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Research paper

Formulation of thermoresponsive and bioadhesive gel for treatment of oesophageal pain and inflammation

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ABSTRACT

The aim of this study was the formulation and examination of a novel thermoresponsive and bioadhesive, in situ gelling drug delivery system, which can be used in the treatment of oesophageal pain and inflammation. A bioadhesive cellulose derivative (Metolose® 60SH) was used as a thermoresponsive material, because Metolose® has thermal gelation properties at certain temperature. The thermal gelation temperature (T_2) of Metolose® 60SH 2 w/w% solution is above body temperature (65–66 °C), but by using different methods (Metolose® 60SH concentration, auxiliary materials), it can be shifted near to body temperature. The pH alteration between pH = 2–10 and the application of different alcohols did not influence the gelation temperature, but using water-soluble salts and changing the concentration of Metolose® 60SH solution between 2 and 3 w/w% the thermal gelation point could be decreased. Different NSAIDs were used as model drugs and which had not influence on thermal gelation temperature, but difference in in vitro liberation and penetration can be observed. In vitro adhesion test pointed out that the condition of investigated membrane can change the adhesion. Morphological test of oesophageal tissue showed that investigated materials had no irritative or tissue-damaging effect on the oesophageal mucosa even after 12 h.

1. Introduction

Several illnesses related to the oesophagus result in inflammation which causes pain, dysphagia and weight of loss for the patient. It is essential for us to focus on the effective analgetic and anti-inflammatory therapy, as the availability of the conventional oral administered dosage forms is limited. Due to its short transit time and the relative impermeability of the stratified squamous epithelium, drug absorption from the oesophagus is not significant in comparison with the other parts of the gastrointestinal tract. However, it would be desirable that locally acting agents should be used in the treatment of the pain and inflammation in several cases (e.g., oesophageal pain in cancer, inflammation during radiation therapy, fungal infection or reflux disease [1]). In order to reach a considerable drug effect and the absorption from the mucosal surface of the oesophagus (which measures approximately 150–200 cm^2), transit time should be prolonged by using different methods. After the administration of solid dosage forms, unwanted bioadhesive property of the mucosal surface in the oesophagus can be observed in those patients who take their medicine with little or no water at all [2,3]. This phenomenon can be positively used for developing oesophageal dosage forms, e.g., bioadhesive systems formulated by sodium alginate [4,5].

In the past few years, an increasing number of publications have been issued in the subject of the oesophageal drug delivery, but most of them focus only on reflux disease and fungal infection. The development of the responsive dosage forms [6], such as in situ gelling hydrogel systems, is considered a new aspect in the diagnosis and the treatment of illnesses related to the oesophagus [7]. Drug release and physico-chemical properties can be influenced by different external or internal factors (e.g., pH [8], temperature [9,10], electric [11], magnetic field, ultrasound [12,13], or visible wavelength in case of photosensitive systems [14,15]) in responsive systems. Drug release from thermosensitive systems can be affected by changes in the temperature, which result in a phase transition; this can be a sol–gel conversion, soluble–insoluble state variations, liquid crystal phase transitions, or crystalline-amorphous phase-oscillations. Several pharmaceutical dosage forms can be prepared as a thermoresponsive system. Many investigations describe the use of liposomes, microcapsules, microspheres, nanoparticles, films, gels and injectable drug delivery system [16].

Thermoresponsive materials can be liquid crystals, e.g., Monooxyethylene trimethylolpropane tristearate or Polyoxyethylene glyceryl tristearate, used in microspheres and TTS [17], Cholesteryl oleyl carbonate (COC) [18], Glyceryl monooleate [19,20], polymers

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(Polyacrylamide derivatives [21–23]) aliphatic polyesters (Poly-ε-caprolactone (polyCL) [24]) macromolecules (gelatine, alginate [4,5], and different cellulose derivatives [25]).

These intelligent and regulated systems can be combined with each other [26], for example, in thermosensitive magnetoliposomes [27–29], which can be used for chemoembolisation in cancer therapy.

The aim of this study was to formulate a novel thermoresponsive and bioadhesive in situ gelling drug delivery system, which can adhere to the mucosal surface, thus improves the bioavailability, and decreases the side effects as the absorbed drug avoids liver's first pass metabolism effect.

In our study a water-soluble cellulose derivative [30] (Metolose® 60SH) was used as a thermoresponsive and bioadhesive material, because it shows thermal gelation and has excellent bioadhesive features [31].

Cellulose is not soluble in water, however, if the hydrogen atoms of some OH groups are substituted for methyl or hydroxypropyl groups, the polymer becomes water-soluble (Fig. 1). Depending on which etherification agent it contains, Metolose® is available in three forms: SM, SH, and SE.

SM type has methyl groups, SH type Metolose® has hydroxypropyl and methyl groups, and SE type is a cellulose with hydroxyethyl and methyl groups.

