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Bioadhesive polymeric film-based integrative platform for the unidirectional carbamazepine release from a volatile microemulsion

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ABSTRACT

Carbamazepine (CBZ) shows inconsistent absorption primarily due to its poor dissolution rate. In this study, we describe a bioadhesive polymeric film, embedded with microemulsion (ME), as a tool to enable improved CBZ dissolution and achieve sustained release. The ME was formulated using pseudo-ternary components; water, oil (n-butyl acetate), surfactant (tocopheryl polyethylene glycol 1000 succinate, TPGS) and cosurfactant (1,4-butanediol). The region at surfactant to co-surfactant ratio of 1:1 was characterized using dynamic light scattering, small angle neutron scattering and differential scanning calorimetry. Scattering studies showed that size distribution did not change upon water addition and temperature. Optimized ME composition containing CBZ was embedded into bioadhesive films composed with a backing layer. We successfully demonstrate the confinement of CBZ-ME into the film matrix and thereupon, the achievement of unidirectional sustained drug release up to 8 h. Our further investigations are directed over testing the system for localized drug delivery applications.

1. Introduction

Carbamazepine (CBZ) is used in first line pharmacological treatment of trigeminal neuralgia [1]. Despite high intestinal permeability, the bioavailability of CBZ is inconsistent primarily due to its poor dissolution-rate and limited absorption [2]. Compensatory high oral dose administration (400–1200 mg/day) results into serious side effects, interrupted treatment and overall treatment failure [1]. A variety of particle engineering approaches have been explored to improve its dissolution rate [3–5]. Typically, nanoparticle matrices are prepared through emulsification of volatile organic phase, containing the drug and carrier, with aqueous stabilizer system. Nanoparticles are formed following the evaporation of organic phase. However, average size of resulting nanoparticles is typically more than 100 nm [6,7]. Alternatively, high-shear forces are employed for nano-milling of drug particles. Still, complex manufacturing, changes in drug crystallinity and limited dispersion stability of reconstituted nanoparticles remain a formidable challenge in the milling process [3,8].

Microemulsions (MEs), being spontaneously assembled nano-droplets (< 50 nm), present high dispersion stability with insignificant energy investment [9]. Considering their easy and inexpensive production approach, MEs have received widespread acceptance among formulation scientists for achieving improved solubilization and permeation of poorly water soluble drugs [10–12]. In accord to the composition of water, oil and surfactants, the system enables achieving a rich variety of self-assembled microstructures. Interestingly, solubilization of CBZ has shown to affect the curvatures of microstructures and the transition points between different phases [13]. In addition, the formulations with solubilized CBZ have shown improved partitioning and drug transport across the Caco-2 cells, without interfering with the barrier integrity [14].

At the same time, MEs have been exploited to prepare water-dispersible drug nanoparticles using 'all solvent removal' approach [12,15]. Essentially, the technique involves inclusion of volatile oil and co-surfactant (CoS) into the system which can directly be converted to nanoparticles through spray drying or lyophilization [12,16].

In this study, we present an integrated platform composed of volatile CBZ-microemulsion embedded into a buccal bioadhesive film composed of sodium alginate and carboxymethyl cellulose; biocompatible, pharmaceutically acceptable polymers. The film was backed with

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ethylcellulose layer to promote unidirectional CBZ release. Here, the film serves dual purpose; first of acting as an ordered confinement matrix for microemulsion (ME) and second, of improving drug's residence at the site of application. Such a tactful incorporation of ME droplets can minimize the incidences of crystal growth and drive the drug directly into systemic circulation, without the inclusion of permeation enhancers. Such films have shown sufficient mechanical strength and flexibility which allow their convenient placement in the buccal mucosa [17]. Given the high permeability of CBZ, enhanced residence time in the highly vascularized buccal mucosa through bioadhesive films is an interesting and largely unexplored approach. A study reports mucoadhesive nanoemulgel composed of oleic acid- labrasol and xanthan gum as anionic mucoadhesive polymer. Intra-nasally administered formulation prolonged the onset time for induced convulsions and improved the survival rate in mice [18].

Film formation was accomplished through solvent-casting of a polymeric dispersion, together with the formulated ME, under convective drying described earlier [19]. The film was tested to demonstrate the successful confinement of ME and capability of releasing CBZ over 8 h. The specific objectives of this research are as follows; (***a***) to formulate and comprehensively characterize an oil/water volatile ME incorporating CBZ, (***b***) to incorporate the ME into a bioadhesive polymeric film, and (***c***) to test if CBZ diffusion can be improved using the tested approach.

2. Materials and methods

2.1. Materials

Methanol, acetone, n-butyl acetate, 1,4-butanediol, glycerol, n-octanol, potassium dihydrogen phosphate, sodium hydroxide, methanol (HPLC grade), acetonitrile (HPLC grade), sodium bicarbonate, paraffin wax and parafilm were purchased from Merck Scientific, India. Heavy water was purchased from Sigma Aldrich, USA. Dialysis membrane was purchased from Hi Media Ltd., India. Amaranth (88% pure), ethylcellulose, carboxymethyl cellulose and polyethylene oxide were purchased from SD Fine Chemicals, India. CBZ (99% pure) and TPGS (98% pure; ≥25% α-tocopherol) were kindly gifted by Jubilient Life Sciences and Bioplus, (India), respectively.

