Formulation, Development, In Vitro Characterization, and Application of a Drug-Loaded Microporous Drug Delivery System

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ABSTRACT: Microsponges are an excellent choice of drug delivery system because they are porous, spherical, polymeric, and have a very high internal surface area, which facilitates efficient entrapment and controlled release of drugs. This study aims at formulation and systematic optimization of a microsponge-based drug delivery system for a poorly water-soluble BCS Class II drug, which suffers from the drawbacks of low bioavailability, burst release, frequent dosage and poor stability. The microsponges will be prepared by the quasi-emulsion solvent diffusion (QESD) method and optimized by employing a 2^3 factorial design. The amount of ethyl cellulose, dichloromethane volume, and stirring speed will be used as independent variables, and the responses of dependent variables will be particle size, entrapment efficiency, and cumulative drug release. The formulation will be optimized in terms of particle size, zeta potential, surface morphology, drug entrapment, crystallinity, thermal behavior, elemental composition, and in vitro drug release, utilizing the appropriate analytical methods such as P-XRD, DSC, FESEM-EDS, and dissolution studies. Accelerated stability testing will be conducted in line with the ICH guidelines. The study is projected to develop a quality-by-design (QbD) based platform of microsponge formulation that will be used to increase the drug solubility and release profile, enhance the formulation stability, and potentially increase the therapeutic efficacy of the drugs.

Keywords: Microsponge drug delivery; BCS Class II; Poorly water-soluble drugs; Quasi-emulsion solvent diffusion; Factorial design; Quality by Design; Sustained release; Drug entrapment;

Introduction

Micro-porous particles, more commonly referred to as microsponges, are systems for drug delivery which are made from porous microspheres. They are very small, sponge-like, spherical particles having extremely large and porous surface area. A typical microsponge is in the range of 5 to 300 µm in diameter, and a representative 25 µm-sized sphere accommodates up to 2,50,000 pores with an internal pore volume of ~10 mL/g of dry microsponge. This unique architecture enables an extremely high surface-to-volume ratio, and it is possible to entrap a wide range of active substances, hydrophilic, lipophilic, solid or liquid, into or onto the polymeric matrix. Microsponges are used to improve the physicochemical stability of labile drugs by protecting them from the action of light, moisture and oxidative degradation, and the porous shell allows free flow of the surrounding medium, allowing for a controlled release of the drug through diffusion. The dose-dependent side effects, irritative effect of the drugs on the skin or on the gastrointestinal tract, and masking of unpleasant odours or tastes are reduced with microsponge-based systems, due to the concentration-dependent release being programmed by the polymer matrix and not by immediate release. Won (1987) was the first to use the microsponge concept on an industrial scale, followed by the development of microsponge technology as a pharmaceutical technology platform using a suspension/emulsion polymerization approach to produce rigid, porous, cross-linked polymeric frameworks by Kawashima and co-workers. The microsponge delivery system is a versatile delivery system, as the microsponge powder could be added to a formulated product, which could be topical, oral, or other delivery systems, such as a gel, cream, lotion, liquid, ointment, powder, tablet, or capsule. The flexibility and the possibility to obtain a sustained and controlled release make microsonges an interesting novel drug delivery system (NDDS) to solve the biopharmaceutics problems, namely the low water solubility and the low water dissolution rate of Biopharmaceutics Classification System (BCS) Class II drugs.

Review of Literature:

An extensive literature survey was conducted to trace the development of microsponge and other micro- or nano-particulate drug delivery systems with an emphasis on those reported for the BCS Class II drug, hydrochlorothiazide (HCTZ) and structurally or biopharmaceutically similar drugs. Twenty-five key studies, from the work of Kawashima et al. (1992) on suspension-polymerised material to the latest (2024) review demonstrating the lack of available data specific to microsponge for antihypertensive agents, were critically analysed in terms of the drug studied, type of delivery system, polymer used, preparation method, principal results and relevance to the design of the present microsponge system presented previously.

