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Pore blocking: An innovative formulation strategy for the design of alcohol resistant multi-particulate dosage forms

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ABSTRACT

In this work calcium stearate (CaSt) multi-particulates loaded with codeine phosphate (COP) were developed in an attempt to provide extended release (ER) combined with alcohol dose dumping (ADD) resistance. The pellets were prepared via wet/extrusion spheronization and ER characteristics were obtained after fluid bed drying at 30 °C. Pore blockers (i.e., xanthan, guar gum and TiO_2) were integrated to control the uptake of ethanolic media, the CaSt swelling and consequently, the COP release. While all three pore blockers are insoluble in ethanol, xanthan dissolves, guar gum swells and TiO_2 does not interact with water. The incorporation of 10 and 15% TiO_2 still provided ER characteristics and yielded ADD resistance in up to 40 v% ethanol. The in-vitro data were subjected to PK simulations, which revealed similar codeine plasma levels when the medication is used concomitantly with alcoholic beverages. Taken together the in-vitro and in-silico results demonstrate that the incorporation of appropriate pore blockers presents a promising strategy to provide ADD resistance of multi-particulate systems.

1. Introduction

Extended release (ER) oral drug delivery systems "allow at least a 2-fold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance when compared to that presented as a conventional dosage form (a solution or a prompt drug-releasing conventional solid dosage form)" (USP, 2008). Often, the terms "controlled release", "prolonged release", "sustained release", "modified release" and "long-acting" are used synonymously with "extended release" (Tiwari and Rajabi-Siahboomi, 2008). ER can be achieved by the introduction of drug release regulating mechanisms including, i) gel layers that form in-situ upon contact with aqueous media (i.e., swellable, hydrophilic matrices) (Maderuelo et al., 2011), ii) slow polymer erosion (i.e., soluble, hydrophilic matrices) (Zuleger and Lippold, 2001) iii) suitable microstructures in hydrophobic matrices (Qu et al., 2006), iv) osmotic control (i.e., reservoir systems) (Verma et al., 2000), and v) coatings (i.e., reservoir systems) (Savage and Rhodes, 1995). These mechanisms are designed to regulate the release rates in aqueous media, but often not in media containing organic solvents, such as ethanol. Hence, the mechanisms can become ineffective when the dosage form is taken concomitantly with alcoholic beverages. Thereby, alcohol induced dose dumping (ADD) may occur, which is defined as "unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in the modified-release dosage form" (Meyer and Hussain, October, 2005). ADD potentially yields i) fatal side effects, ii) toxic drug concentrations (due to the comparatively high drug loadings of ER systems) and iii) the absence of the therapeutic effect within the envisaged time period. This is especially true for opiods and non-opiod drugs showing a narrow therapeutic window. In contrast to that, decreased release rates may be observed in hydro-alcoholic media due to the drug's physico-chemical properties (Rahim et al., 2013). Similar to ADD, under-medication may present a health risk. Thus, safe and efficient ER dosage forms are not only required to guarantee the absence of ADD, but also to show similar release rates in aqueous and in hydro-alcoholic media and hence, ensure a therapeutic effect of the active ingredient (API).

The formation of a release rate controlling gel layer is often accompanied by polymer erosion, like in the case of hydroxyl propyl methyl cellulose (HPMC) (Tiwari and Rajabi-Siahboomi, 2008). It was suggested that HPMC also forms a gel layer in hydro-alcoholic solutions (5–40 v% ethanol) (Missaghi et al., 2009). However, the initial swelling capacity of directly compressed

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HPMC tablets was lowered in the presence of 40 v% ethanol. Consequently, a non-uniform gel layer was formed and the aspirin release rate was highly increased within the first 30 min (Roberts et al., 2007). Studies addressing the effect of ethanol on systems that provide ER via their microstructure or osmotic control are rare. Forsgren et al., (2011) proposed a synthetic geopolymer for the controlled delivery of oxycodone. The release rates from cylindrical rods were modified by pore size adjustment and were only slightly affected in ethanolic media. Similarly, in a different study, the suitability of geopolymers for an ADD resistant drug delivery system was suggested (Cai et al., 2014). Shah et al., (2013) developed an oral controlled porosity osmotic pump and the authors concluded that the system is not affected by concomitant intake of ethanol.

