A Systematic Study on Manufacturing of Prilled Microgels into Lipids for Oral Protein Delivery

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ABSTRACT: The development of novel systems with oral protein delivery as ultimate goal represents an important field of pharmaceutics. Prilling of protein-loaded polymeric solutions into lipid-based hardening baths could provide here an attractive formulating technology. As the obtained microgel dispersion can be directly capsule-filled, no drying step is required and thermal drug degradation is avoided. This study aims to find excipient combinations for the novel prilling process and investigate systematically diverse material and process factors. Bovine serum albumin and mono-N-carboxymethyl chitosan were selected as model protein and prilling polymer, respectively. The prilling suitability of 880 formulations was screened with 60 ternary phase diagrams comprising two co-solvents, 10 different glycerides, and three so-called complementary excipients. Preliminary capsule compatibility was tested for one month on 245 formulations in hard and soft capsules with different shell materials. Ternary phase diagrams' center points were used to evaluate morphology, encapsulation efficiency, and protein stability of the prilled microgels. As result, several formulations proved suitable for prilling and compatible for capsule filling. Statistical analysis using partial least square regression revealed significant factors regarding different quality attributes of microgel dispersions. Therefore, an improved understanding was obtained for this promising drug delivery approach. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:3351–3365, 2015

Keywords: prilling; microgels; protein delivery; capsule compatibility; encapsulation; excipient compatibility; hydrogels; lipids; partial least squares; phase diagram

INTRODUCTION

Oral delivery of protein drugs is a challenging field of modern pharmaceutical sciences, and there is a rising interest in this type of drug delivery.[1–4] However, the gastrointestinal (GI) tract represents a major hurdle in terms of bioavailability for proteins and peptides administered orally. Macromolecules like proteins and peptides generally require protection from gastric degradation and enzymatic digestion. Additionally, they must cross the mucus and mucosal layer if absorption is needed to achieve a therapeutic effect.[5] Depending on the pharmacological target, it is possible that only luminal activity or additional mucus penetration is sufficient to ensure the macromolecule's efficacy. Many approaches have been proposed over the years to overcome the GI tract biopharmaceutical barriers. Microencapsulation was found to be very promising for oral protein delivery especially in terms of protection from enzymatic degradation.[6–8] Furthermore, some polymers used for microencapsulation, such as chitosan derivatives, are known to have mucoadhesive properties and even permeation enhancing characteristics.[9–11] Such properties have been reported for the non-toxic and water-soluble mono-N-carboxymethyl chitosan (MCC), which may thus qualify as a polyfunctional polymer.[12–14] Hydrogels formed from similar polymers are further able to create a suitable environment for a macromolecule, for example, in terms of pH and ionic strength, to ensure drug integrity.[6,8,15,16] Moreover, the microencapsulation may allow protection from the GI milieu.[17] A combination of microgels and lipid-based drug delivery was targeted in this work by means of a prilling process. This approach holds a biopharmaceutical promise, but its primary formulation rationale is of technical nature to enable a manufacturing in capsules as oral dosage form. Prilling is a mild microencapsulation technique that is suitable for protein loading.[7] This technique allows the entrapment of an API into a hydrogel by dropping a drug-containing polymeric solution into a hardening bath.[18,19] During prilling (Fig. 1), a liquid stream of the polymer and API solution is extruded from a nozzle. The stream is disrupted into droplets of the same size by applying a vibration at high frequency. The droplets can be visualized mid-air through a set of vertically aligned stroboscopic lights. The droplets can be charged by falling through a ring electrode, to prevent mid-air coalescence.[20] Finally, they are collected into the hardening bath, where gelling can occur, for example, by ionic crosslinking or by changes in temperature. The conventional hardening baths are water-based,[18,19,21] but this leads to further manufacturing steps, such as drying, that may harm a loaded macromolecule. A notable exception to aqueous hardening baths was presented by Buthe et al.,[22] who proposed n-butanol as a calcium-containing non-aqueous medium to harden alginate beads. However, this reference study neither reported the loading of API into the beads, nor employed an orally acceptable excipient. De Kruif et al.[23] recently introduced a non-aqueous lipid-based hardening bath to obtain protein-loaded hydrophilic microgels formed by ionic crosslinking. This new approach provides a lipid-based fill mass ready

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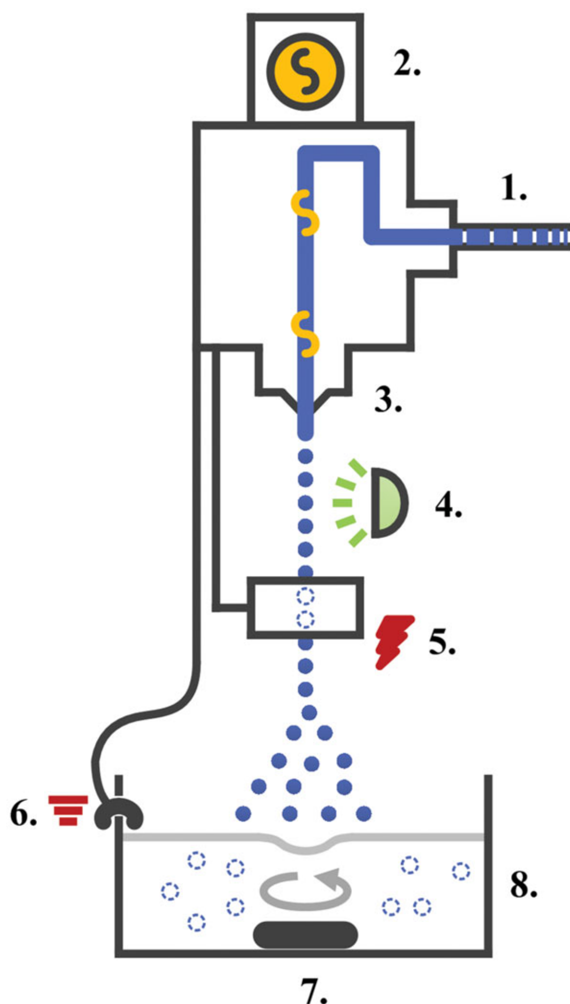

