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Aqueous and hydro-alcoholic media effects on polyols

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ABSTRACT

The ingestion of drug products with alcohol can have an adverse effect on drug levels in a patient's blood. The Food and Drug Agency (FDA) issued an alert in 2005 after hydromorphone was withdrawn from the market after clinical trials showed ingestion with alcohol to potentially result in lethal drug peak plasma concentrations. The potential impact of alcohol on extended release (ER) tablet matrices and the need to develop ER matrices robust to alcohol effects has then been of interest. This study investigated the compaction properties of polyols and their effect on drug release. Polyols (erythritol, xylitol, mannitol and maltitol) with increasing hydroxyl groups were used as diluents for HPMC matrices containing theophylline. Release profiles were determined in pH 1.2 and 6.8 dissolution media with hydro-alcoholic concentrations of 5–40%. Increases in the polyols' hydroxyl groups brought about an increase in tablet strength and a decrease in the drug release rates. This is likely due to stronger bond formation with increasing hydroxyls. The impact of alcohol on drug release was studied further for maltitol formulations. Maltitol was resilient to the presence of ethanol (5–40% v/v) at pH 1.2 ($f2$ = 57–74) but not at pH 6.8 ($f2$ = 36–48). Drug release was not different above 5% alcohol concentration at pH 6.8. The results of this in vitro study suggest that ethanol concentrations as high as 40% do not substantially alter the drug release properties of theophylline from maltitol matrix tablets. However, care and consideration should be given to the choice of polyol or mixture of polyols in obtaining a desired drug release profile.
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1. Introduction

Extended release can be achieved by formulating drugs as matrix devices using swellable polymers such as hydroxypropyl methylcellulose (HPMC). HPMC is also the most commonly used hydrophilic polymer carrier in extended release matrices because of its ability to provide robust formulations and obtain desired release profiles for a wide range of drugs, its stability, global regulatory acceptance, cost effectiveness and non-ionic nature [1]. Researchers have demonstrated that the gel layer formed around hydrophilic matrices, upon its contact with gastro-intestinal (GI) fluids, is eroded allowing drug release. This erosion is the dominant release mechanism for poorly water soluble drugs. The other mechanistic approach is that the soluble portion of drug is released by the process of diffusion through the gel layer [2–5]. Typically, however, drug release occurs by a combination of these two mechanisms [6]. Drug release rate may be significantly affected by the medium to which the matrix is exposed upon ingestion, i.e. pH, electrolytes, surfactants and enzymes [3,7–10]. The rate of drug release from HPMC matrices is dependent on various factors such as type of polymer, drug, polymer/drug ratio, particle size of drug and polymer, and the type and amount of fillers used in the formulation [1,11–16].

Excipients, fillers/diluents account for the major part of tablet composition and can affect both tablet strength and the release rate of the drug. The most common diluent used in tablet manufacture is lactose. Lactose is water-soluble and undergoes fragmentation in the compression phase followed by a very low elastic recovery in the decompression phase resulting in tablets of adequate mechanical strength. Polyols (sugar alcohols) have gained popularity especially in modern formulation however, there is very little work carried out in the application of sugar alcohols as diluents. Polyols are widely accepted by the public due to their sweet taste, low calorific value and they do not affect serum glucose levels which make them ideal for use by diabetic patients. Polyol's also do not cause Maillard reactions, a risk between drugs with functional amino groups and the reactive carbonyl groups of a reducing sugar such as lactose. Polyol's are an attractive option as a diluent in cases where lactose as a diluent could cause intolerance in patients. Many polyols are soluble in water, due to their many hydroxyl groups and although solubility increases with temperature, their molecular configuration and conformation can cause solubility differences. For example, sorbitol, lactitol monohydrate, maltitol and xylitol are highly soluble in water (235 g/100 g H_2O, 140 g/100 g H_2O,

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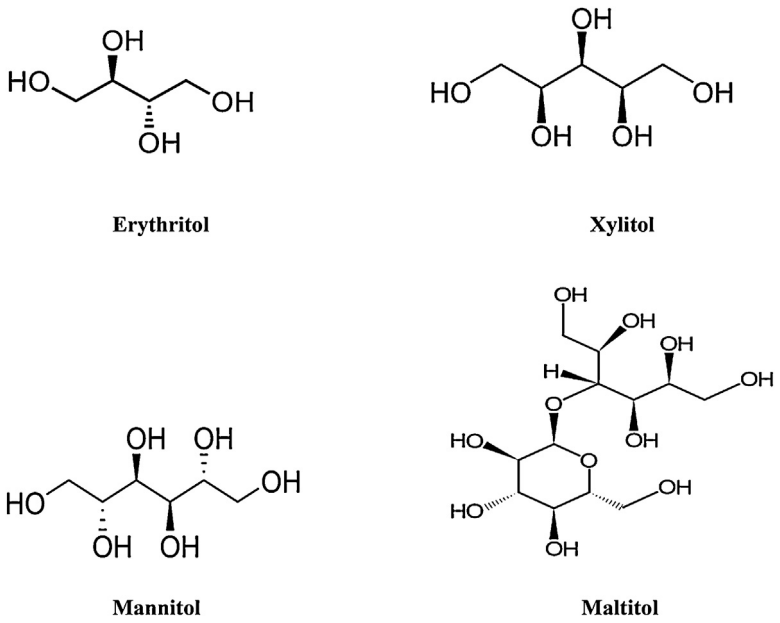

Fig. 1. Structure of polyols used in the study.