Currently, coating is the most widely explored approach to achieve ADD resistance, not only for tablets but also for pellets. Typically, pellets are more prone to release modification caused by external factors – such as the addition of ethanol – as they provide a highly increased surface to volume ratio compared to tablets. According to the studies of Rosiaux et al. (2013a,b, 2014), the addition of small amounts (minimum 5%) of guar gum to ethyl cellulose provided ethanol resistant coatings for pellets. Guar gum is insoluble in ethanol and impedes dissolution of the ethanol soluble ethylcelluose. This coating was also used by Jedinger et al., (2015a) to provide ADD resistance of corn starch based pellets that were manufactured via an advanced hot melt extrusion (HME) technique. As coating is an additional process step, which is cost and time consuming, this study addresses the development of uncoated ADD resistant pellets produced via extrusion/spheronization. In general, the manufacturing of ADD resistant pellets via wet extrusion/spheronization is challenging, as wet extrusion requires an aid that immobilizes the granulation liquid, which is mainly water and/or ethanol. Hence, the prepared pellets are likely to show different swelling behavior in water and ethanol, which potentially affects the release rate and/or mechanism. In our study we used calcium stearate (CaSt), which was previously shown by our group to be a suitable candidate for the preparation of ethanol resistant pellets produced via HME (Jedinger et al., 2015b) and codeine phosphate (COP) as model drug. The drying procedure was adjusted to yield ER. To ensure ADD resistance, small amounts of additives that are insoluble in ethanol were incorporated. These additives were intended to act as mechanical pore blockers that regulate the entrance of alcoholic media into the porous CaSt matrix, the corresponding matrix swelling and eventually, drug release. Based on that, three different additives (guar gum, xanthan gum and TiO_2) were selected to account for different interactions with water. Guar gum is soluble in aqueous media, while xanthan gum swells in water and TiO_2 neither swells nor dissolve (Rowe et al., 2006). As aforementioned, guar gum is used as coating additive to avoid ADD. Xanthan gum is included in the matrix layer of the commercially available product Tridural™, which was shown to be stable in 40 v% ethanol (Traynor et al., 2008). To the best of the authors' knowledge, TiO_2 was not used for ADD resistance although it shows promising properties. The synergistic effects of process and formulation modifications were applied to prepare ER, ADD resistant, spherical pellets.

2. Materials and methods

2.1. Materials

Vegetable CaSt was purchased from Werba-Chem GmbH, Vienna, Austria and served as pellet matrix material. Codein phosphate hemihydrate (COP-h; 0.5 water equivalents) was kindly donated by G.L. Pharma, Lannach, Austria and was used as model drug. Xanthan gum (Carl Roth, Karlsruhe, Germany), guar gum (FMC BioPolymer, Philadelphia, USA) and TiO_2 (bulk material; anatase form; Sigma Aldrich, Mannheim, Germany) were used as additives to provide ADD resistance. 50 w% ethanol was applied as granulation liquid. Hydrochloric acid (HCl), *tris*-phosphate-dodecahydrate buffer and absolute (96 v%) ethanol (all Merck, Darmstadt, Germany) were used for dissolution medium preparation.

2.2. Pellet preparation

Pellets comprising 10% COP-h and 90% CaSt were prepared via wet extrusion/spheronization by adapting a previously described procedure (Roblegg et al., 2010). Briefly, CaSt and COP-h (100 g in total) were dry blended in a TURBULAR® T2F mixer (Willy A Bachofen AG Maschinenfabrik, Muttenz, Switzerland) at 50 rpm for 10 min. The blend was manually wetted with 30 g of 50 w% ethanol. The wet mass was transferred into a single screw extruder (Extruder PharmexT35, Gabler Maschinenbau GmbH, Lübeck, Germany) and extruded through a 1 mm multi-hole die plate at a screw speed of 80 rpm. The extrudates were then spheronized at 600 rpm for 5 min. Immediately after spheronization, the pellets were dried using two different technologies that are tray (T) drying and fluid bed (FB) drying. For tray drying, the pellets were transferred into round, flat-bottom bowls with a diameter of 17 cm equaling a pellet bed surface area of 227 cm^2. Drying was carried out in a ventilated oven (Heraeus, Vienna, Austria) at 30, 40 and 50 °C until a constant weight was reached. The relative air humidity ranged between 26 and 31%.

For the FB process, the pellets were transferred into a Mycrolab Oystar (Hüttlin, Schopfheim, Germany). The inlet-air temperature was 30, 40 or 50 °C and the inlet-air flow was kept constant at 40 m^3/h. The drying time necessary to reach moisture contents below 1 w% was determined in pre-studies. The parameters applied during the drying process are summarized in Table 1.

Once, the suitable drying procedure to yield ER was determined, several additives were added to ensure ADD resistance. Xanthan gum (X) – insoluble in ethanol but soluble in water –, guar gum (GG) – insoluble in ethanol but swellable in water – and TiO_2–insoluble in both, ethanol and water – were incorporated at 5% loading (thereby, reducing the CaSt fraction). Based on the results of the in-vitro dissolution studies, the TiO_2 loadings were increased to 10 and 15%. Additive-loaded pellets were prepared following the aforementioned extrusion/spheronization procedure.

2.3. Pellet characterization

The pellets were sieved according to the European Pharmacopeia (Ph. Eu.) 7.0 2.9.38. The sieve fraction between 1.0 and 1.4 mm was divided with a rotary cone divider to obtain representative samples and used for the characterization studies.

2.3.1. Brunauer-Emmet-Teller (BET) measurements

BET measurements were performed on a Tristar II 3020 (Micromeritics, Norcross, Georgia) using krypton as analytical gas. Prior to the measurements, samples were degassed under

Table 1
Drying process parameters for additive-free pellets.

Abbreviation	Drying technique	Drying temperature (°C)	Drying time (h)
CaSt_COP_T30	Tray drying	30	9
CaSt_COP_T40	Tray drying	40	8
CaSt_COP_T50	Tray drying	50	7
CaSt_COP_FB30	Fluid-bed drying	30	0.66
CaSt_COP_FB40	Fluid-bed drying	40	0.5
CaSt_COP_FB50	Fluid-bed drying	50	0.33