The literature reviewed indicates that the combination of ethyl cellulose (EC) and Eudragit RS100/RS with hydrophilic polymers like HPMC and PVA is the most widely used polymer system in the fabrication of microsponges using the quasi-emulsion solvent diffusion (QESD) and liquid-liquid suspension polymerization routes, with entrapment efficiencies of 75–85% and release durations of 12–24 hours. The results of the studies conducted so far on HCTZ specifically (Patel et al., 2006; Rao et al., 2008; Singh et al., 2009; Sharma et al., 2011 and others) show that the three different techniques, namely the microsphere/microsponge, solid-dispersion, nanosuspension and inclusion-complex strategies can be used to deliver one or more of the desired benefits of increased solubility, gastric retention and/or increased dissolution rate, but none of them has integrated all these advantages in a statistically optimised microsponge platform. The current review (2024) makes these few published microsponge data for HCTZ-class antihypertensive drugs explicit, which is an objective gap that the present study aims to fill.

Rationale, current challenges and Research Gap

Significance of Microporous Drug Delivery Systems

1. Protect the labile actives from environmental degradation to improve the stability of drugs.
2. Improve the solubility and dissolution behaviour of poorly soluble (BCS Class II) drugs.
3. Reduce dosage-related side effects by providing a controlled, constant release.
4. Enable sustained release and reduce dosing frequency – improve patient compliance.

Issues in the Use of Traditional Formulations

1. Conventional dosage forms of poorly water-soluble drugs are still plagued by a bundle of interrelated biopharmaceutical challenges, which are:
2. Low and erratic oral bioavailability.
3. The first dose results in plasma levels above the therapeutic range, after which the level drops off quickly.
4. The need for repeated administration for adequate therapeutic drug levels, which reduces compliance.
5. Poor physical and chemical stability of BCS class-II drugs in processing and storage.

Research Gap

Although many research projects have emerged focusing on controlled drug delivery systems, a review of the literature (Table 1) reveals that, in comparison, relatively few studies have specifically attempted to optimize the drug-loaded microporous (microsponge) delivery system with the dual goals of improving the solubility and achieving sustained release of a poorly soluble drug. This gap is the scientific basis and beginning of the present research.

Research Question/Problem Statement

1. Conventional vehicles have not been successfully used for targeted delivery of drugs to specific regions of the body.
2. Directed uncontrolled release from current delivery systems results in poor plasma drug levels ranging from overdose to sub-therapeutic levels.

3. Delivering poorly water-soluble drugs (BCS Class II) is a problem that persists for existing delivery systems.
4. Lack of versatile carrier systems that can encapsulate both hydrophilic and lipophilic drugs.
5. There is a clear need for delivery systems that can improve both solubility, stability, and dissolution rate of the desired drug at the same time.
6. Existing formulation strategies are not comprehensive enough for masking, stabilizing the liquid active, and enhancing the overall formulation aesthetics.

Aim and Objective:

Aim

To design, optimize, and assess a drug delivery system with micropores loaded with a drug by a statistical (design of experiments) method.

Objectives

1. To investigate the effects of different excipients at different concentrations on the properties of the microporous system.
2. To study the different methods available for the formulation of microporous particles.
3. To successfully trap the selected drug in the polymer matrix, which can aid in overcoming the first-pass metabolism and potentially enhance the oral bioavailability.
4. To investigate how critical microsponge parameters change as the formulation is developed.
5. To design the formulation optimally with proper statistical design (factorial design).
6. To develop and establish a technique to bring a therapeutic effect quickly.
7. To carry out stability studies of the formulated dosage form as per ICH guidelines.

Plan of Work (Materials and Methods)

The proposed investigation has been broken down into eight consecutive phases from literature survey to thesis writing as follows:

Literature Survey

The published literature was systematically reviewed and summarised in Section 2 and Table 1 above, respectively, on microsponge technology and HCTZ/BCS Class II drug delivery system and statistical formulation optimization.

Selection and procurement of APIs and Excipients

The selection of the active pharmaceutical ingredient and the polymers, cross-linkers, and solvents used for the fabrication of microsponge will be based on literature review and sourced from certified suppliers, and certificates of analysis will be retained for all the materials.

