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Laminated sponges as challenging solid hydrophilic matrices for the buccal delivery of carvedilol microemulsion systems: Development and proof of concept via mucoadhesion and pharmacokinetic assessments in healthy human volunteers

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ABSTRACT

Carvedilol (CVD) suffers from low absolute bioavailability (25%) due to its limited aqueous solubility and hepatic first-pass metabolism. Hydroxypropyl methylcellulose (HPMC) laminated buccal sponges loaded with CVD microemulsions (CVD-ME) were exploited to surmount such limitations. Six pseudoternary-phase diagrams were constructed using Capmul® MCM C_8/Capmul® PG_8, Tween® 80, propylene glycol and water. Six CVD-ME systems (0.625% *w/v*) were incorporated into HPMC core sponges backed with Ethocel® layers. The sponges were preliminary evaluated via FT-IR, DSC and XRD. The surface pH, morphology and in vitro drug release studies were evaluated. *In vivo* mucoadhesion and absorption studies of the best achieved laminated sponges (F4) were assessed in healthy volunteers. CVD-ME systems displayed nano-spherical clear droplets. The sponges showed interconnecting porous matrices through which CVD was dispersed in amorphous state. No intermolecular interaction was detected between CVD and HPMC. The surface pH values were almost neutral. The sponges loaded with CVD-ME systems showed more sustained-release profiles than those loaded with CVD-powder. Compared to Dilatrend® tablets, the significantly ($P < 0.05$) higher bioavailability (1.5 folds), delayed T_{max} and prolonged $MRT_{(0-\infty)}$ unraveled the dual-potential of F4 sponges for water-insoluble drugs, like CVD, in improving drug oral bioavailability and in controlling drug release kinetics via buccal mucosa.

1. Introduction

The buccal mucosa has good accessibility, an expanse of smooth muscle and relatively immobile mucosa. Therefore, it could be considered as a suitable transmucosal route for administration of multidirectional or unidirectional drug release systems exerting local or systemic actions (Sudhakar et al., 2006). Bioadhesive buccal drug delivery systems offer many advantages including the direct access to the systemic circulation via the internal jugular vein (a pathway to circumnavigate the hepatic first pass metabolism), the avoidance of the possible gastrointestinal enzymatic degradation, the painless administration, the facile termination of therapy as well as the ability to include enzyme inhibitors, permeation enhancers or pH modifiers in the developed systems (Sudhakar et al., 2006; Alur et al., 2001).

Carvedilol (CVD) is a non-cardioselective beta blocker that is used in the management of hypertension, angina pectoris, heart failure and left ventricular dysfunction following myocardial infarction. CVD suffers from low absolute bioavailability (25%) following oral administration, probably due to the limited solubility of CVD in water as well as the considerable first-pass metabolism in the liver (Sweetman, 2011). The buccal delivery of CVD has been explored as a promising alternative to surmount these problems and consequently improve the drug bioavailability, allow a possible reduction in the dose and the associated side effects. In view of the aforementioned, various traditional formulation approaches like films (Meher et al., 2013), patches (Kaur and Kaur, 2012) or tablets (Cappello et al., 2006) were developed for the buccal delivery of CVD. Outside this conceptual framework, laminated sponges loaded with CVD-ME systems are currently evaluated as promising systems combing the advantages of microemulsions and sponges for potential buccal delivery.

ME systems could improve the solubility and bioavailability of hydrophobic drugs (Fernández Campos et al., 2012). They can promote drug permeation across the buccal mucosa due to many factors including the small droplet size (<200 nm), the presence of permeation enhancers and the facile access to difficult-to-reach areas in the entire buccal surface. It is worth noting that the adequate selection of oils, surfactants and co-surfactants should be considered to promote the development

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of ME systems with harmless effects on the buccal mucosa (Solans et al., 2005). ME systems were investigated for the buccal delivery of drugs like ketoprofen (Srivastava et al., 2014), flufenamic acid (Schwarz et al., 2013) and genistein (Gavin et al., 2015). Josef and Bianco-Peled (2013) reviewed the traditional solidification techniques of ME systems and concluded that they involved (i) the adsorption of ME systems onto porous carriers like Aerosil® 200 or NeusilinUS2® (Thongrangsalit et al., 2015), (ii) the incorporation of ME systems into solid matrices like polyethylene glycol 3350 (Li et al., 2009), (iii) the transformation of ME systems into pellets via the extrusion/spheronization technique (Setthacheewakul et al., 2011) and (iv) the spray drying of ME (Choi et al., 2012). The resulting ME-loaded powders could be simply packed into capsules or further processed, along with other excipients, into other solid dosage forms like tablets (Josef and Bianco-Peled, 2013).

Herein, HPMC buccal sponges were evaluated as solid hydrophilic carriers for CVD-ME systems. They were expected to offer many advantages over conventional buccal tablets, films or patches. Being prepared by freeze drying, they are lighter and show faster hydration/gelation than tablets. They could allow more effective drug permeation due to their ability to maintain their swollen gel structure for longer residence times and consequently, promote gradual drug release (El-Mahrouk et al., 2014). Compared to the thin and denser solvent-evaporated films or patches, the porous nature and high surface area of the sponges would confer the advantages of higher water absorption rates and drug loading capacities (Boateng et al., 2010). In fact, the incorporation of ethylcellulose as a backing layer would ensure unidirectional drug diffusion through buccal mucosa (Kassem et al., 2015). To confirm their potential for buccal delivery, CVD pharmacokinetics following the administration of the best achieved laminated buccal sponges (F4) were estimated, relative to oral Dilatrend® tablets, in healthy human volunteers.