Figure 1. Scheme of vibrating nozzle system. 1, polymeric solution feed; 2, vibrating unit; 3, nozzle; 4, stroboscopic light; 5, electrode ring; 6, grounding; 7, magnetic stirrer; 8, hardening bath. Not to scale.

to be directly loaded into hard or soft shell capsules without any intermediate drying step. Nevertheless, there are multiple formulation and process factors that can influence the microgel dispersion quality. Therefore, our aim was to systematically study the influence of different excipient factors on various formulations attributes. The final purpose was to explore a potential design space for the formulation principle.

MATERIALS AND METHODS

Materials

Transcutol® HP (diethylene glycol monoetheyl ether; DEGEE), Maisine™ 35-1 (glyceryl monolinoleate), and Labrafil® M2125CS (linoleoyl macrogol-6 glycerides) were kindly offered by Gattefossé SAS (Saint Priest, France). Absolute ethanol was obtained from Brenntag Schweizerhall AG (Basel, Switzerland). Capmul® MCM EP (glyceryl monocaprylocaprate), Capmul® MCM-C10 EP (glyceryl monocaprate), Capmul® MCM-C8 EP (glyceryl monocaprylate), Captex® 8000 (glyceryl tricaprylate), Captex® 1000 (glyceryl tricaprate), and Acconon® CC-6 (caprylocaprate macrogol-6 glycerides) were purchased from ABITEC Company (Janesville, Wisconsin). Miglyol® 812 (glyceryl tricaprylocaprate), Imwitor® 742 (glyceryl caprylocaprate), and peppermint oil were bought from Hänseler AG (Herisau, Switzerland). Polyethylene glycol (PEG) 600 was obtained from AppliChem GmbH (Darmstadt, Germany). MCC (deacetylation degree 96.1%, carboxymethylation degree 82.1%, loss on drying 20.5%, molecular weight 9000–13,000 g mol^{-1}) was supplied by Shanghai Boyle Chemical Company Ltd. (Shanghai, China). Beta-mercaptoethanol, bovine serum albumin 96% (BSA), calcium chloride anhydrous, propylene carbonate, potassium dihydrogen phosphate, sodium dihydrogen phosphate dihydrate, sodium hydroxide and dipotassium hydrogen phosphate were purchased from Sigma–Aldrich (Saint-Louis, Missouri). The Low Molecular Weight Reagent Kit was purchased from PerkinElmer (Schwerzenbach, Switzerland) and the Micro BCA™ Protein Assay Kit was obtained from Thermo Fisher Scientific AG (Rockford, Illinois).

Polymeric Solution Preparation

The polymeric solution was prepared by modifying a previously reported method.[23] Briefly, a 4.5% (dry substance; w/v) solution of MCC was prepared by dissolving the polymer in demineralized water. The complete hydration of the polymer solution was allowed by mixing thoroughly overnight. The polymeric solution was then vacuum-filtered through glass microfiber filters Whatman™ GF/D and BSA was added to the solution to obtain a 2.5% (w/v) concentration. This solution was subsequently stored in a brown glass bottle at +4°C, and it was allowed to reach room temperature before each use. The solutions were discarded after 1 week from preparation, to avoid possible microbial contamination. Placebo solutions were prepared in the same way without adding any BSA to the solution.

Ternary Phase Diagrams

The ternary phase diagrams were prepared by mixing three components at different ratios, namely one co-solvent (DEGEE or ethanol), one glyceride (Acconon® CC-6, Capmul® MCM, Capmul® MCM-C8, Capmul® MCM-C10, Captex® 8000, Captex® 1000, Imwitor® 742, Labrafil® M2125CS, Maisine™ 35-1, or Miglyol® 812), and one complementary excipient (PEG 600, propylene carbonate, or peppermint oil). The glycerides were chosen according to their high diversity in chemical composition. In fact, the glycerides' composition varied in terms of fatty acid chain length (caprylates, caprates, and linoleates), predominance of unsubstituted glyceride hydroxyl groups ("free hydroxyl groups"), as well as presence of a PEG group. The predominance of unsubstituted glyceride hydroxyl groups was categorized according to the hydroxyl value of the glycerides in low (less than 150 mg_{KOH} g^{-1}), medium (between 150 and 300 mg_{KOH} g^{-1}) and high (more than 300 mg_{KOH} g^{-1}). The hydroxyl values were obtained from the glycerides' certificate of analyses. Table 1 summarizes the properties of all the components employed in the ternary phase diagrams. Each ternary phase diagram comprised 25 mixtures. Although all the mixtures were prepared at room temperature, the single components were heated or melted before use, according to the excipient manufacturers' instructions. The components were weighed into a glass vial to the appropriate ratio and subsequently mixed at room temperature for 1 h with a magnetic stirrer. After 1 h equilibration, the miscibility of the components was visually assessed and a score was assigned to each

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