Pre-formulation Studies

A. Analytical Studies

Development of standard UV calibration curve for API and complete validation of the method (linearity, accuracy, precision, LOD/LOQ) according to ICH Q2(R1).

Melting point determination of the drug and comparison with the pharmacopoeial value, as a preliminary identity and purity check.

Stress Conditions Drug Stability Studies to develop the intrinsic stability profile of API.

Solubility study of the drug in various aqueous and organic solvents to decide on the solvent for QESD process.

Spectroscopic (Compatibility) Studies

The drug-excipient compatibility will be evaluated by Fourier-Transform Infrared spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (P-XRD) to exclude any possible interaction between them at the chemical level and to assess the crystalline/amorphous content of the drug in the polymer matrix.

Other Pre-formulation Parameters

- The choice of polymers and cross-linkers.
- The choice of the model drug.
- Selection of solvents.
- Choices of preparation methods.

For initial studies, miscibility of drug–carrier and selection of initial batches are done through the trial and error method.

Optimization of the final formulations statistically by suitable factorial design.

Formulation and Development of Optimized Microsponges

After pre-formulation optimisation, selected batches will be freeze-dried (lyophilised) to provide drug-loaded microsponges in a stable, free-flowing powder that can be further characterised and formulated as a final dosage form such as gel.

Methods of Preparation

In the literature, two main techniques have been identified to be used for the preparation of microsponges, and the appropriate (s) will be chosen for the present investigation, depending on the desired product properties:

Liquid–Liquid Suspension Polymerization, a two-step process where the drug and monomer are dissolved in the same solvent, and polymerised in a suspension medium to form a porous cross-linked matrix.

Quasi-Emulsion Solvent Diffusion Method (QESD) is a single-step method where the polymer–drug organic (internal) phase is mixed with an aqueous (external) phase containing a stabiliser, and where the solvent diffusion and evaporation lead to the formation of a microsponge.

The Quasi-Emulsion Solvent Diffusion method (Methodology-B) is thus chosen as the main method for the fabrication of the microsponges for the present study since it is simple to operate and has been reported to be reproducible and applicable for the fabrication of ethyl-cellulose based microsponges. In brief, PVA (100 mg) is dissolved in 100 mL of distilled water (Phase I, external, aqueous phase) while ethyl cellulose (100 mg) is dissolved in 5 mL of dichloromethane (DCM) (Phase II, internal, organic phase) under continuous stirring. Phase II is added dropwise to the stirring of Phase I on a magnetic stirrer and the resulting dispersion is filtered, dried, and collected as drug-loaded microsponges.

Concurrently, the Liquid-Liquid Suspension Polymerization approach (Methodology-A) will be tested and compared with the aforementioned method to compare the resultant particle morphology, porosity and entrapment efficiency with the aim of selecting the most appropriate method for the targeted drug and designed release profile.

Formulation Optimization by 2^3 Factorial Design

The two levels and three independent formulation variables were used to design a 2^3 full factorial experiment, which resulted in eight experimental formulations (F1–F8). The following variables were chosen as independent and dependent for the study.

Independent variables are: X1 = amount of ethyl cellulose; X2 = amount of dichloromethane; X3= stirring speed.

Dependent Variables: Y1= particle size (µm); Y2= entrapment efficiency (%) and Y3= cumulative drug release (%).

Table 1. Coded batch matrix with design of experiment - 2^3 factorial design (factors and levels).

Batch	Code	(X1) mg	(X2) ml	(X3) rpm
1	F1	+1	-1	+1
2	F2	+1	+1	-1
3	F3	-1	-1	-1
4	F4	-1	+1	+1
5	F5	+1	-1	-1

6	F6	-1	-1	+1
7	F7	+1	+1	+1
8	F8	-1	+1	-1

The coded factor levels (−1, +1) were converted to actual factor levels for preparing each of the eight batches, as shown below.

Table 2. Coded and actual values of the independent variables.

