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Research Paper

Characterization and in vivo evaluation of ocular minitablets prepared with different bioadhesive Carbopol–starch components

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Abstract

The purpose of this study was to evaluate different bioadhesive ocular formulations based on drum dried waxy maize® starch (DDWM), Amioca® starch and Carbopol® 974P. The concentrations of Carbopol® 974P in the mixtures varied between 5 and 25% (w/w). The rheological properties of the non-sterilized and gamma-irradiated physical blends of Carbopol® 974P with either DDWM or Amioca® were compared to those of the corresponding co-spray dried Amioca® starch/Carbopol® powders. Higher viscosity or consistency values were measured for sterilized co-spray dried powder mixtures containing an amount of Carbopol® 974P equal or above 15% (w/w) compared to the physical blends.

Sustained release minitablets (Ø 2 mm, 6 mg), consisting of sodium fluorescein as model drug and the bioadhesive powders, were manufactured at a compression force of 1.25 kN. Afterwards, the tablets were sterilized with gamma-irradiation. The amount of Carbopol® in the co-spray dried powder mixtures on the one hand and gamma-irradiation on the other hand had no significant influence on the crushing strength and friability of the minitablets evaluated. However, these two factors affected the in vitro release properties of the minitablets. The slowest release was obtained with tablets containing 25% Carbopol® 974P, which unfortunately possess mucosal irritating properties. By using co-spray dried Amioca® with 15% (w/w) Carbopol® 974P, a slower release can be achieved compared to the physical mixtures of DDWM or Amioca® starch with Carbopol® 974P. Moreover, this ocular formulation is very promising and is preferred, as it did not cause any mucosal irritation and released the model drug for at least 12 h, after application in the fornix.

Keywords: Ocular minitablet; Bioerodible; Carbopol; Starch; In vitro release; In vivo study

1. Introduction

Most common ocular diseases are treated with medication administered locally to the eye. Dosage forms for topical application comprise aqueous or oily drops, ointments, gels and delivery systems. Inserts like Ocusert® and soaked collagen shields or films, placed in the lower fornix or on the cornea for a prolonged period of time, have been presented as alternatives to eye-drops in order to improve bioavailability and efficacy and also better patient compliance. These ophthalmic dosage forms are more effective, requiring less frequent administration, and diminishing the number of additives needed [1–2].

Recently an ocular minitablet (Ø 2 mm, 6 mg) with sustained release properties was developed and optimized. The bioadhesive polymers employed were a physical mixture of drum dried waxy maize® starch (DDWM) and 5% (w/w) Carbopol® 974P. This minitablet was bioerodible, well accepted by humans in a preliminary investigation and showed no mucosal irritation potential. The gelling behavior in the fornix is an advantage since it results in an extended residence time of 8 h at the absorption site [3–5].

The aim of present study is to evaluate new bioadhesive powder mixtures in tablets in order to obtain a longer residence time in the fornix, compared to the tablets containing DDWM with 5% (w/w) Carbopol® 974P, used as reference formulation. Bioadhesive mixtures based on DDWM or Amioca® starch with Carbopol® 974P and the corresponding minitablets were characterized and evaluated. Herewith, the influence of varying amounts of Carbopol® 974P (i.e. from 5 to 25%, w/w) in

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combination with DDWM or Amioca starch® was studied. Furthermore, instead of freeze drying, described by Ameye et al., co-spray drying was investigated as modification technique of the polymer mixtures of Carbopol® 974P with Amioca® starch [6].

As ocular dosage forms must be sterile, gamma-irradiation (25 kGy) of the powders and the minitablets was performed and the influence of gamma-rays on the properties of the polymers and the minitablets was examined.

The rheological behavior of the co-spray dried polymers and the physical blends was compared, while for the minitablets physical properties were measured such as the friability, crushing strength, and in vitro release rate. Since, not all powder mixtures were directly compressable, the effect of dry granulation or an extra precompression step was evaluated. Sodium fluorescein, a frequently used diagnostic agent in ophthalmology was selected, because its tearfilm concentrations can be monitored easily as a function of time. The in vivo release property of the most adequate ocular minitablet obtained in vitro was evaluated in human volunteers.