Each type of Metolose® aqueous systems is in sol phase at room temperature so it can easily be swallowed, and above body temperature it turns into gel phase which results a prolonged adhesivity. The temperature where the viscosity increases and gelation can be observed is referred to as thermal gelation temperature. The background of thermal gelation is the associations between the highly substituted parts and coverage of hydrophobic molecule parts in the network of polymer chain. This thermal gel is opalescent and reverts to its original solution form when it is cooled down [32]. Different substitution types have different gelation behaviors. The consistence of the Metolose® SM thermal gel is hard, while Metolose® SH thermal gel is soft. In our work, Metolose® 60SH was used as the viscosity of the thermal gel is lower, so it is more tolerable for the patients.

In our previous study [33], Metolose® 60SH was applied as a matrix in thermoresponsive transdermal therapeutic system, diclofenac-sodium was used as a drug, and we demonstrated the thermal gelation of Metolose® 60SH. The process can be characterized by two temperatures (T_1 and T_2). If the temperature is increased, the viscosity of aqueous solution decreases, and at T_1 a breakpoint can be observed where we can experience a dramatic fall in viscosity. Further increasing the temperature, we can observe gelation at T_2. In our previous study, we used the viscosity fall at T_1 as release controlling factor of thermoresponsive TTS.

The T_1 of Metolose® 60SH is above the skin temperature where the TTS is applied but by using 8% KCl this T_1 can be shifted to the desired temperature. The static drug release test confirmed that thermoresponsive drug release at skin temperature was developed from TTS using Metolose® 60SH gel, where the drug release rate constant significantly increases above the skin temperature.

In this present study, the thermal gelation temperature (T_2) of Metolose® 60SH 2 w/w% was used in order to develop a thermoresponsive and bioadhesive gel. At T_2 we can observe an increase in gelation and viscosity. The thermal gelation temperature of Metolose® 60SH 2 w/w% is between 65 and 66 °C, but by using different methods and types of auxiliary materials this T_2 can be shifted to the target temperature. In our study 39 °C was determined as the target temperature, because in the human body the oesophageal temperature corresponds to the core temperature and patients suffering from inflammation or cancer often develop low grade fever. This can be explained by the fact that the released substances change the metabolism, therefore, the body's thermoregulatory set-point temporary elevates and the core temperature rises up to 38–39 °C. Low grade fever can be also a side effect of the chemotherapy in the case of chemotherapy-induced neutropenia [34]. Our aim was developing and evaluating a thermoresponsive and bioadhesive gel for patients suffering from inflammation and fever. In this present study, we have examined the influence of different factors (pH, additives and drugs) on T_2 of Metolose® 60SH gel in order to shift down thermal temperature to target temperature, formulating a novel thermoresponsive and bioadhesive oral hydrogel. In vitro drug release and permeation were investigated by using different NSAIDs as model drugs.

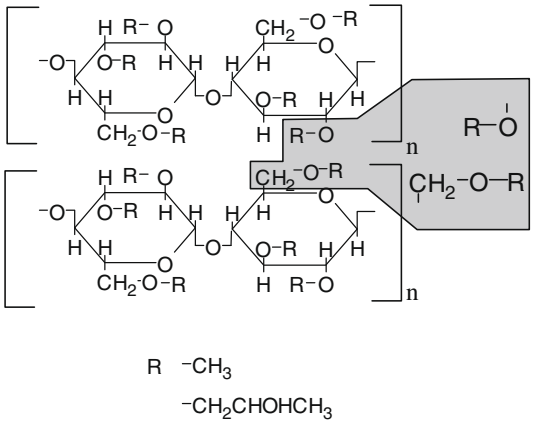

Fig. 1. Chemical structure of Metolose® (R = CH_3 → → Metolose® SM; R = $CH_2CHOHCH_3$ → → Metolose® SH).

2. Materials and methods

2.1. Materials

Piroxicam (PX), acetyl salicylic acid (ASA), ibuprofen (IB), indometacin (IM) (Boots Chemicals, Nottingham, England), aminophenasone (AM) (Reanal Chemicals Ltd., Budapest, Hungary) were used as drugs. Hydroxypropyl methylcellulose (Metolose® 60SH, Metolose® 90SH Shin-Etsu Chemical Co., Tokyo, Japan) was used to formulate a thermoresponsive gel system. Auxiliary materials: sodium chloride, sodium hydrogen carbonate, citric acid, glycerine, propylene glycol, polyethylene glycol 400 were supplied by Reanal Chemicals Ltd. (Budapest, Hungary) and were of analytical grade.

2.2. Apparatuses

The analytical determination of the active ingredient was carried out with Shimadzu UV-16A spectrophotometer (Shimadzu Corporation Spectroscopic Instruments, Kyoto, Japan). HAAKE VT550 Rheometer (HAAKE GmbH, Karlsruhe, Germany) was used to determine the viscosity of gel, and the change in the temperature was controlled by TC81 Peltier thermocontroller (HAAKE GmbH, Karlsruhe, Germany), in vitro drug release and permeation tests were carried out with a Franz-cell.

2.3. Methods

2.3.1. Preparation of the Metolose® gel

Metolose® powder of 0.2 g was continuously mixed with 5.0 g of water (70 °C) on a heated magnetic stirrer. Cold water (4.8 g) was added to the opaque mixture and was stirred until it became transparent. Drug of 0.05 g was dissolved in cold distilled water