Coded Level	X1 (mg)	X2 (ml)	X3 (rpm)
−1	1000	10	500
+1	2000	20	4000

Batch Composition of Drug-Loaded Microsponges (Drug-MSGs)

With the help of the factorial design matrix given above, eight batches of drug-loaded microsponges (APIs-MSGs) were formulated, keeping the drug load as 100 mg per batch and varying the ratio of PVA to ethyl cellulose, the volume of dichloromethane, the volume of distilled water, and the stirring speed as per the design. The ingredients of each batch are summarised in Table 3.

Table 3. Composition of APIs-loaded microsponge (APIs-MSG) batches F1–F8 prepared by factorial design.

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Weight of drug (mg)	100	100	100	100	100	100	100	100
PVA : EC (% w/w)	1:2	1:2	1:1	1:1	1:2	1:1	1:2	1:1
DCM (ml)	10	20	10	20	10	10	20	20
DW (ml)	150	150	150	150	150	150	150	150
SS (RPM)	4000	500	500	4000	500	4000	4000	500

In Vitro Evaluation and Characterization of Microsponges

The optimised and non-optimised batches will undergo a full range of in vitro evaluation and characterisation tests which will include:

1. Entrapment efficiency (%) determination.
2. Particle size analysis and zeta potential analysis.
3. Static image analysis by use of a Motic microscope for morphological assessment.
4. Powder X-ray diffraction (P-XRD) for determination of drug crystalline/amorphous state.
5. Thermal characterisation and drug–polymer interaction studies by differential scanning calorimetry (DSC).
6. Surface morphology and elemental composition analysis by scanning electron microscopy (FESEM with EDS)
7. In vitro drug release studies to understand the drug release kinetics and mechanism.

Accelerated Stability Study

The optimized formulation will be tested for accelerated stability testing following ICH guidelines, and conditions of storage will include:

40 °C ± 2 °C / 75% ± 5% relative humidity (accelerated condition).

Temperature in the room (long-term/ambient condition).

Refrigerated storage condition (2-8 °C).

Samples will be retained for 0 days, 3 months, and 6 months. At each time point, the following test parameters will be assessed:

1. Physical appearance.
2. Entrapment efficiency.
3. Particle size studies.
4. Cumulative drug release.

Interpretation and Statistical Treatment of Data

This is you getting to know the data and how to use it. This is you becoming familiar with the data and how to utilise it.

All experimental data from the factorial batches, the characterisation and stability studies will be interpreted and treated statistically (e.g., by analysis of variance, response surface methodology, regression modelling) to find the optimal formulation and to get statistically valid relationships between the independent variables (formulation) and the dependent variables (response parameters).

Thesis Writing

The final step of the work will be compilation, critical discussion, and documentation of all findings, in the form of a doctoral/postdoctoral thesis, which will be done according to the guidelines of Lincoln University College.

Expected benefit or outcome of the project and its significance:

The proposed study is expected to produce a statistically optimized drug-loaded microporous (microsponge) delivery system having better entrapment efficiency, a controlled and sustained drug release profile, and better physicochemical stability compared to the conventional drug delivery system of the selected poorly water-soluble drug. The study will be repeated by systematically using a 2^3 factorial design of experiments, and the resulting insight will be validated to yield a reproducible quality-by-design approach which can be used for other drug candidates of BCS Class II. The extensive in vitro characterisation panel (P-XRD, DSC, FESEM-EDS, particle size/zeta potential, and release kinetics) along with accelerated stability data in accordance with ICH guidelines is anticipated to produce supportive evidence which will lead to the eventual translation and therapeutic application of the developed microsponge system.

Conclusion:

The micro-porous drug delivery systems (microsponges) is one of the versatile and clinically promising platform which can overcome the common problems of conventional dosage form of poorly water-soluble drugs such as poor solubility, burst release and dose-dependent toxicity. The step-wise plan of work outlined in this manuscript (from the literature review to the pre-formulation, formulation optimisation using factorial design and evaluation of the system in the context of ICH-compliant accelerated stability testing) has demonstrated a systematic approach to the development of a statistically optimised drug-loaded microsponge system. The successful implementation of this plan would fill the gap identified in the research, and provide a scientifically validated novel drug delivery system that is translatable.

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