2.2. Methods

2.2.1. Phase diagram construction

Phase behavior was examined by constructing a pseudo-ternary phase diagram in which the three components were as follows; oil, distilled water and a mixture of surfactant (TPGS) and co-surfactant (1,4-butanediol, BuOH). TPGS was mixed with 1,4-butanediol (2:1, 1:1 and 1:2 weight ratio) to obtain a surfactant mixture (S_{mix}). For phase diagram construction at a specific surfactant/co-surfactant ratio, oil (n-butyl acetate) and S_{mix} were used in 1:9 ratio. Inclusion of volatile components (oil and BuOH) was expected to facilitate rapid evaporation of the liquids and production of drug deposits stabilized by TPGS (Fig. 1).

Our investigations were focused on maximizing the monophasic region with the minimum possible surfactant since other components were volatile. Water was gradually added to S_{mix} and phase boundaries were delineated by observing the transition from turbidity to transparency or *vice versa*. ME region was approximated as an optically transparent system through visual inspection and verified in terms of transmittance value more than 95%. Following optimization, a test dose of CBZ was incorporated into the system under gentle magnetic stirring. Drug loading was calculated as the weight fraction of CBZ into the total weight of ME components. Samples, stored at 4 °C, were equilibrated at RT before their characterization.

2.2.2. Characterization of the type of ME

Dye test was conducted through visual inspection after adding amaranth dye (0.2 μg/ml). In addition, electrical **c**onductance was recorded at 25 ± 1 °C following gradual addition of water along a dilution line (Systronics 304, India). Care was taken not to include other electrolytes in the sample.

2.2.3. Droplet size analysis

The average size and zeta potential distributions of ME droplets were determined by dynamic light scattering (DLS) using a He–Ne laser (Nano ZS, Malvern, UK). Size was further verified by transmission electron microscopy (TEM) and small angle neutron scattering (SANS). SANS experiments were carried out at Dhruva Reactor, Bhabha Atomic Research Centre (BARC), India. An incident neutron beam of mean wavelength (λ) 5.2 Å with wavelength resolution (Δλ/λ) 15% using a neutron velocity selector was employed. Angular distribution of the scattered neutrons was recorded using a one-dimensional position sensitive detector. The accessible wave vector transfer [$q = 4\pi \sin\theta/\lambda$, where 2θ is the scattering angle] range of the diffractometer was set as 0.015–0.40 $Å^{-1}$. The acquired data were fitted to a core-shell model [20].

2.2.4. Effect of water addition upon ME characteristics

Size distribution and thermal behavior of the optimized formulation was studied following water addition at RT. Thermal events were analyzed using differential scanning calorimetry (DSC). The instrument was equipped with a cooling system (STAR^e System, Mettler Toledo, Switzerland). Nitrogen was used as purge gas (50 ml/min) and empty aluminum pan was used as a reference. The sample was subjected to the following thermal cycle; equilibration at 25 °C for 3 min, cooling down up to −60° C and heating up to 25 °C. Linear cooling/heating was fixed as 10 °C/min. Enthalpy changes were obtained by integrating the peak area using inbuilt program of the instrument.

2.2.5. Rheological measurements

Changes in rheological behavior of ME, following water and oil addition, were evaluated at 30 °C using a rheometer with double gap measuring cylinder geometry (DG 26.7) (Anton Paar Physica MCR 101, Germany). The shear rate was varied from 0.1 to 200 s^{-1}.

2.2.6. Stability test

Time scale stability test for ME was conducted following its storage at RT for 90 days. The droplet stability was further challenged through exposure to freeze-thaw cycles and centrifugation (14,000 rpm/25 min). Latter procedures ascertained the susceptibility of droplets under the imposed thermodynamic stress. In freeze-thaw test, sample stored at -20 °C was rapidly equilibrated to 30 °C. Microscopic stability was recorded in terms of changes in the percent transmittance (Shimadzu 3092, Japan) and hydrodynamic size from DLS measurements.

2.2.7. CBZ quantification by high performance liquid chromatography (HPLC)

CBZ was estimated using HPLC, equipped with UV detector and an automatic sampling system (LC-2010CHT, Shimadzu, Japan). Following was the instrumental set up; mobile phase - methanol and water (60:40), flow rate - 1 ml/min, mode of separation – isocratic, and detection wavelength - 285 nm. The separation was achieved at RT using a reversed phase column with an average particle size of 5 μm (Dr. Maisch GmbH, Germany). A retention time of 4.5 min was observed.

2.2.8. Film formation and CBZ release

A mixture of carboxymethyl cellulose (95% w/v) and sodium alginate (5% w/v) was added into the ME to prepare its 1.5% w/v dispersion. This dispersion was casted over ethylcellulose (5% w/v)