Industrial Crops and Products 44 (2013) 603–610

Contents lists available at SciVerse ScienceDirect

Industrial Crops and Products

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

Design of *Pistacia lentiscus* (mastic gum) controlled release spheroids and investigating the influence of roll compaction

Rohan D. Deshpande*, D.V. Gowda, Nawaz Mahammed

Department of Pharmaceutics, JSS College of Pharmacy, JSS University, S.S Nagar, Mysore 570015, India

ARTICLE INFO

Article history:
Received 8 June 2012
Received in revised form
16 September 2012
Accepted 19 September 2012

Keywords:
Mastic gum
Extrusion–spheronization
Roll compacted tablets
Diclofenac sodium

ABSTRACT

A gum isolated from *Pistacia lentiscus* of *Pistacia* genus was used as a release modifier in the preparation of diclofenac sodium spheroids, using the extrusion–spheronization technique. Spheroids prepared were formulated using diclofenac sodium, mastic gum (2.5–15%) and microcrystalline cellulose. Here, variables were studied and spheroids were characterized for average size, surface morphology, friability, bulk density and flow properties. *In vitro* drug release profile indicated an increase in drug release retardation with increasing mastic gum concentration. The formulated spheroids were stable with respect to their physicochemical characters and drug content over a period of 60 days at different temperatures and relative humidity. The objective of this study was to evaluate the influence of roll compaction and tableting on release of diclofenac sodium. Tablets prepared at different compression force played a key role in the dissolution of drug. Finally, the sustained release properties of spheroids were also maintained after compression.

1. Introduction

The process of extrusion/spheronization is a popular and accepted method of producing spheroids. This process consists of basic five unit operations, i.e.,—blending, wet massing, extrusion, spheronization and drying resulting in the formation of spherical spheroids showing a homogeneous surface. Spheroids are agglomerates of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi spherical solid units, typically from ~0.5 to 1.5 mm and are intended for oral administration (Gajdos, 1984; Kristensen and Schaefer, 1987; Ghebre-Sellassie, 1989). Thus, multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet (Pharma Polymers News, 2002). The spheroids offer certain specific advantages over conventional solid dosage forms like – free flow and ease of packing, resulting in reproducible and uniform fill weight of capsules. It has been found that spheroidal particles smaller than 2.4 mm diameter are free from digestive function of the stomach and the closing system of pyloric sphincter of stomach (Davies et al., 1987; Feely et al., 1987). Implants of small cylinders formed by compression from medicated masses are also defined as spheroids in pharmacy (Cox and Spanjers, 1970; Niskanen, 1992). Many methods have been reported for the preparation of spheroids: melt spheronization, compaction, globulation drug layering, melt spheronization, globulation, balling, compression, and extrusion–spheronization. Among these, extrusion–spheronization is the most popular method (Ghali et al., 1990; Reynolds, 1970).

Spheroids offer great flexibility in designing and development of pharmaceutical solid dosage form. Spheroids are suitable candidates for coating due to their ideal spherical shape and a low surface area-to-volume ratio (Rowe, 1985; Vertommen et al., 1997). Spheroids containing different drugs can be blended together and formulated in a single unit dosage form. This approach facilitates the advantage of delivering two or more drugs which are chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract (Ghebre-Sellassie, 1989; Wan and Lai, 1991). The dosage form containing pelletized product can freely disperse in the gastrointestinal tract as a subunit, thus providing the advantage by maximising drug absorption and reducing peak plasma fluctuation. Finally, potential side effects can be minimized without affecting drug bioavailability. It adds another advantage by preventing local irritation derived from high local concentrations of a drug from a single-unit dose, in certain class of drugs. Mastic gum is a natural oleoresin exudate obtained from the stem and main leaves of a cultivated variety of *Pistacia lentiscus* var. They find a wide range of pharmaceutical applications that include their use as disintegrant, binder in tablets, emulsifiers and gelling agents. They are also used as sustaining agents in tablets. Mucilages

* Corresponding author. Tel.: +91 821 2548353/9902159774; fax: +91 821 2548359.
E-mail address: rohan11in@gmail.com (R.D. Deshpande).

0926-6690/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.indcrop.2012.09.014

and gums have been popularly used to sustain the drug release from matrix tablets (Kulkarni et al., 2002; Baveja et al., 1988). It has been reported that mastic gum has been used extensively as herbal remedy and dietary supplement from centuries in the middle eastern and Mediterranean countries. Recently, medical trials shown that mastic gum possess cytoprotective or antacid effects for gastrointestinal system and possess anti-tumor activity against human colorectal cancer (Al-Habbal et al., 1984; Al-said et al., 1986; Huwez and Al-Habbal, 1986; Balan et al., 2007; Dimas et al., 2009). Oleanolic acid a major constituent of gum mastic is well-known triterpenes has shown biological properties against chemically induced liver injury in laboratory animals, exerting anti-tumor and anti-inflammatory effects (Liu, 2005). In past studies mastic gum has been reported for use as controlling the drug release from matrix type dosage form. However, there are no reports regarding the use of mastic gum as a release modifier in spheroids using diclofenac sodium as model drug.

