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Lyophilized sponges loaded with curcumin solid lipid nanoparticles for buccal delivery: Development and characterization

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ABSTRACT

This study aimed to prepare and evaluate mucoadhesive sponges as dosage forms for delivering solid lipid nanoparticles. For this purpose curcumin (Cur) was formulated as solid nanoparticles (SLN) using Gelucire 50/13, and polaxomer 407. The prepared CurSLN dispersion was thickened with different mucoadhesive polymers. Different concentrations of glycerol, and mannitol of range (0.25–20%), and (0–1%), respectively were also examined. The formed gel was poured into oblong molds and freeze dried to form mucoadhesive sponge to be applied to the buccal mucosa. The prepared sponges were evaluated for their, *in-vivo* residence time, *in-vitro* and *in-vivo* drug release, and hydration capacity. Surface morphology for the different sponges were examined using SEM. TEM was also carried out for sponge fragments previously dispersed into water. Infrared spectroscopy was conducted to investigate interaction between used ingredients. The results showed that the CurSLN loaded HPMC, and Polycarbophil sponges showed 4, and 15 h *in-vivo* residence time, respectively, providing a considerable amount of curcumin into saliva. The incorporation of glycerol and mannitol at concentration of 1% provided elegant and flexible sponges. The SEM showed that the deposition of CurSLN differed according to the type of polymer used. TEM confirmed the integrity of liberated CurSLN from sponges. IR spectra showed an interaction between HPMC and poloxamer 407, which affected its behavior as a gelling agent. The obtained results provide an efficient approach for delivering solid lipid nanoparticles in a solid dosage form keeping the nanoparticle characters and integrity.

1. Introduction

The promises held within drug delivery systems using solid lipid nanoparticles (SLN), necessitate the investigation of the feasibility of delivering such systems through an administrable dosage forms. Generally, the applicable and most commonly used dosage forms for the treatment of oral mucosal diseases are tablets, films or gels (Bruschi and de Freitas, 2005). Tableting or film casting may jeopardize the integrity of the SLN structure and size due to the stress or heat the SLN will be subjected to. Although gels could be considered suitable, its main limitation is the short *in-vivo* residence time (25 min) (Hazzah et al., 2015a,b). Therefore, in attempt to increase the mucoadhesion time, solid dosage form in the form of sponge, a porous structure, was considered for loading SLN.

Sponge could be defined as a dispersion of gas (usually air) into a solid matrix to give a porous solid structure (Lai et al., 2003). It is an alternative to tablets but lacks the compression step. Preparation procedure depends mainly on using polymers, and a freeze drying procedure to eliminate all water incorporated leaving a soft solid structure with acceptable flexibility. Lyophilization is a preferred drying method as it overcomes most limitations associated with the formulation of lipid based formulated system. Lyophilized formulations offer stable products, extend shelf life and allow storage of products at room temperature instead of refrigeration.

Sponges have been developed in several studies either as wound dressing (Dai et al., 2009; Rossi et al., 2012; Sandri et al., 2013), ocular application (Refai and Tag, 2011), and buccal for transmucosal delivery (Portero et al., 2007; Kassem et al., 2014).

Abbreviations: Cur, curcumin; SLN, solid lipid nanoparticles; P, polycarbophil sponge; H, HPMC sponge; G_l, glycerol; M, mannitol; G50/13, Gelucire50/13; PX4 07, poloxamer 407.

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A special interest has been shed on the natural gift, the golden pigment from the golden spice, curcumin (Cur). The pace of curcumin research has grown rapidly, with thousands of citations studying its antioxidant (Sharma, 1976), anti-inflammatory (Gupta et al., 2010), antimicrobial (Negi et al., 1999), cancer chemo-preventive and potentially chemotherapeutic properties (Prasad et al., 2014). However, it suffers poor chemical stability, rapid metabolism, and photochemical instability (Tønnesen et al., 1986). Various strategies have been taken to overcome curcumin limitations and to allow its therapeutic application, including the incorporation in delivery systems (Mazzarino et al., 2012; Sun et al., 2013; Peng et al., 2014; Prasad et al., 2014). Nanoscale particles may represent a future where activity is ensured, and the problems associated with using medicinal plants are overcome (Bonifácio et al., 2014). Recently, application of curcumin locally to oral mucosa has been reported to be an efficient approach for treatment of precancerous oral lesions at a low dose 6 mg/day for six week course treatment (Hazzah et al., 2015a,b). The study adopted the use of mucoadhesive gel loaded with curcumin solid lipid nanoparticle. The results obtained intensify the importance of delivering curcumin to the oral mucosa with higher *in-vivo* residence time.

Solid lipid nanoparticles loaded sponge aiming to target buccal mucosa has not been studied. In this domain, the work aimed at shedding lights on new approaches to optimally deliver CurSLN (curcumin solid lipid nanoparticles) into single unit sponge, in addition to examining the effect of freeze drying process and formulation variables on SLN integrity and sponge characters.

