International Journal of Pharmaceutics 391 (2010) 79–89

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Construction and *in vitro* characterization of an optimized porosity-enabled amalgamated matrix for sustained transbuccal drug delivery

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ARTICLE INFO

Article history:
Received 21 June 2009
Received in revised form 10 February 2010
Accepted 11 February 2010
Available online 20 February 2010

Keywords:
Mechanistic characterization
Porosity-enabled amalgamated matrix
Transbuccal drug delivery
Experimental design
Simultaneous optimization

ABSTRACT

This research focused on constructing and characterizing an optimized porosity-enabled amalgamated matrix (P-EAM) for sustained transbuccal drug delivery. An interphase, co-particulate, co-solvent, homogenization technique and lyophilization guided through a Box–Behnken experimental design was employed in the fabrication, characterization and optimization of 15 P-EAMs. The effects of varying factor levels on the characteristic *in vitro* physicochemical performances of the P-EAMs were explored. Formulations had an average weight of 128.44 ± 3.48 mg with a dimensional size of 8 mm by 5 mm. Surface morphology showed varieties of pore structures, widespread distributions and uneven interconnectors. Satisfactory drug-loading was achieved (53.14 ± 2.19–99.02 ± 0.74%). Overall amount of drug released in 8 h was measured by the $MDT_{50\%}$ value which ranged between 22.50 and 225.00 min. Formulation demonstrated significant levels of *ex vivo* bioadhesive strength measured as detachment force (F_{det} = 0.964 ± 0.015 to 1.042 ± 0.025 N) and work of adhesion (ω_{adh} = 0.0014 ± 0.00005 to 0.0028 ± 0.00008 J). The potential of the P-EAMs to initiate and sustain *ex vivo* transbuccal permeation of drug was shown and measured as a cumulative value of between 25.02 ± 0.85 and 82.21 ± 0.57% in 8 h. Formulations were mesoporous in nature with pore sizes ranging from 40 to 100 Å characterized by the presence of interconnectors. Statistical constraints were simultaneously set to obtain levels of independent variables that optimized the P-EAM formulation.

1. Introduction

Porous matrices can be described as those possessing characteristic pore (hole) and interconnecting structures which have a significant influence on their performance. They have been studied over the years for their drug delivery applications and they continue to attract great research interest as they possess attractive features such as: (i) stable configuration, (ii) high surface area, (iii) flexible pore sizes, arranged in various distribution patterns, and (iv) defined surface properties, which are due to their unique porous structural configurations. They have found potential biomedical and drug delivery applications such as in the fabrication of biological tissue scaffolds (Kim et al., 2004; Sohier et al., 2006), implants (Moon Suk et al., 2005), hydrogels (Tang et al., 2005), ceramics (Netz et al., 2005; Miao et al., 2004; Rodríguez-Lorenzo and Ferreira, 2004), biocomposites (Wang et al., 2007), sponges (Portero et al., 2007), microcapsules (Chu et al., 2004), wafers (Bromberg et al., 2001; Matthews et al., 2005; Patel et al., 2007), membranes (Park et al., 1997; Åkerman et al., 1998), nanoparticles (Li et al., 2004) as well as in biomaterials engineering, life sciences and other relevant scientific spheres (Hoa et al., 2006). The above-mentioned qualities provide them with the potential to adsorb/load drug molecules and release them in a reproducible and predictable manner; enhance bio-adhesion to mucosal sites as well as augment permeation for the systemic delivery of drug molecules, which would be specifically useful for drug delivery via the transbuccal route, i.e. via the buccal mucosa (Sher et al., 2007; Zhang et al., 2007). In recent years, the demand for such sophisticated approaches for the delivery of therapeutic agents is on the increase (Tao and Desai, 2003). The particular focus on porous systems for transbuccal delivery lies in the potential use of these systems as inexpensive devices for the release of drugs at controlled, and perhaps time-independent rates. As investigated by Korsmeyer et al. (1983) for a hydrophilic porous system, progressive swelling of the polymer particles occur, emanating in considerable structural changes, which include alteration of the mobility of the macromolecular chains, macromolecular relaxations, and changes of the porous structure (e.g. alteration of the shape and size distribution of the pores). These ultimately impact on the porosity and tortuosity of the system during swelling and diffusional release. Finally, as swelling progresses, diffusion of the drug occurs both through the water-filled pores, and through the swollen polymer, which are influenced by the physical structure of the polymer, as well as the thermodynamic interactions between polymer and solute (Korsmeyer et al., 1983). Such a hydrophilic

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doi:10.1016/j.ijpharm.2010.02.023

system may provide favorable drug release owing to its porous nature.

Conventionally, drugs are delivered to the body employing the predominant routes of administration namely the oral route or injection. The use of injections (e.g. intravenous, intramuscular) which provides rapid physiological relief of symptoms is associated with a high level of pain during administration and may lead to high drug concentrations being released into the systemic circulation which can be fatal. The oral route of drug delivery on the other hand offers several advantages, namely that it is more acceptable, less invasive and can be painlessly self-administered (Tao and Desai, 2003). However, research has shown that after oral administration, many drugs are subject to extensive pre-systemic elimination by gastrointestinal degradation and/or hepatic first pass metabolism as well as resistance exerted by the intestine that may result in low systemic bioavailability, short duration of therapeutic activity and/or formation of inactive or toxic metabolites (Ponchel et al., 1997; Ahmed et al., 2002; Orive et al., 2003; Sudhakar et al., 2006). In order to circumvent some of the above-mentioned limitations associated with the oral and injection routes of drug administration, transmucosal drug delivery has been explored as an alternative route of administering drugs (Smart, 2005; Chien, 2006; Sudhakar et al., 2006). It offers the potential for the non-invasive, regulated systemic absorption of drugs and may serve as useful sites with good accessibility for easy application of drug delivery systems (Chien, 2006).

