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How to easily provide zero order release of freely soluble drugs from coated pellets

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ABSTRACT

Coated pellets offer a great potential as controlled drug delivery systems. However, constant drug release rates are difficult to achieve with this type of dosage forms if the drug is freely water-soluble. This is because diffusional mass transport generally plays a major role and with time the drug concentration within the system decreases, resulting in decreased concentration gradients, which are the driving forces for drug release. Thus, generally "curve-shaped" release profiles with monotonically decreasing slopes are observed. This type of release kinetics might be inappropriate for an efficient and safe drug treatment. Despite the great practical importance of this potentially crucial formulation challenge, surprisingly little is yet known on how to effectively address it. In this study, a novel approach is presented based on sequential layers of drug and polymer (initially free of drug) to provide a non-homogeneous initial drug distribution, combined with lag-time effects, and partial initial drug diffusion towards the pellet's core. Sugar and microcrystalline cellulose beads were used as starter cores, metoprolol succinate as freely soluble drug, ethylcellulose, and poly(vinyl acetate) as release rate controlling polymers. The type, number, thickness, and sequence of the drug and polymer layers were varied. Interestingly, a rather simple four layer system (two drug and two polymer layers) allowed providing about constant drug release during 8 h. Compared to previously proposed coated pellets aiming at constant release of freely water-soluble drugs based on non-homogeneous initial drug distribution, the total coating level in this study was very much reduced: to only about 20%. Hence, the suggested formulation approach is relatively simple and can help overcoming a potentially major hurdle in practice. Its applicability has also been demonstrated for another type of drug: propranolol hydrochloride.

1. Introduction

Polymeric film coatings offer a great potential for oral controlled drug delivery (e.g., Siepmann et al., 2013). Numerous products based on coated tablets, pellets or capsules are available on the market. Importantly, the right choice of polymers, application techniques, and coated substrates allows providing large ranges of long term stable drug release profiles (e.g., Kolter et al., 2013; Sauer et al., 2013; Siepmann and Siepmann, 2013; Haaser et al., 2013). This includes for instance pulsatile drug delivery (Maroni et al., 2013a), site specific drug delivery to the colon, (Maroni et al., 2013b) and drug delivery at a constant rate (also called zero order release kinetics). The latter type of drug release profile is frequently used to compensate drug elimination out of the human body in order to provide about constant drug concentrations at the site of action.

In the case of drugs exhibiting limited water solubility, such constant drug release rates can for instance be provided using coated reservoir systems: the drug is located in the system's core, which is surrounded by a water-insoluble film coating. The latter is often based on a polymer and controls drug release. Once the dosage form comes into contact with aqueous body fluids, water penetrates into the system, and dissolves the drug. Importantly, not all of the drug can dissolve immediately, since, drug solubility is limited. Thus, dissolved and non-dissolved drug co-exist within the system's core. The dissolved drug molecules (or ions) are available for diffusion and – due to concentration gradients – diffuse through the film coating out of the dosage form. Often, this

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diffusional mass transport step plays a major role for the control of drug release (Siepmann and Siepmann, 2008, 2012). Since the dissolution of the drug is generally much more rapid than drug diffusion through the coatings, released drug molecules (or ions) are rapidly replaced by the dissolution of parts of the remaining non-dissolved drug excess. Thus, a constant concentration of dissolved drug (a saturated solution) is provided within the system as long as non-dissolved drug excess is present. If the drug concentration outside of the dosage form is negligible, this results in constant drug concentration gradients. If the film coating does not dissolve, swell, erode or otherwise change with time, also the length of the diffusion pathways and the drug's mobility in the barrier membrane remains constant, resulting in a constant drug release rate.

In contrast, if the drug is freely water-soluble (or if the initial drug loading is sufficiently low), all of the drug is rapidly dissolved upon water penetration into the system. Hence, released drug molecules (or ions) are not replaced and the drug concentration inside the dosage form decreases with time. This leads to drug release rates, which decrease with time. Different approaches have been suggested to overcome this challenge (e.g., Lee 1984a,b, 1986; Chang and Himmelstein, 1990; Danckwerts, 1994; Hildgen and McMullen, 1995). Most of them refer to matrix systems [such as multi-layered tablets (Conte et al., 1993; Hariharan et al., 1994; Qiu et al., 1998; Chidambaram et al., 1998)], osmotic pumps, (Malaterre et al., 2009) and/or devices with special geometry, e.g., hemispheres with a central orifice (Hsieh et al., 1983; Narasimhan and Langer, 1997), biconcave tablets (Benkorah and McMulle, 1994), or donut-shaped systems (Kim, 1995). Only a very few studies refer to coated dosage forms with standard geometry, such as coated pellets. An interesting system has been proposed by Scott and Hollenbeck (1991): a pellet starter core, which was layered with polymer layers containing different drug concentrations. The drug concentration in these layers increased towards the system's core to compensate the increasing length of the diffusion pathways. A theoretical framework was presented to calculate an optimal drug concentration profile. However, the total coating thickness in this case was about 400%, which is difficult to manufacture at the industrial scale. Since the drug loaded polymer matrices represented about 80% of the system's total mass (and the starter core only about 20%), it was actually more a matrix-type delivery system than a coated reservoir device.

