressures. All mini-tablet formulations showed acceptable hardness (within the range of 1.16 to 3.93 Kp) and friability (<0.1%). The melt-granulated captopril in matrix systems containing 50% EC (45P, 100P or 100FP) and the melt-granulated metformin hydrochloride in reservoir systems coated with Kollicoat® SR 30D and Opadry® II (80:20 with 10% weight gain or 70:30 with 20% weight gain) exhibited release profiles adequate to sustained release formulations, for over 450 min. Therefore, carnauba wax proved to be a promising excipient in melt granulation targeting the preparation of mini-tablets for sustained release of soluble drugs.

1. Introduction

The successful formulation of a sustained release dosage form starts at the understanding of the physical, chemical, and biopharmaceutical properties of the active pharmaceutical ingredient, such as pKa, logP, solubility, polymorphism, permeability, half-life ($t_{1/2}$), among others. In this sense, the drug solubility plays an important role in the development of sustained release dosage forms [2,20,29,55]. A good alternative for sustaining the release of highly soluble drugs is preparing matrix or reservoir systems instead of traditional dosage forms. Among the excipients that can be used to control the release rate of drugs, lipid components are largely employed due to their low cost, negligible toxicity, biodegradable properties, ease of use and versatility [53].

A recent review highlighted the importance of carnauba wax as a lipid excipient in drug delivery systems [41]. This compound is insoluble in water due to its chemical structure, formed by long chain fatty acid esters and it has a low melting point, allowing its use in melt granulation [41]. Carnauba wax, a plant exudate obtained from a Brazilian palm tree (*Copernicia cerifera*) [40] has been studied as an excipient to modify drug release in tablets prepared by direct compression [9], as well as to produce gastroretentive tablets [33]. It was also target of study in the development of granules [30], film-coated products [5,40] and nanoparticles [1,52].

There is a great number of sustained release technologies available for the development of new dosage forms. Among those, the multiparticulate systems (*e.g.* mini-tablets) present several advantages over monolithic dosage forms. Mini-tablets are smaller than conventional tablets, offering advantages such as improved patient adherence [15,16], as well as excellent size uniformity, regular shape and a smooth

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surface, thereby showing an excellent base for coating with different polymeric systems [11,19,26]. Moreover, mini-tablets present other advantages, such as low risk of gastrointestinal tract irritation, reduced variability of drug absorption and low risk of dose dumping. In addition, these systems can promote efficient drug release control when proper excipients are used, combined with high flexibility of dose adjustment [12,28]. Mini-tablets formulations are easily produced by compression and they can be prepared as matrix or reservoir systems as means to sustain the drug release [19]. Therefore, mini-tablets are an excellent platform for the development of sustained release formulations and an important focus of current research.

There are few articles in the literature that report the use of mini-tablets to sustain the release of soluble drugs, these studies include: a mini-matrix composed of Compritol® 888 ATO, using theophylline as model drug [39], a mini-matrix composed of hydroxypropyl methylcellulose (HPMC) containing pregabalin [48], a coated mini-tablet with Ethocel™ (EC) and HPMC to control the release of galantamine hydrobromide [22] and a coated mini-matrix of HPMC and EC to prolong the release of theophylline [31]. However, studies are still required in order to achieve a better understanding of sustained release mini-tablets with highly soluble drugs, especially when it comes to lipid-based mini-tablet formulations containing carnauba wax as a melt granulation excipient. Moreover, the literature does not report the use of this type of formulation so far.

The water-soluble drugs selected as model drugs in the current study were captopril and metformin hydrochloride, which are classified as "freely soluble in water" according to the British Pharmacopeia [4]. The selected drugs belong to Biopharmaceutics Classification System (BCS) class III [49]. Both drugs are known to be rapidly absorbed following oral administration, and bioavailability is not an issue. However, their elimination half-lives are short in humans ($t_{1/2}$, ~1.9 h and ~5 h, respectively), leading to the need of consecutive administrations to maintain adequate therapeutic drug concentrations in plasma [14,21,27]. In this sense, the development of sustained release formulations containing these drugs are justifiable. In addition, the combination of these two compounds is pharmacologically relevant, as they can be used in the development of a fixed dose combination (FDC), presenting many benefits to the patient's pharmacotherapy plan.

The combination between captopril and metformin hydrochloride can be beneficial in the treatment of diabetic nephropathy, a kidney manifestation that demands a strict control of blood pressure [38]. The FDC presents many advantages over the conventional monotherapy, such as decreasing pill burden, improving patient compliance, simplifying complex dosage regimens and increasing efficiency and safety compared to the monotherapy. In addition, FDCs can be less expensive to manufacture and easier to distribute, generating less costs for both patients and institutions [3].