175 g/100 g H_2O and 200 g/100 g H_2O respectively) but mannitol (an isomer of sorbitol), erythritol and anhydrous isomalt (a mixture of sorbitol and mannitol) are relatively less soluble (22 g/100 g H_2O, 61 g/100 g H_2O and 39 g/100 g H_2O respectively). Erythritol is used as an excipient in rapidly dissolving tablets [17]. Kuno and coworkers [18] and Zajc and coworkers [19] reported the use of sugar alcohols for solubilising poorly soluble drugs. Zajc and coworkers [19] showed that dissolution rate enhancement of nifedipine was as a result of the improved wettability of nifedipine crystals due to mannitol particles attached to the surface of the drug. Arias and coworkers [20] also reported the successful employment of mannitol in a hot melt procedure as a carrier to improve the solubilisation of the poorly water soluble drug Triamterene. Ohmori and coworkers [21] also found erythritol to be a useful agent for tablet coating.

In 2005, Palladone®, an extended-release capsule, was withdrawn from the market after clinical testing showed subjects who took the product with alcohol had increased levels of the drug in their blood. The Food and Drug Agency (FDA) then issued an alert to healthcare professionals regarding this as the ingestion of hydromorphone with alcohol potentially resulted in lethal peak plasma concentrations of drug. This sparked an interest to investigate the potential impact of alcohol on extended release (ER) tablet matrices and the need to develop ER matrices robust to alcohol effects. Since then, Roberts and coworkers [22] studied the influence of alcohol on the release of aspirin from HPMC matrix tablets. They found that ethanol affects kinetics and mechanism of aspirin release, but does not result in a dose-dumping effect. Levina and coworkers [23] investigated the hydroalcoholic solution effect on hydration, gel formation and drug release from HPMC matrices. None of the investigated matrix formulations (felodipine, gliclazide, and metformin hydrochloride) resulted in dose-dumping when exposed to ethanol solutions. HPMC compacts made of three different viscosity grades of Methocel® showed consistent swelling and gel formation when exposed to hydro alcoholic media. In 2010, Smith and co-workers studied the in vitro drug release of 27 oral modified-release products in alcohol-containing media. In 40% alcoholic medium, 9 of 10 capsules and 2 of 17 tablets showed accelerated drug release. The drug products were also tested in 5% and 20% alcoholic media and in simulated gastric fluid (without enzyme) containing 20% alcohol. They found that no tested capsules or tablets exhibited a significant increase in drug release in media containing only 5% alcohol [24]. The mechanistic effect of this phenomenon was however not discussed. The authors however stressed on the need for more work on ethanol effects on excipients as it had a substantial effect on drug release.

Theophylline is a bronchodilator which is used in the treatment of respiratory conditions such as bronchial asthma. It is known as a partially water soluble drug. As the absorption of theophylline is prone to the effects of meals as well as having a narrow therapeutic index, the management of dosing can prove to be difficult. Although controlled release formulations of theophylline exist, the drug release rate is often difficult to control. Moreover, as the manufacturing process can be complex, the drug release rate is likely to vary among formulations [25]. Drug absorption is influenced by conditions within the gastrointestinal tract and can affect the bioavailability [26]. The first part of this study was to develop controlled release formulations of theophylline as a model drug in matrix tablets using polyols as diluents namely, erythritol, xylitol, mannitol and maltitol as depicted in Fig. 1. The effect of polyols on tablet strength and on the release of theophylline was investigated. The most robust of the polyol formulations from the first part of the study were further investigated in 5–40% absolute ethanol solutions. The effect of hydration, gel formation and theophylline drug release from their matrices in the hydro-alcoholic solutions were also studied.

2. Materials and methods

2.1. Materials

Hypromellose (Methocel K15 M, Colorcon Ltd, UK) was used as the matrix former. Anhydrous theophylline (TCI, Japan) was used as the model drug. Erythritol and maltitol (E0021 and M0601 respectively) (TCI, Japan), xylitol (X3375) (Sigma, UK) and D-mannitol (63560) (Fluka Analytical, UK) were used as the diluents.

Dissolution media were prepared using hydrochloric acid (Fisher Scientific, UK) for 0.1 M pH 1.2. Potassium phosphate monobasic-white crystals (Fisher Scientific, UK) and sodium hydroxide (Fisher Scientific, UK) were used in the preparation of

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