In this study, we present a novel approach to provide about constant drug release for freely water-soluble drugs from coated pellets: sequential layers of drug and polymer were coated onto sugar or microcrystalline cellulose (MCC) starter cores. Importantly, the polymer layers were initially free of drug. Metoprolol succinate was used as freely water-soluble drug, ethylcellulose, and poly(vinyl acetate) as release rate controlling polymers. Both are well established as film coating materials for controlled drug delivery (e.g., Struebing et al., 2007, 2008; Siepmann et al., 2007). The initial drug loading was intentionally low (5%) to minimize potential drug saturation effects and assure a real formulation challenge. The type, number, and sequence of drug and polymer layers was varied. The basic idea was to provide different types of non-homogeneous initial drug distributions, which combined with lag-time effects and partial initial drug diffusion towards the pellet's core, could provide about constant drug release during major parts of the release period.

2. Materials and methods

2.1. Materials

Metoprolol succinate and propranolol hydrochloride (Safic Alcan, Puteaux, France); sugar starter cores (710–850 μm in diameter, suglets; NP Pharm, Bazainville, France); microcrystalline cellulose starter cores (MCC starter cores, 710–850 μm in diameter, celphere; Seppic, Puteaux, France); hydroxypropyl methylcellulose (HPMC, Methocel E5; Colorcon, Dartford, UK); aqueous

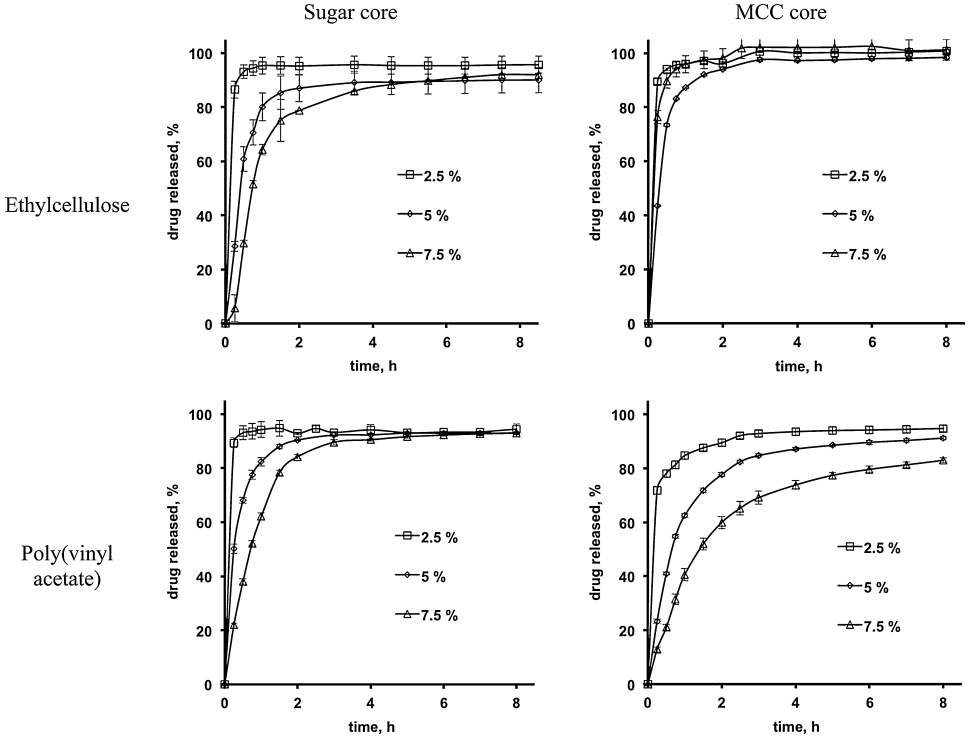

Fig. 1. Metoprolol release from pellets coated with ethylcellulose (top raw) or poly(vinyl acetate) (bottom raw), containing sugar starter cores (left hand side) or MCC starter cores (right hand side). The coating level is indicated in the diagrams. The drug (5% initial loading) was directly layered onto the starter cores.