International Journal of Pharmaceutics 478 (2015) 796–803

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Moisture diffusion and permeability characteristics of hydroxypropylmethylcellulose and hard gelatin capsules

Ahmad S. Barham [a,*], Frederic Tewes [b,c], Anne Marie Healy [b]

[a] Basic Sciences Department, College of Engineering and Information Technology, University of Business and Technology, Jeddah, Saudi Arabia
[b] School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland
[c] INSERM U 1070, Pôle Biologie-Santé, Faculté de Médecine & Pharmacie, Université de Poitiers, Poitiers, France

ARTICLE INFO

Article history:
Received 10 November 2014
Accepted 13 December 2014
Available online 16 December 2014

Keywords:
Hard capsules
Gelatin
HPMC
DVS
Sorption–desorption
Diffusion
Permeability

ABSTRACT

The primary objective of this paper is to compare the sorption characteristics of hydroxypropylmethylcellulose (HPMC) and hard gelatin (HG) capsules and their ability to protect capsule contents. Moisture sorption and desorption isotherms for empty HPMC and HG capsules have been investigated using dynamic vapour sorption (DVS) at 25 °C. All sorption studies were analysed using the Young–Nelson model equations which distinguishes three moisture sorption types: monolayer adsorption moisture, condensation and absorption. Water vapour diffusion coefficients (D), solubility (S) and permeability (P) parameters of the capsule shells were calculated. ANOVA was performed with the Tukey comparison test to analyse the effect of %RH and capsule type on S,P, and D parameters. The moisture uptake of HG capsules were higher than HPMC capsules at all %RH conditions studied. It was found that values of D and P across HPMC capsules were greater than for HG capsules at 0–40 %RH; whereas over the same %RH range S values were higher for HG than for HPMC capsules. S values decreased gradually as the %RH was increased up to 60% RH. To probe the effect of moisture ingress, spray dried lactose was loaded into capsules. Phase evolution was characterised by scanning electron microscopy (SEM), X-ray powder diffraction (XRD), and differential scanning calorimetry (DSC). The capsules under investigation are not capable of protecting spray dried lactose from induced solid state changes as a result of moisture uptake. For somewhat less moisture sensitive formulations, HPMC would appear to be a better choice than HG in terms of protection of moisture induced deterioration.

1. Introduction

In the pharmaceutical field, hard capsules are used as a storage medium for finely divided blends or formulations containing active pharmaceutical ingredients (APIs) that are to be delivered orally or by inhalation (Hosny et al., 2002; Steckel et al., 2004). Capsules containing drugs are usually made of hard gelatin (HG) or hydroxypropylmethylcellulose (HPMC) (Bae et al., 2008; Berntsson et al., 1997).

Gelatin is a naturally occurring protein of animal collagen that has notable hygroscopic properties and is used to manufacture HG capsules (Chang et al., 1998). It is a good film-forming material suitable for preparing capsule shells that dissolve readily in biological fluids at body temperature (Pennings et al., 2006). Gelatin has characteristics which make it suitable for the capsule manufacturing processes, including gels, film-forming and surface active properties (Sherry Ku et al., 2010). However, HG capsules undergo shell brittleness after exposure to low humidity conditions, are incompatible with hygroscopic materials, susceptible to hydrolysis, and inherently reactive toward many substances, including reducing sugars, plasticizers and preservatives (Missaghi and Fassihi, 2006). HPMC capsules proved to be a suitable alternative to gelatin, with many patents granted for the manufacturing process, including thermal gelation and a gelling system with additives (Ogura et al., 1998). Moreover, HPMC capsules have several distinct advantages over HG. Besides the fact that it has no animal-derived raw materials risk, HPMC is a non-ionic polymer and the capsule has fewer compatibility issues with most drugs and excipients (Ogura et al., 1998). HPMC capsules are

* Corresponding author at: Department Head of Basic Sciences, College of Engineering and Information Technology, University of Business and Technology, P. O. Box 11020, Jeddah 21361, Saudi Arabia. Tel.: +966 12 2159372; fax: +966 12 2159010.
E-mail address: ahmad.s@ubt.edu.sa (A.S. Barham).

http://dx.doi.org/10.1016/j.ijpharm.2014.12.029
0378-5173/

made from a cellulose–like polymer consisting of glucose units linked together by β-1,4 glycosidic linkages and considered to be a hydrophilic material, as characterised by its high moisture sorption characteristics (Laksmana et al., 2009; Siroka et al., 2008).

A main limitation to the use of hard capsules resulted from an exchange of moisture between the capsule shell and the fill (Strickland and Moss, 1962). The usefulness of such capsules is strongly dependent on their capacity to protect the contents in the presence of moisture. The typical moisture content of HG capsules generally may vary between 13 and 16% by weight of water (Chang et al., 1998) compared to 2 and 6% for HPMC capsules (Sherry Ku et al., 2010) when received from the suppliers. Sherry et al. (2010) concluded that the water content of the polymeric material of the capsules is a function of the relative humidity (RH) of the surroundings and temperature. When the capsules are filled and stored in a vapour tight container, the moisture will redistribute between the various components until a uniform relative humidity is attained in the capsule shell, fill and surrounding (Sherry Ku et al., 2010).