2. Materials and methods

2.1. Materials

Carvedilol (CVD) – crystalline form II – and torsemide (TOR; an internal standard) were kindly provided by GNP (6th of October city, Egypt) and Multi-Apex Pharma (Badr City, Egypt), respectively. Glyceryl monocaprylate (Capmul® MCM C_8) and propylene glycol monocaprylate (Capmul® PG_8) were grant samples from Abitec Corporation (Janesville, USA). Ethylcellulose-20 (Ethocel®) and hydroxypropyl methylcellulose K4M (HPMC) were donated by Dow Chemical Company (Midland, US). Acetonitrile (HPLC grade), formic acid (HPLC grade), ethyl acetate (HPLC grade) and polyoxyethylene sorbitan monooleate (Tween® 80) were purchased from Sigma Chemical Co. (St. Louis, USA). Potassium dihydrogen phosphate and disodium hydrogen phosphate were acquired from Merck Millipore (Darmstadt, Germany). Diethyl phthalate was obtained from Veb Laborchemie (Apolda, Germany). Propylene glycol and ethanol (95%) were derived from El-Nasr pharmaceutical chemicals Co. (Cairo, Egypt). All other chemicals were of analytical grade and were used as received.

2.2. Development of CVD-ME systems

Six pseudoternary systems consisting of Capmul® MCM C_8 or Capmul® PG_8 as an oily phase, Tween® 80 as a non-ionic surfactant and propylene glycol as a cosurfactant were prepared by the water titration method. The corresponding pseudoternary phase diagrams were constructed using Tri-plot software Ver. 4.1.2 (Graham and Midgley, Loughborough University, Leicestershire, England). Homogenous blends of oils and surfactant/cosurfactant (S/CoS) mixtures (2:1, 1:1 and 1:2, respectively) ranging from 1:9 to 9:1 (*w*/*w*) were prepared by vortexing (1400 rpm, 3 min). The blends were left for equilibration between each addition of water. The developed systems were visually observed for phase clarity and flowability (Tayel et al., 2013a).

The values of oil, S/CoS mixture and water were used to plot the boundaries of the microemulsion region. The area under the curve (AUC) representing the clear ME region in each phase diagram was calculated using AutoCAD® software (Autodesk Inc., San Rafael, CA, USA) (Ammar et al., 2009). Statistical significance of the results was evaluated via SPSS Software (SPSS Inc., Chicago, USA) applying one-way ANOVA test at $P < 0.05$.

Based on the calculated AUC values of the developed phase diagrams, six CVD-ME systems (0.625%, *w*/*w*) were prepared at a fixed S/CoS ratio (1:1) and concentration (60%, *w*/*w*) by vortex mixing with variable ratios of oil (5, 10 and 15%, *w*/*w*) and water (35, 30 and 25%, *w*/*w*), respectively. CVD-ME systems (Table 1) were stored at room temperature (25 °C) until further use.

2.3. Characterization of CVD-ME systems

2.3.1. Determination of mean droplet size (MDS)

The hydrodynamic diameter and the polydispersity index (PI) of CVD-ME systems were evaluated via the Dynamic Light Scattering (DLS) technology using a Zetasizer Nano ZS Ver.6.20 (Malvern Instruments Ltd., Worcestershire, England). All measurements were performed at room temperature, in triplicate, at 90° with respect to the incident beam. The fluctuations in light scattering due to the Brownian motion of particles were analyzed and consequently, the MDS was estimated. PI values lower than 0.3 could indicate homogenous droplet size distribution (Dragicevic-Curic et al., 2009).

2.3.2. Topographic examination via transmission electron microscopy (TEM)

One drop of each CVD-ME system was deposited onto the surface of a carbon-coated 400-mesh copper grid and allowed to settle for 3–5 min. The excess fluid was removed with a filter paper and left to dry at room temperature. The deposited systems were stained for 60 s with one drop of phosphotungstic acid aqueous solution (2%, *w*/*v*) before investigation, at 80 kV, using a transmission electron microscope (Jeol JEM-1400, Tokyo, Japan) under a magnification power of 25,000×.

2.4. Development of laminated buccal sponges

HPMC core sponges loaded with CVD-ME systems were backed using impervious layers of Ethocel®. For the development of HPMC

Table 1
The composition (%), the MDS and the PI of the investigated CVD-ME systems.

ME systems	Composition (%)					MDS (nm)	PI
	Capmul® PG_8	Capmul® MCM C_8	Tween® 80	Propylene glycol	Water		
MCM5	–	5	30	30	35	58.23 ± 1.24	0.11 ± 0.04
MCM10	–	10	30	30	30	121.04 ± 6.78	0.13 ± 0.02
MCM15	–	15	30	30	25	160.55 ± 9.57	0.15 ± 0.03
PG5	5	–	30	30	35	123.76 ± 4.57	0.14 ± 0.05
PG10	10	–	30	30	30	147.23 ± 5.67	0.21 ± 0.06
PG15	15	–	30	30	25	188 .29 ± 4.71	0.18 ± 0.04