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Influence of additives on a thermosensitive hydrogel for buccal delivery of salbutamol: Relation between micellization, gelation, mechanic and release properties

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ABSTRACT

Thermosensitive hydrogels developed for buccal delivery of salbutamol were prepared using poloxamer analogs (Kolliphor® P407/P188), xanthan gum (Satiaxane® UCX930) and NaCl. P188 increased gelation temperature ($T_{sol-gel}$) by 2.5–5 °C, micellization temperature (<1 °C) and gelation time by >3 s. To obtain a suitable $T_{sol-gel}$ at 28–34 °C, P407 and P188 concentrations were set to 18–19% and 1%. NaCl reduced $T_{sol-gel}$ (>2 °C) out of the optimal range. Six formulations containing 0.05–0.1% Satiaxane® fulfilled the temperature criteria. Concerning the gel strength, 1% P188 had no significant effect, NaCl increased it at 20 °C, and Satiaxane® enhanced it at 20 °C and 37 °C. The release study using membrane-less (to mimic oral cavity) and membrane (to mimic buccal mucosa side) methods allowed a complete investigation showing that erosion and diffusion both contributed to the drug release but differed according to the formulation. In the membraneless method, simple P407 formulations had weak ability to retain salbutamol (T_{80} = 35 min). P188 accelerated drug release. NaCl accelerated release in the membraneless method by 5–11 min but slightly reduced it in the membrane method. The hydrogels containing Satiaxane® exhibited the slowest release. In the membrane method, combination of P407/P188/Satiaxane® provided a sustained diffusion with a burst effect (T_{25} = 9.6 min, T_{80} = 97.8 min), which provides potential clinical interests.

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1. Introduction

Although oral drug administration is the most common route, and usually preferred by patients and clinicians, many drugs cannot be delivered effectively this way. The buccal mucosa is considered as an attractive target to administer several classes of pharmaceutical agents (Chinna Reddy et al., 2011). Indeed, as it is richly vascularized, drugs can directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver, which may result in a rapid onset of action (as in intravenous administration) and a higher bioavailability. Additionally, buccal drug delivery has an excellent patient acceptability compared to other routes of drug administration. Finally, buccal drug delivery does not require complicated technical equipment and expertise, and is thus more cost-effective than invasive therapies.

Salbutamol sulfate (SS) is a relatively selective beta 2 adrenoceptor agonist which has been widely used in the treatment of reactive airway diseases, such as asthmatic disorders and chronic obstructive pulmonary diseases (COPD) ("Asthme", n.d., "Bronchopneumopathie Chronique Obstructive", n.d.). It can also be used by intravenous and subcutaneous routes as a uterine relaxant to suspend premature labor (tocolysis) (Boulton and Fawcett, 2001).

Nowadays, salbutamol is commonly administered by inhalation in aerosol or nebulizer solution. However, pulmonary delivery requires special training on the part of patients, and the nebulizer solution demands special equipment. This may be particularly difficult for pediatric and geriatric patients. Furthermore, the plasma half-life of the drug has been estimated from 4 to 6 h, so 2–3 inhalations must be administered every 4–6 h to maintain therapeutic activity, which otherwise can lead to tolerance of its bronchodilator effect. When given orally (*e.g.*, tablets and syrup), its systemic bioavailability has been shown to be low and variable

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(10–50%, in human), and it is subjected to a first-pass intestinal or hepatic metabolism. Some studies suggest that the major part of salbutamol metabolism occurs in the intestine, resulting in a relatively low bioavailability and extensive enantioselective disposition following oral absorption (Boulton and Fawcett, 2001; Goldstein et al., 1987; Morgan et al., 1986). Thus, oral dosage forms must be taken 3–4 times daily. In addition, due to its solubility and permeability, salbutamol is considered as a class I drug in the Biopharmaceutics Classification System (BCS) (Murtaza et al., 2009). As an amphoteric compound with an acidic phenolic group and a basic secondary amine group, SS has two ionization constants: $pK_{a1} = 9.07$, $pK_{a2} = 10.37$. At a physiological pH, its solubility is not expected to be affected by its ionization (Imboden and Imanidis, 1999). On account of these facts, SS seems to be an interesting candidate for the preparation of a controlled buccal delivery system.

In recent years, various dosage forms have been developed for buccal delivery of SS, including bioadhesive film (Singh et al., 2010) and patch (Patel and Poddar, 2009; Vasantha et al., 2011), but not much research work has been done on the thermosensitive hydrogel and the development of drug release techniques. Additionally, the preparation of film or patch requires long process, and may raise conservation and tolerance questions.

