Porous Polymeric Carrier System for Modified Drug Release of Boswellic Acid

Rodrigues K
Department of Pharmacy, Goa College of Pharmacy, Goa, Panaji, India, Tel: 917741901719

Abstract

Microsponges being the polymeric drug delivery systems consist of porous microspheres that can entrap a wide range of active ingredients. Boswellic acid is a pentacyclic triterpenoid having anti-inflammatory, anti-hypertensive, anti-cancer activities. The aim of the study was to develop, characterize and formulate microsponge delivery for topical application. The Microsponges were prepared by quasi emulsion solvent diffusion method using QbD approach. Drug excipient compatibility study was carried out by FT-IR, DSC and XRD. The prepared Microsponges were further evaluated for its physicochemical properties by scanning electron microscopy (SEM), photomicroscopy, transmission electron microscopy (TEM), particle size, zeta potential, and porosity analysis. The optimized Microsponges were incorporated into gel base formulation and evaluated for in-vitro drug release, dissolution studies and ex-vivo permeability studies. Further, microsponge formulations, subjected for animal studies for skin irritation test and clinical efficacy. The present study confirmed the formation of Microsponges of Boswellic acid. It also proves the sustained release of drug through microsponge formation.

Introduction

Boswellic acids are pentacyclic triterpenoids are the major constituents of the gum resin derived from the plant Boswellia serrata belonging to the family Burseraceae [1]. It consist of various Boswellic acids namely β-Boswellic acid, 11-keto-β-boswellic acid (KBA) and other corresponding acetates like acetyl β-boswellic acids (ABA), acetyl-11-keto-β-boswellic acid (AKBA), acetyl-α-boswellic acid [2].

Boswellia has traditionally been used for a number of topical applications, including treatment of bacterial and fungal infections, boils, acne wound healing, scars, and varicose veins [3]. It has a lot of medicinal value like antiinflammatory [4], diuretics [5], anti-cancer, peptic ulcer diseases, analgesic and sexually transmitted diseases (STDs) [6].

Boswellic acid readily penetrates through the hydrophobic stratum corneum while the lower epidermal and dermal layers are hydrophilic in nature, which limits its solubility and transfer of the drug from stratum corneum [7]. Both KBA and AKBA are highly lipophilic drug, they have relatively poor absorption through GIT but high retention. The elimination half-life of 11-keto-β-boswellic acid (KBA) is approximately 6 h. This implies that boswellic acids should be taken every 6 h postoperative to achieve maximum plasma levels. BAs should be taken along with fatty meal as it significantly increases their plasma concentration [8].

To achieve targeted and sustained release of drugs, microparticles and nanoparticles being increasingly investigated. Microsponges are porous, polymeric and tiny, sponge-like spherical particles. It contains a number of interconnecting voids within a non-collapsible structure that imparts a large porous surface [9].

Thus, the aim of the present investigation was to design ethyl cellulose Microsponges as a novel carrier for the controlled topical delivery of Boswellic acid fraction (BAF). This novel carrier is expected to prevent the excessive accumulation of the drug in the skin, improve its efficacy and decrease the frequency of application and the systemic

absorption. The present work included the preparation, optimization and evaluation of BAF Microsponges. A QbD factorial design assisted in the statistical optimization. The optimized Microsponges were incorporated into a gel and evaluated for their performance. Studies revealed that no study carried out to formulate sustained release medication containing Boswellic acid.

Materials and Methods

Boswellic acid fraction (BAF) was received as a gift sample from Central India Pharmaceuticals Ltd. Nagpur, Maharashtra, India. All other chemical solvents were of laboratory grade and were used as procured.

Methods

The organic internal phase containing BAF and ethyl cellulose in dichloromethane was gradually added into external phase, which contained PVA as emulsifying agent. The mixture was stirred at 500 rpm for a specific period of time at room temperature to remove dichloromethane from the reaction flask. The formed Microsponges were filtered, washed with distilled water, and dried at room temperature. Microsponges were weighed, and production yield was determined [10].

Drug content analysis

Microsponge powder equivalent to 10 mg of drug was weighed and dissolved in 50 ml of ethanol under sonication for about 10 mins at 30°C. It was analysed spectrophotometrically, after further dilution in ethanol to obtain 20 µg/ml concentration solutions. The drug content and entrapment efficiency were calculated by using following equations: [11].

Drug content (%) = M act/Mms × 10

Entrapment efficiency (%) = M act/M the × 100

Where,

M act is the actual amount of drug in the weighed quantity of Microsponges

Mmsis the weighed quantity of microsponge powder

Mthe is the theoretical amount of drug in the Microsponges

Optimization of formulation parameters and process variables

Preliminary trials were undertaken to establish the effect of drug/ethyl cellulose ratios on the physical characteristics of Microsponges. To optimize dependent variables such as drug: polymer ratio, emulsifier concentration and stirring time, a series of formulations were prepared by factorial design study using Design Expert 11 version software using stirring rate as independent variable [12,13].

Characterization

Formed Microsponges were viewed at a magnification of 40X using photomicroscopy (Model: eclipse E200, Make: Nikon). Surface topography was studied by using a scanning electron microscope (SEM), (Model: EVO special edition, make: Zeiss).

