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Ethanol-resistant polymeric film coatings for controlled drug delivery

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ABSTRACT

The sensitivity of controlled release dosage forms to the presence of ethanol in the gastro intestinal tract is critical, if the incorporated drug is potent and exhibits severe side effects. This is for instance the case for most opioid drugs. The co-ingestion of alcoholic beverages can lead to dose dumping and potentially fatal consequences. For these reasons the marketing of hydromorphone HCl extended release capsules (Palladone) was suspended. The aim of this study was to develop a novel type of controlled release film coatings, which are ethanol-resistant: Even the presence of high ethanol concentrations in the surrounding bulk fluid (e.g., up to 40%) should not affect the resulting drug release kinetics. Interestingly, blends of ethylcellulose and *medium* or *high viscosity* guar gums provide such ethanol resistance. Theophylline release from pellets coated with the aqueous ethylcellulose dispersion Aquacoat® ECD 30 containing 10 or 15% *medium* and *high viscosity* guar gum was virtually unaffected by the addition of 40% ethanol to the release medium. Furthermore, drug release was shown to be long term stable from this type of dosage forms under ambient and stress conditions (without packaging material), upon appropriate curing.

1. Introduction

"Dose dumping" is often referred to as "Unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form" [1]. This phenomenon can represent a major risk for the patient, because: (i) toxic drug concentrations might be attained with potentially severe consequences for the patient, and/or (ii) the therapeutic efficiency might no more be assured during the intended time period. Such "dose dumping" can for example be caused by the consumption of alcoholic beverages, leading to high ethanol concentrations in the contents of the stomach [2]. If drug release is controlled by a polymer, which is insoluble in water and the contents of the stomach under "normal" conditions, but soluble in aqueous media containing significant amounts of ethanol, the co-ingestion of alcoholic beverages can lead to unintended polymer dissolution. Thus, drug release can be rapid, instead of being controlled during prolonged periods of time. This is true for drug reservoirs, which are surrounded by release rate controlling polymeric films, as well as for drug matrix systems, in which the drug is embedded within a polymeric matrix. Significant warning labels on the drug products are considered to be insufficient in the case of highly potent drugs with narrow therapeutic windows, because: (i) the Behavioral Risk Factor Surveillance System reported that 1 out of 3 drinkers in the U.S. reported "binge drinking", that means they consume 4 or 5 drinks (in the case of women or men) in a short period of time [3], and (ii) it was shown that heavy drinkers suffering from chronic low back pain did not reduce their opiate use, despite warnings about concomitant use of alcohol and opiates [4].

Palladone extended release capsules are a good example for such dosage forms, exhibiting a risk for dose dumping upon consumption of alcoholic beverages: Once daily capsules are filled with hydromorphone HCl containing sustained release pellets comprising ethylcellulose, ammonia methacrylate copolymer type B and stearyl alcohol [5]. A pharmacokinetic study in healthy subjects showed that co-ingestion of a 12-mg Palladone capsule with 240 mL of 40% alcohol resulted in an average peak hydromorphone concentration, which was approximately six times greater than when taken with water [6]. One individual even showed a 16-fold increase in c_{max}. As the incorporated drug is highly potent and the side effects are severe, the manufacturers decided to suspend the marketing of this product. Also, Walden et al. [7] showed that the in vitro release of hydromorphone from Palladone SR capsules significantly depended on the ethanol content of the surrounding bulk fluid.

Furthermore, Fadda et al. [5] demonstrated that 5-aminosalicylic acid release from 3 commercially available products (Pentasa, Asacol, Salofalk) was significantly affected by the addition of up to 40% ethanol to the release medium. Interestingly, the changes in the resulting drug release patterns strongly depended on the type of formulation.

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Recently, Smith et al. [8] reported on in vitro studies performed with 27 oral modified release products. The drugs were opioid analgesic, calcium channel blocking, antianginal, antidepressant, stimulant for ADHD or antiarrhythmic. Importantly, 9 out of 10 capsule formulations and 2 out of 17 tablet formulations showed accelerated drug release in media containing 40% ethanol. Traynor et al. [9] studied the impact of the presence of 40% ethanol on the release of tramadol from 24 h controlled release formulations. For instance, a significant increase in the release rate was found in the case of capsules marketed under the trade name "T-long". Levina et al. [10] reported only moderate effects from certain hydroxypropyl methylcellulose (HPMC) matrix formulations. In contrast, a significant increase in the release rate of aspirin from HPMC matrix tablets was reported by Roberts et al. [11] when adding 40% ethanol to the release medium, which might at least partially be explained by slower tablet swelling and increased drug solubility. Furthermore, the release rate of verapamil from controlled release matrix systems was shown to significantly increase by the addition of 40% ethanol to the release medium [12]. One melt-extruded system, based on hydroxypropyl cellulose and hydroxypropyl methylcellulose, showed similar verapamil release in ethanol-free and 40% ethanol-containing medium, but drug release was significantly slower when 20% ethanol was present. Larrson and co-workers [13] studied the water permeability of films made from organic solutions of ethylcellulose and hydroxypropyl cellulose (HPC) as a function of the presence of ethanol. Interestingly, they found that the water permeability of films with low HPC contents increased with increasing ethanol concentration, probably because of a more pronounced swelling of ethylcellulose in the presence of ethanol. In contrast, the water permeability of films with high HPC contents decreased with increasing ethanol concentration. The latter effect was explained as follows by the authors: At high HPC contents a continuous HPC network is formed, through which water can be relatively rapidly transported. The presence of ethanol leads to increased ethylcellulose swelling, which probably at least partially closes the "HPC pores". These various examples illustrate the complexity of the potential effects of the presence of ethanol in the surrounding bulk fluid on the release performance of oral controlled drug delivery systems. In the case of potent drugs with narrow therapeutic windows ethanol resistant formulations are highly desirable.