Diclofenac sodium is a non-steroidal anti-inflammatory drug which has anti-inflammatory, analgesic and antipyretic properties. Diclofenac sodium is rapidly dissolved in intestinal fluid and reaches its maximum blood concentration (C_{max}) within 30 min and is metabolized mainly by hepatic hydroxylation and subsequent conjugation. It has short biological half life of 1.2–1.8 h and is administered in a dose of 100 mg 2–3 times a day. Therefore, diclofenac sodium is an ideal candidate for developing sustained release dosage forms which could result in reduced frequency of administration, prolonged clinical efficacy and less side effects.

2. Materials and methods

2.1. Materials

Mastic gum (commercial grade) was obtained from Chios gum Mastic growers association, Chios, Greece. Diclofenac sodium was a kind gift from Micro Labs Ltd. (Bangalore, India). Microcrystalline cellulose (MCC), Lactose anhydrous and Avicel® PH 200 was obtained from Loba Chemie (Mumbai, India). All other chemicals and reagents used in the present study were of analytical reagent grade.

2.2. Characterization of gum

The viscosity of 1% solution of the mastic gum polysaccharide was determined in distilled water, pH 1.2 and pH 7.2 phosphate buffer using a Brookfield RVDV II+ viscometer (Brookfield Engineering, USA) with spindle # S28, at 50 rpm. The pH of the mastic gum solution (1%, w/v in distilled) was determined using digital pH meter (Oakton Benchtop pH 700 Meter). The surface characteristics of polysaccharide powder were studied by scanning electron micrograph (SEM). The powder was sputtered with gold to make the samples electrically connected. The SEM was taken in Joel-LV-5600, USA equipment.

2.3. Preparation of drug-loaded spheroids

For the preparation of spheroids, Extruder (EXT-65/037, R.R. Enterprises, Mumbai, India) and Spheronizer (SPH-150/010, R.R. Enterprises, Mumbai, India) were used. In the formulation of spheroids, MCC was used as spheronization enhancer. Here, different batches were prepared like BD-1, BD-2, BD-3, BD-4 BD-5 and BD-6 containing MCC–mastic gum–drug in different ratios such as 72.5:2.5:25% (w/w), 70:5:25% (w/w), 67.5:7.5:25% (w/w), 65:10:25% (w/w), 62.5:12.5:25% (w/w) and 60:15:25% (w/w). The powder mixes were prepared as 100 g batches by geometric mixing in polyethylene bag for 10 min. Then the above mixture of dry blend was granulated by using demineralized water as granulation fluid. The wet mass was extruded using cylinder roll type extruder with 1 mm opening diameter at 40 rpm. The obtained extrudates were spheronized in a spheronizer fitted with a cross-hatched rotor plate of 150 mm diameter and 2.5 mm thickness. The resulting spheroids were dried in hot air oven (Memmert 30, Germany) at 40 °C for 8 h. For the optimization of spheronization speed, extrudates from all the selected ratios of MCC–mastic gum–drug were subjected to spheronization at different speeds such as 400, 600, 800, 1200, 1400 and 1600 rpm. For optimization of spheronization time, the ideal batch of spheroids was subjected to spheronization at 1600 rpm for different duration of time such as 5, 10 and 15 min.

2.4. Characterization of spheroids

2.4.1. Particle size analysis

The particle size of the prepared spheroids was measured using a Malvern master sizer 2000 version 5.1 (Malvern, UK). The drug loaded diclofenac sodium spheroids were dispersed in 1:20 with methanol and measured at temperature of 37 °C.

2.4.2. Micromeritic properties

Tap densities of the prepared spheroids were determined using tap density tester and percentage Carr's index was calculated.

2.4.2.1. Angle of repose. Angle of repose was assessed by fixed funnel method to know the flowability of spheroids. Diclofenac sodium spheroids were carefully poured through the funnel until the apex of the conical pile just reaches the tip of the funnel. The radius (r) and height of the pile (h) were then determined. The angle of repose (θ) for samples were calculated using the following Eq. (1):

$$\text{Angle of repose} \quad (\theta) = \tan^{-1}\frac{h}{r} \tag{1}$$

2.4.2.2. Compressibility. Carr's index is a dimensionless quantity, which proved to be useful to the same degree as the angle of repose values for predicting the flow behaviour. The compressibility of the spheroids was determined by Carr's compressibility index using the Eq. (2) given below (Wong et al., 2002).

$$\text{Carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \tag{2}$$

2.4.3. Scanning electron microscopic (SEM) studies

SEM photographs were taken with a scanning electron microscope Model Joel-LV-5600, USA, at the required magnification at room temperature. The photographs were observed for morphological characteristics and to confirm spherical nature of the spheroids.

2.4.4. Spheroid size

Spheroid size was determined using an image analysis system. Photomicrographs were taken with a digital camera (Sony, Cybershot, DSC-HX20V/B, Japan). The obtained images were processed by image analysis software (AnalySIS®; Soft Imaging System, Münster, Germany) to characterize each individual spheroid by mean Feret diameter (FD) (average of 180 calliper measurements with an angle of rotation of 1°), aspect ratio (AR) (ratio of longest Feret diameter and its longest perpendicular diameter) and two-dimensional shape factor (e_R) as in Eq. (3):

$$e_R = \frac{2\pi r}{P_m} - \sqrt{1 - \left(\frac{b}{l}\right)^2} \tag{3}$$

where r is the radius, P_m the perimeter, l the length (longest Feret diameter) and b the width (longest perpendicular diameter to the longest Feret diameter) of the spheroid (Cosijins et al., 2009).