2. Materials

Curcumin (Hebei food additive Co., Ltd., China), poloxamer 407 (Kolliphore 407, a sample gift from BASF, Germany), polycarbophil (Noveon AA-1 a sample gift Lubrizol, Belgium), potassium di-hydrogen phosphate, sodium lauryl sulphate (SLS), glycerol, and mannitol (El-Nasr pharmaceutical Co., Egypt), tri-ethanol amine (TEA) (Nice Chemicals, Pvt. Ltd., Kerla, India), Gelucire 50/13 (stearoyl macrogol-32 glycerides) (kind gift from Gattefosse, France), HPMC 4000, were kindly provided by Pharo Pharmaceutical Co., Borg El-Arab city, Alexandria, Egypt, carboxy methyl cellusloe sodium (CMC sodium), polyvinyl alcohol PVA (Mwt 30,000, Merck), gellan gum, and sodium alginate (BDH Chemical Ltd., Poole, England), mucin was obtained from porcine stomach, Type II, (Sigma, St. Louis, USA)

3. Methods

3.1. Formulation of sponges

3.1.1. Preparation of placebo sponge

Six placebo gels of different polymers (CMC sodium, polyvinyl alcohol, gellan gum, HPMC 4000, polycarbophil, chitosan) were prepared. A calculated amount of each polymer was added to distilled water (except for chitosan was added to 1% w/w acetic acid) on a magnetic stirrer (Wisestir® (DAIHAN-Scientific Co., Ltd., Seoul, Korea)) until homogenous gel was obtained. The concentration of polymer was kept at 2% w/w. Glycerol (G_L) as a plasticizer and mannitol (M) as a cryoprotectant were kept at a concentration of 0.25% w/w of the gel formula (*i.e.*, 10% of solid content of sponge calculated on dry base). The gels were kept in a refrigerator for 2 h to remove entrapped air bubbles.

Ten gram of each homogenous gel was poured into 10 wells plastic moulds of dimensions (0.5 cm × 1 cm × 2 cm). The molded gel was frozen at −25 °C for 4 h prior lyophilization step using lyophilizer (Lyph lock® 4.5, LABconco, Kansas, USA) at vacuum set at 40 mTorr, for 10 h.

3.1.2. Preparation of curcumin solid lipid nanoparticles

The lipid (5% Gelucire 50/13) was melted at 55–60 °C followed by the addition of (0.6%) curcumin. Calculated amount of aqueous phase, (water to 100%) with 8% poloxamer 407 maintained at 70–80 °C squirted gently into the lipid (oil) phase under magnetic stirring at 600 rpm. Next, the mixture underwent high-shear dispersion at 12,000 rpm for five minutes using homogenizer T18 ULTRA-TURRAX® (IKA, Germany). The emulsion obtained was cooled gradually to room temperature forming SLN.

3.1.3. Characterization of curcumin solid lipid nanoparticles

3.1.3.1. Measurement of particle size (PS) and polydispersity index (PDI). The average of three for particle size and polydispersity index of the solid lipid nanoparticles formula was determined using Nano-ZS Zeta-sizer (Malvern Instruments, Malvern, UK). SLN dispersion was diluted 20 times with double distilled water filtered through 0.45 μ membrane filters to ensure that the light scattering intensity was within the instrument's sensitivity range.

3.1.3.2. Entrapment efficiency determination. One ml SLN dispersion diluted to 10 folds was centrifuged using cooling centrifuge (Centurion Scientific Ltd., UK) at speed 15, 000 rpm, for one hour at 4 °C. The supernatant was carefully separated, appropriately diluted, and filtered through syringe milli-pore filter 0.2 μm to remove any suspend particulates. The amount of drug in the filtrate was measured spectrophotometrically at λ max 420 nm.

% EE was calculated as follows:

$$\frac{w_i - w_f}{w_i} \times 100 \quad (1)$$

where w_i is the amount of initial drug and w_f is the amount of free drug.

3.1.3.3. Zeta potential (ZP) measurement. The ZP of the SLN dispersion was measured at 25 °C, under an electrical field of 40 V/cm using the Nano-ZS Zetasizer. The measurements were carried out in triplicates.

Table 1
Composition of different sponge formulations using 2% w/w HPMC, or 2% w/w polycarbophil with 0.6% w/w curcumin loading, and the moisture content of the sponge % w/w.

Formulae code	Glycerol (%)[a]	Mannitol (%)[a]	Moisture content(%)
HPMC (2%) based sponges			
H_{CurSLN} $G_{L0.25}$ $M_{0.25}$	0.25	0.25	2.4
H_{CurSLN} $G_{L0.5}$ M_0	0.5	0	3.5
H_{CurSLN} $G_{L0.5}$ $M_{0.5}$	0.5	0.5	2.5
H_{CurSLN} G_{L1} M_0	1	0	1.8
H_{CurSLN} G_{L1} M_1	1	1	2.2
H_{CurSLN} G_{L2} M_0	2	0	ND
$H_{Cur\text{-}px407}$ G_{L1} M_1	1	1	ND
H_{Cur} G_{L1} M_1	1	1	ND
Polycarbophil (2%) based sponges			
P_{CurSLN} $G_{L0.25}$ $M_{0.25}$	0.25	0.25	0
P_{CurSLN} $G_{L0.5}$ M_0	0.5	0	0
P_{CurSLN} $G_{L0.5}$ $M_{0.5}$	0.5	0.5	0
P_{CurSLN} G_{L1} M_0	1	0	0
P_{CurSLN} G_{L1} M_1	1	1	0.4
P_{CurSLN} G_{L2} M_0	2	0	0.8
P_{CurSLN} G_{L5} M_1	5	1	ND
P_{CurSLN} G_{L10} M_1	10	1	ND
P_{CurSLN} G_{L20} M_1	20	1	7.7
$P_{Cur\text{-}px407}G_{L1}$ M_1	1	1	ND
P_{Cur} G_{L1} M_1	1	1	ND

[*] P = polycarbophil, H = HPMC, GL = Glycerol, M = Mannitol.
[**] Subscripts represent the type of dispersed curcumin, and concentration of glycerol and mannitol in % of original gel formula).