For transmission electron microscopy (TEM) a small amount of BAF microsponge was negatively stained with 2% uranic acid and placed on copper grid (Make: Jeol, Model: JEM 2100, SAIF, Cochin University). Spectra were determined to understand the drug-excipient compatibility, by Fourier transform- IR (FT- IR).

The sample crystallinity was determined using X-ray diffraction using voltage 40 kV; current 20 mA; scanning speed 1/min. The results were recorded over a range of 5–60° (2θ) using the Cu-Anode X-ray tube and scintillation detector (Model: Rigaku, Ultima IV, National Institute of Oceanography, Donapaula). Particle size studies were carried out using photon correlation spectroscopy with dynamic light scattering using Zetasizer 2000 (Model: Nano series, S90 Zetasizer Malvern, Sinhgad Institute of Pharmacy, Pune). Electrophoretic mobility of Microsponges were determined by zeta

potential. The porous properties were determined by Mercury Intrusion Porosimeter (Model: Nova Station A, Quantochrome, Shivagi University) by using adsoption-desorption isotherms.

Dissolution studies

In the in-vitro dissolution study, accurately weighed samples equivalent to 50 mg of drug was added to the surface of the stirred dissolution medium (900 mL phosphate buffer, pH 6.8) at the beginning of the study in a USP type II dissolution apparatus.

The dissolution was carried out at 100 rpm at 37°C. Samples were withdrawn at regular time intervals. The filtered samples were analysed by UV spectroscopy at 203nm for BAF respectively [14,15].

Preparation of BAF microsponge loaded gel

Carbopol gel based was prepared by dispersing Carbopol 934 in a mixture of water and soaked overnight.

The dispersed mixture was neutralized to a pH 7.0 with triethanolamine to form a gel base. 50 mg of drug equivalent BAF microsponge was taken and uniformly dispersed in the gel base to obtain BAF microsponge loaded gel [16] (**Table 1**).

Ingredients	**B1**
Carbopol 934	1.0%
Drug Concentration	1%
Propylene Glycol	2.5%
Triethanolamine	q.s
Methyl Paraben	0.1%
Propyl Paraben	0.01%
Distilled Water	q.s

Table 1. Batches of gel formulation In-vitro release studies of gel.

The in-vitro release study was carried out using Franz-diffusion cells with a receptor compartment volume of 50 mL and an effective diffusion area of 3.14 cm2. Dialysis membrane was soaked overnight in phosphate buffer (pH: 7.4). A predetermined amount of BAF Microsponges gel was placed on the donor side. The receptor medium was continuously stirred at 150 rpm to ensure homogeneity and maintained at 37 ± 0.5°C. At predetermined time interval 5 mL of release medium was withdrawn for analysis and was compensated by equal volume of fresh buffer. The drug release data were analysed to determine the release kinetics (zero-order and first-order) as well as diffusion controlled mechanism (Higuchi model, Peppas, Hixson-Crowell and Korsmeyer-Peppas) using linear regression analysis.

Primary skin irritation studies

Primary skin irritation studies of the optimized formulations were performed using Wistar Albino rats in accordance with the guidelines of OECD 404. Group I served as the control (gel without drug) and group II received gel respectively. The scores were recorded after 1, 3, 5 and 7 days for reactions such as erythema and edema [17].

Ex-vivo permeation study

Wistar albino rat was anesthetized using excessive dose of thiopental through i.v route and sacrificed by cervical dislocation to procure the dorsal side of rat skin. The excised skin was washed and mounted on Franz diffusion cell with stratum corneum facing the donor compartment and the dermis side facing the receptor compartment. A weighed quantity of formulation gel was placed on to the skin in the donor compartment and was immersed slightly in 50 mL of receptor medium. The cell content was stirred on magnetic stirrer at a temperature 37 ± 0.5ºC. An aliquot of 5 mL was withdrawn at specific time intervals up to 8 h, and was estimated spectrophotometrically at 203 nm for BAF. After each withdrawal, the diffusion medium was replaced with an equal volume of fresh diffusion medium [18].

Conclusion

The present study reported development of BAF loaded Microsponges using ethyl

cellulose by quasi-emulsion solvent diffusion method. The aim behind developing a polymeric microsponge delivery system was to deliver BAF in a sustained manner for an extended period of time, to reduce frequency of administration and to improve its bioavailability. Therefore, in present study, sustained release formulation of BAF was prepared by incorporating it in polymeric Microsponges. Prepared Microsponges were then incorporated into a gel dosage form. The quasi-emulsion solvent diffusion method implemented was found to be simple, reproducible and rapid. Formed Microsponges were spherical in shape, had high porosity and good flow. Varied drug-polymer ratio reflected remarkable effect on particle size, drug content and encapsulation efficiency and stirring time. The dissolution studies showed the highest regression value for zero order kinetics. The formulation B2 was selected as optimized formulation as it showed lowest % cumulative drug release. Skin irritation test was carried out on rats and the formulation showed no adverse reaction such as redness, erythema and edema. Ex-vivo permeation study for BAF was carried out. The maximum amount of gel that permeated during 8 hrs of the study in case of plain gel was 63.32% CDR whereas the BAF optimized gel was 55.94 % CDR.

Thus, BAF Microsponges prepared in this study was found to be promising new delivery system offering prolonged release of BAF and hence would be more useful than conventional formulation therapy.

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