Considering the context above presented, this study aimed to employ carnauba wax associated to Ethocel™ (EC) or Kollicoat® SR 30D to sustain the drug release of two highly soluble compounds (captopril and metformin hydrochloride), using the dosage form mini-tablets and two different technological approaches: matrix and reservoir. In accordance with the current literature, carnauba wax has never been studied as a melt granulation excipient to achieve sustained release of soluble drugs in mini-tablets. Also, the association of carnauba wax granules and the polymers Ethocel™ or Kollicoat® SR 30D as investigated herein is an innovation from the pharmaceutics point of view. Moreover, the impact of the granulation with carnauba wax on the flow and tabletability of the drugs used to produce the mini-tablets was evaluated, as well as its effect on their release kinetics.

2. Materials and methods

2.1. Materials

Captopril was purchased from Pharma Nostra (Brazil) and metformin hydrochloride was donated by Apsen Pharma (Brazil). Carnauba wax was purchased from PharmaSpecial (Brazil). The excipients Ethocel™ Std. Premium (ethylcellulose; 45P, 100P and 100FP), Opadry® II (poly(vinyl alcohol)-based), microcrystalline cellulose 101, stearic acid, magnesium stearate and colloidal silicon dioxide were donated by Colorcon® (Brazil). Kollicoat® SR 30D was donated by BASF The Chemical Company (Brazil). All other chemicals and reagents used in the study were of analytical or HPLC grade.

2.2. Methods

2.2.1. Mini-tablets development

Melt granulation of the drug with carnauba wax was applied as an intermediate step to obtain sustained release mini-tablets, using captopril (6.25 mg/mini-tablet) and metformin hydrochloride (15.0 mg/mini-tablet) as highly soluble model drugs. Ethocel™ (EC) and Kollicoat® SR 30D were used as sustained release excipients in matrix and reservoir systems, respectively. EC 45P, 100P and 100 FP are different grades of ethylcellulose in terms of molecular weight and/or particle size with the same ethoxy content (48.0–49.5%). The designations 45 and 100 indicate the viscosity (41–49 cP or 90–110 cP, respectively) of a 5% solution in a mixture of toluene and ethanol, and they are related to the molecular weight of the polymer. The P and FP designations identify the granular or fine particle powder, respectively. Kollicoat® SR 30D is a commercial suspension for film-coating where SR stands for sustained release, and 30D indicates that it is constituted of a 30% (w/v) aqueous dispersion of polyvinyl acetate colloidal particles.

2.2.1.1. Preparation of granules by melt granulation. Carnauba wax was melted at 60 °C on a hot plate. Once the lipid was completely melted, the drug was slowly added and stirred until a disperse and homogenous mixture was achieved. The mixture was transferred onto a glass plate until solidification at room temperature. The solidified dispersion was manually grounded through a 1000 μm sieve to homogenize the particle size of the granules. The captopril (G_{cap}) and metformin hydrochloride (G_{met}) granules were prepared according to the compositions described in Table 1.

2.2.1.2. Preparation of the captopril mini-tablets and metformin hydrochloride mini-tablets cores. Different formulations of captopril matrix mini-tablets (C1 to C4) and one formulation of metformin hydrochloride mini-tablets cores (M1) were prepared according to the compositions shown in Table 2. All the excipients, except the lubricant, were sieved through an 850 μm mesh and mixed with captopril or metformin hydrochloride granules (G_{cap} or G_{met}) for 5 min. Then, the lubricant was sieved, added to the powder blend, and mixed for 3 min. Finally, the formulations were compressed into 3 mm diameter mini-tablets using a rotary press (Talleres Sanchez, Argentina) equipped with multi-tip punches.

2.2.1.3. Film-coating of metformin hydrochloride mini-tablet cores. M1 formulations were coated using different polymeric dispersions and weight gains, resulting in four coated formulations, named M1-A, M1-B, M1-C and M1-D (Table 3). The coating process was performed in a bench-top fluid bed system (Mini Coater Drier-2, Caleva, England) with the top spray configuration. The polymers were dispersed in water under stirring and atomized on the surface of the cores using the following conditions: inlet air of 14.5 $m^3\ s^{-1}$ at 60 °C, at an

Table 1
Composition of captopril (G_{cap}) and metformin hydrochloride (G_{met}) granules.

Ingredients	Weight (g)	
	G_{cap}	G_{met}
Captopril	55.6	–
Metformin hydrochloride	–	75
Carnauba wax	44.4	25