This investigation employed the buccal mucosa as a model for transmucosal drug delivery because among the various sites, it is most suitable for administration of retentive dosage forms. This is due to its excellent accessibility for self-administration, short recovery times after stress or damage, rich blood supply, an expanse of smooth muscle, direct access to the systemic circulation which allows drugs to bypass the pre-systemic metabolic processes thus leading to an increased bioavailability and rapid onset of action. Other advantages include painless administration, versatility and simplicity, easy drug withdrawal whenever desired and the ability to include permeation enhancers, enzyme inhibitors, pH modifiers or bioadhesive compounds and other pharmaceutical additives in the formulation for local or systemic actions (Alur et al., 2001; Sudhakar et al., 2006).

The present study focuses on the construction and optimization of a novel bioadhesive porosity-enabled amalgamated matrix (P-EAM) for sustained drug release *via* the transbuccal route into the systemic circulation employing phenytoin sodium as a model drug. Phenytoin sodium is widely utilized as a first-line drug in the effective treatment of epilepsy worldwide. It possesses relatively slow rates of systemic absorption (Darwish et al., 1996; Alvarez-Nύñez and Yalkowsky, 1999; Wang and Patsalos, 2003; Pellock et al., 2004). Phenytoin sodium has been reported to exhibit a high dissolution rate in water but under gastrointestinal acidic pH conditions, the sodium salt is rapidly converted to the practically insoluble acid form which may have some influence on its bioavailability (Darwish et al., 1996). Consequently, a need exists to design an optimized drug delivery system with potential capabilities to overcome the reported demerits of phenytoin sodium.

As far as we know, inadequate explorative studies exist relating to the construction, mechanistic characterization, and optimization of novel porosity-enabled systems which may be described as superior to conventional formulations employed for controlled systemic drug delivery through the buccal transmucosal site. In order to construct the porosity-enabled amalgamated matrix, an interphase, co-particulate, co-solvent, homogenization technique coupled with lyophilization were utilized. The choice of method of preparation was based on its simplicity and optimum efficiency in generating robust and stable formulations which would enable an undemanding industrial process operation and minimized production cost, enhancing patient affordability. The construction of the unique matrices was guided through a high performance statistically and mathematically robust experimental design approach. Relevant physicochemical characterizations, which involved determination of formulation weight, *in vitro* drug release behaviour, drug loading capacity, *ex vivo* bioadhesive strength, rheological assessments, surface morphology, *ex vivo* permeation efficiency, quantitative evaluation of matrix porosity and elucidation of physical or chemical transitions were performed.

2. Materials and methods

2.1. Materials

Chitosan (CHT) (food grade) and menthol (MTH) were purchased from Warren Chem Specialties, Johannesburg, South Africa. Gelatin (GEL), phenytoin sodium (PS-Na), polyvinyl alcohol (PVA) (molecular weight = 72,000 g/mol) and magnesium stearate (MS), were purchased from Sigma Chemical Company (St. Louis, USA). Span® 80 (Sorbitan ester 80) (SP 80) and ethanol (EtOH) (95%) were procured from Merck Chemicals (Darmstadt, Germany) and Saarchem (Johannesburg, Gauteng, South Africa), respectively. Carbopol® 974P NF (CARB) was acquired from Noveon, Inc., (Cleveland, Ohio, USA). Ethylcellulose (Ethocel® 10) (ETH) was obtained from Protea Industrial Chemicals (Pty) Ltd. (Wadesville, South Africa). Hydroxyethylcellulose (HHX 250 Pharm) (HEC) was purchased from Hercules, Aqualon (Germany). All other reagents utilized were of analytical grade and used as received.

2.2. Preparation of the porosity-enabled amalgamated matrices (P-EAM) in accordance with a Box–Behnken experimental design template

Fifteen P-EAMs were prepared using various combinations of independent variables by the processes of interphase homogenization and lyophilization guided through a three factor, and three centre points Box–Behnken quadratic design using Minitab Statistical Software, Version 14 (Minitab Inc., State College, PA, USA). Three categories of independent variables composed of the solutes, solvents and surfactant, Span 80 were employed in fabricating the P-EAMs and were based on statistically and mathematically generated Box–Behnken design template and these included:

(i) Aqua-based co-particulate dispersion (ACD) composed of PVA, HEC, CARB, GEL and DW.
(ii) Ethanol-based co-particulate dispersion (ECD) composed of ETH, MS, MTH, CHTS and EtOH.
(iii) Span® 80 (SP 80) only.

Tables 1 and 2 present the levels of the independent variables employed and the experimental design template for the 3 factors, 3 centre points and 15 experimental runs, respectively. The lower and upper limits for the factors were set based on their ability to

Table 1
Levels of the independent variables employed in the Box–Behnken design template.

Independent variables	Levels		Units
	Low	High	
ACD[a]	0	2	mg/20, 25 or 30 mL
ECD[b]	3	5	mg/13, 11 or 7 mL
SP 80[c]	0.3	0.7	mL

[a] Aqua-based co-particulate dispersion.
[b] Ethanol-based co-particulate dispersion.
[c] Span 80.