The aim of this study was to develop a novel type of polymeric film coatings providing ethanol insensitive drug release patterns. The basic idea was to add small amounts of an ethanol-insoluble polymer to a commonly used polymer used for film coating (ethylcellulose). The presence of this second compound (guar gum) was intended to effectively hinder the potential dissolution of ethylcellulose in aqueous media containing high ethanol concentrations. Also, the presence of ethyl cellulose was intended to effectively hinder the potential dissolution of the ethanol-insoluble polymer in pure aqueous media. It is well known that blending two types of macromolecules can be very helpful to adjust desired film coating properties [14–16] which cannot be provided by one single polymer [17,18]. The aqueous ethylcellulose dispersion Aquacoat® ECD 30 was chosen, because it is a commonly applied, commercially available product, which avoids the use of toxic organic solvents. It was blended with guar gum, a natural polysaccharide extracted from the seeds of *cyamopsis tetragonolobus*. Guar gum is a well-known excipient in pharmaceutical dosage forms [19], often used as a stabilization agent, thickener, binder or disintegrant. Furthermore, guar gum is a good film former [20] and can also be used in coatings allowing for colon targeting [21,22]. Importantly, guar gum is practically insoluble in ethanol and, thus, provides the potential to effectively hinder the undesired dissolution of an ethylcellulose network. On the other hand, guar gum is soluble in water. Consequently, pure guar gum film coatings do not allow for controlled oral drug delivery during long time periods. The presence of the water-insoluble ethylcellulose can be expected to effectively limit undesired guar gum dissolution upon contact with aqueous bulk fluids. Furthermore, guar gum as well as ethylcellulose are non-ionic. Hence, the impact of variations in the ionic strength of the release medium on the film coatings' properties is likely to be limited. The following definition of the term "ethanol-resistance" is used in this manuscript: A solid dosage form is called "ethanol-resistant", if the in vitro drug release data in 0.1 M HCl is compared with and without 40% ethanol for 2 h at 37 °C and the difference throughout the 2 h period in release profiles between the ethanol-free medium and ethanol-containing medium is: (i) less than 15%, when less than 20% of the drug is released in the ethanol-free medium, and (ii) less than 30%, when 20–80% of the drug is released in the ethanol-free medium.

2. Materials and methods

2.1. Materials

Theophylline matrix pellets (70% drug content, diameter: 0.71–1.25 mm; FMC BioPolymer, Philadelphia, PA, USA); Ethylcellulose Aqueous Dispersion NF (Aquacoat® ECD 30; FMC BioPolymer); *very low viscosity* guar gum (*very low η* guar gum, apparent viscosity of a 1% aqueous guar gum = 15 mPa·s; TIC Pretested Nutriloid 215 LV powder; TIC Gums, Belcamp, MD, USA); *low viscosity* guar gum (*low η* guar gum, apparent viscosity of a 1% aqueous guar gum solution = 52 mPa·s; TIC Pretested Gum Guar TICOLV FCC Powder; TIC Gums); *medium viscosity* guar gum (*medium η* guar gum, apparent viscosity of a 1% aqueous guar gum solution = 320 mPa·s; Polygum 240/80; Polygal Trading, Maerstetten, Switzerland); *high viscosity* guar gum (*high η* guar gum, apparent viscosity of a 1% aqueous guar gum solution in the range of 575–625 mPa·s; Guar HV 225; Alland & Robert, Port-Mort France, France); dibutyl sebacate (DBS; Morflex, Greensboro, NC, USA); ethanol (Fisher Bioblock Scientific, Illkirch, France); glyceryl monostearate (Cutina GMS V PH; Cognis, Duesseldorf, Germany); talc (Luzenac Val Chisone, Porte, Italy); polysorbate 80 (Montanox 80; Seppic, Paris, France).

2.2. Preparation and characterization of thin polymeric films

Aquacoat® ECD 30 was plasticized for 1 day with 25% DBS (w/w; based on the ethylcellulose mass). Guar gum was dissolved in purified water at 65 °C [very low η: 2%, low η: 1.5%, high η: 1%, and medium η: 0.7%; 100% reference value = total coating formulation; 2 h stirring] and cooled down to room temperature. The two liquids were blended and stirred for 30 min prior to use. Films (approximate thickness = 200 μm) were prepared by casting Aquacoat® ECD 30:guar gum blends onto Teflon plates and subsequent controlled drying for 24 h at 60 °C.

The dry mass loss kinetics of the films were determined as follows: Pieces of 5 cm × 5 cm were placed into 100 mL plastic flaks filled with 100 mL pre-heated release medium (0.1 M HCl or 0.1 M HCl:ethanol 60:40), followed by horizontal shaking (37 °C, 80 rpm; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points, samples were withdrawn and dried to constant weight at 60 °C [dry mass (t)]. The dry film mass (%) at time t was calculated as follows:

$$dry\ film\ mass\ (\%)\ (t) = \frac{dry\ mass\ (t)}{dry\ mass\ (t=0)} \cdot 100\% \quad (1)$$

The mechanical properties of the films (puncture strength, percent elongation and energy at break) in the dry and wet state were measured using the puncture test and a texture analyzer (TAXT.Plus, Swantech, Villeneuve la Garenne, France). Film specimens were mounted on a film holder (n = 6). The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (5 kg) and driven downward with