2. Materials and methods

2.1. Materials

Drum dried waxy maize® starch (DDWM), a pregelatinized starch, was supplied by Eridania Béghin-Say Cerestar (Vilvoorde, Belgium) and Carbopol® 974P by Noveon (Cleveland, Ohio, USA). Amioca® starch and its co-spray dried combination with Carbopol® 974P were received from National Starch and Chemical Company (Bridgewater, NJ, USA). Amioca® starch, a pregelatinized waxy starch too, was prepared by jet cooking, followed by spray drying (National Starch and Chemical Company, Bridgewater, NJ, USA). Sodium stearyl fumarate (Edward Mendell Co. Inc., New York, USA) has been established to be the most suitable glidant to be employed in the bioadhesive formulation [7]. Sodium fluorescein was purchased from Sigma Chemical Co. (St Louis, MO, USA)

An isotonic phosphate buffer solution (pH 7.4) was prepared with 4.030 g/l sodium dihydrogen phosphate dihydrate and 16.252 g/l disodium hydrogen phosphate dihydrate from Merck (Darmstadt, Germany).

2.2. Preparation of minitablets

Table 1 presents the composition of the minitablets used in this study. The powders were firstly homogeneously mixed with a pestle in a mortar, and secondly blended in a laboratory mixer for 10 min (Turbula T2A, Willy A. Bachoffen-WAB, Maschinenfabrik, Basel, Switzerland). Due to the poor flowing properties and the low bulk density of most powder mixtures, it was necessary to prepare granules by slugging in order to obtain minitablets of required quality. Large tablets (Ø 13 mm, 250 mg) were compressed at 0.5 kN using an eccentric tabletting machine Korsch (Type EKO, Berlin, Germany). The tablets were crushed in a mortar and the granules obtained were sieved on a Retsch VE 1000 shaker (Retsch, Haan, Germany), equipped with 45, 90, 250 and 500 μm sieves. The granule fractions $F_{45–250\ \mu m}$ and $F_{90–250\ \mu m}$ were used for, respectively, the physically blended powder and the co-spray dried mixtures. A summary of the powder mixtures and granules chosen used for the manufacturing of ocular minitablets is given in Table 2. The choice of the two granule fractions is based on previously performed experiments, demonstrating that otherwise it would be impossible to manufacture minitablets with the settings available on the tabletting machine.

The powder mixtures PM90dd and PM95dd, employed as reference formulations, and the bioadhesive granules were then compressed into minitablets (6 mg) at a compression force of 1.25 kN, using Korsch tabletting machine, but equipped with four concave punches (Ø 2 mm). Afterwards, gamma-irradiation of the minitablet was performed at room temperature, using a 1.8 MCi activity ^{60}Co source (Gammir-I-Sulzer irradiator unicell, IBA-Mediris, Fleurus, Belgium). The dose rate was set at 1.0 kGy/h and the total radiation dose was 25 kGy [5].

2.3. Physical characterization methods

2.3.1. SEM

The surface structure of the powder mixtures was evaluated by scanning electron microscopy (SEM) (JSM 5600 LV-SEM,

Table 1
Composition of ocular minitablets

	Physical mixture based on DDWM				Physical mixture based on Amioca		Co-Spray dried powder mixture based on Amioca and Carbopol			
	PM 95 dd	PM 90 dd	PM 85 dd	PM 75 dd	PM 95 am	PM 85 am	CS 95	CS 90	CS 85	CS 75
DDWM	92	87	82	72	–	–	–	–	–	–
Amioca	–	–	–	–	92	82	92	87	82	72
Sodium fluorescein	2	2	2	2	2	2	2	2	2	2
Sodium stearyl fumarate	1	1	1	1	1	1	1	1	1	1
Carbopol 974 P	5	10	15	25	5	15	5	10	15	25

CS, Co-spray dried; PM, Physical mixture; dd, drum dried waxy maize starch; am, amioca starch.