Since they were introduced in the late 1950s, the thermosensitive hydrogels of poloxamer, which can undergo a sol–gel transition in response to temperature, have been of great interest in drug delivery and administration (Dumortier et al., 1994, 2006a,b; Koffi et al., 2006; Sandri et al., 2011). The Kolliphor® P grades with the former tradename Lutrol® F are synthetic triblock copolymers of a hydrophobic ethylene oxide (PEO) block and two hydrophilic propylene oxide (PPO) blocks that conform to the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$, and are listed in the US and European Pharmacopoeia (Rowe et al., 2005). Kolliphor® P407, known as poloxamer 407 with an average molecular weight of 12,600, and Kolliphor® P188, labelled poloxamer 188 with an average molecular weight of 8400, are two non-ionic water-soluble poloxamers which can form hydrogels (Schmolka, 1994). A poloxamer 407 formulation that is liquid at room temperature, usually 20–25 °C, and that quickly forms a gel at 34–35 °C, would be convenient to use with a buccal spraying device (Sandri et al., 2011). Thermoreversible gelation is a result of micellar entanglement and packing when the temperature increases. The micellization of poloxamer is more complex than that of common amphiphile molecules. Due to hydrophobic interactions between PPO blocks, the poloxamer molecules self-assemble as micelles in solution above the critical micellization concentration (CMC). Moreover, micelles can form as a function of temperature (CMT, critical micellization temperature) (Singh et al., 2013). The differential scanning calorimetry experiments demonstrates that the micellization process of poloxamer in water is endothermic. Increasing temperature leads to greater interactions between PPO blocks. Bringing some energy to the systems by raising temperature, allows reducing the CMC. In brief, the micellization can occur in two ways: setting the concentration of poloxamer above the CMC, or adjusting the temperature to CMT. The CMC and CMT depend on the PPO/PEO ratio and also on the molecular weight of the poloxamer, however no sharp or identical values have been observed (Alexandridis and Hatton, 1995). The micellization process corresponds to the very first step of gelation. As the hydrophobic block PPO lowers the micellization and gelation temperatures, and the hydrophilic PEO increases them, the gelation performance can be modulated by mixing the two poloxamer analogs P407 and P188 (Qi et al., 2007; Xuan et al., 2011). Additionally, the high solubilizing capacity and the low toxicity also make them an attractive vehicle for buccal drug delivery (Dumortier et al., 2006a,b). Nevertheless, the main drawbacks of poloxamer hydrogels for drug delivery applications include a limited stability, poor mechanical properties and short residence times due to a rapid dissolution once placed in biological environments. As a consequence, many attempts have been done to chemically modify poloxamer gels (Chen et al., 2011; Hsu et al., 2009) so as to obtain appropriate mechanical properties. An interesting approach focuses on blending poloxamer with mucoadhesive polymers (Baloğlu et al., 2010; Chang et al., 2002; Chen et al., 2013; Ur-Rehman et al., 2011), which are able to form entanglements or non-covalent bonds with the mucus covering epithelial tissues, thus prolonging the hydrogel's *in vivo* residence time. As a high-molecular mass polysaccharide composed of D-glucose and D-mannose as the dominant hexose units, xanthan gum is considered to be biocompatible and biodegradable, and has been widely used as a suspending, thickening and stabilizing agent in oral and topical formulations. It can also be used to increase bioadhesive strength (Ceulemans et al., 2002; Vermani et al., 2002). To increase gel mechanical strength, some small molecular ionic agents like NaCl can be incorporated into the poloxamer gel. Some studies suggest that salts might have a significant influence on the gelation and strength properties of poloxamer gel (Choi et al., 1999; Ricci et al., 2005) as well as on the drug release profile (Moore et al., 2000; Pandit and Wang, 1998).

In this context, we wished to design a novel thermosensitive sprayable hydrogel base for buccal delivery of salbutamol with optimized gelation temperature (28–34 °C), suitable mechanical properties (*e.g.*, viscosity less than 200 mPa s at room temperature, higher than 10,000 mPa s after gelation *in situ*), mucoadhesive properties, and also relatively sustained drug release. To obtain these properties, four components: P407, P188, xanthan gum and NaCl were combined with various concentrations, and then their influences were evaluated *in vitro*. In this paper, we focus on the measurement of gelation and micellization temperatures, the determination of mechanical force and apparent viscosity, and finally the drug release study by a membraneless and a membrane diffusion methods based on the USP4 apparatus (flow through cell), completed with a mathematical modeling. The relations between the different parameters were statistically analyzed.

2. Materials and methods

2.1. Materials

SS of European Pharmacopoeia grade (molecular weight 576.7) was purchased from Farmalabor srl (Canosa di Puglia, Italy). Kolliphor® P407 and Kolliphor® P188 of pharmaceutical use grade were obtained gratis from BASF (Ludwigshafen, Germany). Satiaxane® UCX930 (xanthan gum) was obtained gratis from Cargill France (Saint-Germain-en-Laye, France). The sodium chloride (NaCl), sulfuric acid (H_2SO_4) and chloride acid (HCl) of analytical grade were obtained from VWR International (Fontenay-sous-bois, France). The sodium phosphate buffer (NaPi) powder (0.1 M) was purchased from Euromedex (Strasbourg, France). All the solutions were prepared using sterile water Versylene® purchased from Fresenius Kabi France (Sèvres, France).

2.2. Preparation of formulations

The hydrogel was prepared on a volume basis. Concentrations of all the components reported here are expressed as weight/volume percentage (% w/v). The poloxamer solutions were prepared using the cold method (Schmolka, 1972). P407 (17–19%) or P407 combined with P188 (1%) were slowly added to a certain volume of sterile water, and then the preparations were left at 4 °C until clear solutions were obtained. The preparations were then gently homogenized with magnetic stirrers. Sterile water was then added to adjust the volume to the total amount.

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