Lactose is the most widely used excipient in the pharmaceutical industries due to its low toxicity, ready availability and compatibility with the majority of low molecular weight drugs (Guenette et al., 2009). It is well known that the solid state of lactose can be either amorphous or crystalline and it exists in two isomeric forms, namely, α-lactose monohydrate and β-lactose (Larhrib et al., 1999). Amorphous lactose can be prepared by spray drying or freeze drying. Spray dried lactose is thermodynamically unstable and hygroscopic. It has a tendency to gain moisture from its surroundings with ease and subsequently plasticize or cake (Barham and Hodnett, 2005). Several researchers have investigated the crystallisation kinetics of lactose at different relative humidities at room temperature. They found that the amorphous lactose will initially sorb moisture from its surroundings and then release the moisture when it crystallizes. This process will occur spontaneously above 50% RH at 25 °C (Barham and Hodnett, 2005; Islam et al., 2010; Jouppila et al., 1997; Shrestha et al., 2007).

In general, the overall aim of the current study was to determine the effectiveness of the capsules at protecting a moisture sensitive compound and identifying which is better in this regard. Amorphous lactose was chosen as a moisture sensitive model compound to investigate the impact of encapsulation methods such as hard capsules on lactose stability upon exposure to controlled humidity environments. Evolution of lactose phases obtained upon crystallisation and their interactions with water vapour were evaluated. Sorption–desorption isotherms, water permeability, solubility, and diffusion coefficients of empty HPMC and HG capsules were determined at various relative humidity values at 25 °C.

2. Materials and methods

2.1. Materials

2.1.1. Hard capsules

Hard gelatin (HG) capsules of size no. 3 were purchased from Farillon Ltd. (Essex, UK). Hydroxypropylmethylcellulose (HPMC) capsules of size no. 3 were received as a gift from Capsugel®, France. Specifications of HPMC capsules were the same for body and cap, i.e. Coni-snap (V43.700), Vcaps® Capsules (Natural TR. V900). Hypromellose (E464) was 100% of the total HPMC capsule composition.

2.1.2. Preparation of spray-dried lactose

Anhydrous spray-dried lactose was produced by spray drying a 5% (w/v) α-lactose monohydrate (Sigma–Aldrich, Ireland) solution in deionised water with a Büchi 290 mini spray dryer (Büchi Labortechnik GmbH, Germany), using a standard 2-fluid nozzle with a 0.7 mm tip and 1.5 mm cap. The spray drying process was carried out in the open mode at 8 ml/min solution feed rate. The inlet temperature was adjusted to 160 °C and the resultant outlet temperature was 95–97 °C. Aspirator setting and the atomising air flow rate were set at 40 m^3/h and 473 l/h, respectively. After the spray drying process, anhydrous lactose was collected in air tight glass containers and kept in desiccators containing silica gel to protect it from environmental humidity. Amorphicity of the spray-dried lactose was verified by X-ray diffraction as described in Section 2.4.3 Deionised water used in this work was HPLC grade and obtained from a Purite Prestige Analyst HP water purification system.

2.2. Methods

2.2.1. Dynamic vapour sorption (DVS)

Moisture sorption and desorption characteristics of empty HPMC and HG capsules was determined at a constant temperature of 25 ± 0.1 °C using a DVS Advantage-1 automated gravimetric vapour sorption analyser (Surface Measurement Systems, London, UK). The DVS-1 measures the ingress and loss of water vapour gravimetrically with a mass resolution of ±0.1 μg. Prior to being exposed to any vapour, capsules were equilibrated at 0% RH to establish a dry reference mass. After drying, all empty capsule shells in the DVS were exposed to a stepwise increase of %RH (0%; 20%; 30%; 40%; 50%; 60%; 70%). The same %RH profile was employed for desorption. At each stage, the equilibrium behaviour was defined when the mass variation versus time dm/dt was ≤0.002 mg/min for at least 10 min before the partial pressure was increased or decreased. An isotherm was then calculated from the completed sorption and desorption profiles using the DVS-1 analysis software, Surface Measurement Systems®, 2003. The amount of water taken up by the capsules was expressed as a percentage of the dry capsule mass (equilibrated at 0% RH). All DVS measurements reported in this work were conducted in triplicate.

2.2.2. Mathematical modelling: moisture distribution analysis using the Young–Nelson equations

The Young–Nelson model equations were fitted to the sorption–desorption data of the isotherms. The model can differentiate between bound monolayer, normally condensed, externally adsorbed moisture and internally absorbed water and is based on equations of the form (Bravo-Osuna et al., 2005; Kachrimanis et al., 2006; Tewes et al., 2010):

$$M_s = A(\beta + \theta) + B\theta RH \tag{1}$$

$$M_d = A(\beta + \theta) + B\theta \mathrm{RH}_{max} \tag{2}$$

where M_s and M_d are, respectively the mass percentage of water sorbed and desorbed on the polymers at the equilibrium for each % RH. A and B are constants characteristic of each system. In this model, θ is the fraction of the surface covered by at least one layer of water molecules Eq. (3), where E is an equilibrium constant between monolayer water and the normally condensed water adsorbed externally to the monolayer (Bravo-Osuna et al., 2005; Kachrimanis et al., 2006), and β is defined by Eq. (4).

$$\theta = \frac{RH}{RH + (1 - \mathrm{RH})E} \tag{3}$$

$$\beta = -\frac{E \times RH}{E - (E-1)RH} + \frac{E^2}{E-1}\ln\left(\frac{E - (E-1)RH}{E}\right) - (E+1)\ln(1 - \mathrm{RH}) \tag{4}$$