RESEARCH ARTICLE

Novel Starch-Based PVA Thermoplastic Capsules for Hydrophilic Lipid-Based Formulations

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ABSTRACT: For decades, gelatin has been used in the rotary die process as a shell-forming material of soft capsules because of its unique physicochemical properties. However, with respect to the encapsulation of comparatively hydrophilic lipid-based formulations, gelatin has one considerable drawback: Immediately after production, the capsule shell contains a large amount of water (up to 35%). There is the potential for water to migrate from the capsule shell into the formulation, which will lead to a decrease in drug solubility and, in turn, the potential for drug crystallization. The present study introduces a novel capsule material that was obtained from extrusion. The starch-based polyvinyl alcohol thermoplastic capsules (S-PVA-C) mainly comprised a blend of starch and PVA. Gelatin and the novel material were used to encapsulate a hydrophilic lipid-based system of fenofibrate. Considerable water migration was observed from the soft gelatin shell to the hydrophilic formulation during drying and drug crystallization resulted in soft gelatin capsules. In contrast, S-PVA-C displayed no substantial water exchange or drug crystallization upon storage. The thermoplastic capsule material further exhibited more surface roughness and higher resistance to mechanical deformation compared with gelatin. In conclusion, S-PVA-C provided a robust drug product following encapsulation of a rather hydrophilic lipid-based formulation. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION

The production of soft capsules from gelatin has a long tradition in pharmaceutics.[1] However, gelatin also has a number of drawbacks: Ingestion of gelatin as an animal-derived material can be an issue for patients living under religious or dietary (vegetarians or vegans) restrictions. Moreover, identification of transmissible spongiform encephalopathies in animals (especially bovine spongiform encephalopathy, first case in UK, 1986) raised anxiety among gelatin manufacturers and consumers. Today, most national and international authorities have guidelines (i.e., in the EU EMA/410/01 rev.3, Ref. 2) that ensure the safety of gelatin raw material by inspecting the geographical origin, the manufacturing method, and the quality system.

Another potential issue of unmodified gelatin is its susceptibility to cross-linking. It can affect *in vitro* drug release depending on whether or not the dissolution medium contains enzymes that are able to digest gelatin (e.g., pepsin). This *in vitro* effect of gelatin capsules seems, however, to be of lesser importance for drug absorption *in vivo*.[3] Another critical aspect of gelatin is that its mechanical properties depend greatly on temperature and moisture content. Thus, climatic conditions of hot and humid regions can soften capsules, which is unfavorable for their handling by patients.[4] A considerable drawback of soft gelatin capsules (SGCs) is also the potential migration of the drug into the shell. This diffusion depends on the amount of water in the shell, the formulation, as well as the properties of the drug.[5] Such drug migration may be promoted by marked

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water partitioning between the capsule shell and a hydrophilic lipid-based formulation. Apart from the drug migration, the water exchange between the shell and the formulation can also be critical. Substantial water partitioning is especially expected with gelatin shells and hydrophilic formulations. Even temporary water uptake of the formulation is a risk for drug precipitation in the fill mass. Small amounts of water can already be sufficient to greatly reduce the drug solubility in the formulation.[6]

To overcome the disadvantages of gelatin, a great deal of effort has gone into finding gelatin substitutes for soft capsules during the last decade. However, only a few nongelatin soft capsule prototypes and methods of encapsulation have so far been patented. All materials were based on plant-derived hydrocolloids, except one that mainly comprised a synthetic polymer. In 2002, the patent by Tanner et al.[7] was granted for combining iota carrageenan and modified starch to produce mechanically strong, elastic films. After the casting of polymer bands, the rotary die process was employed for encapsulation. Later Brocker et al.[8] described in their patent the production of soft capsules that were mainly based on potato starch with special amylopectin content. They suggested a single-screw-type extruder for producing polymer films that directly feed into a conventional rotary die process. As a result of this research on thermoplastic shell materials, VegaGels® were introduced to the market as the first starch-based vegetarian soft capsule.[9] In 2005, Fonkwe et al.[10] proposed another hydrocolloid-based film consisting of iota and kappa carrageenan, and the subsequent research activities focused on the production of this shell formulation. It appears that options for manufacturing capsules from carrageenan or starch-based materials are limited due to the technical difficulties. Carrageenan, like other hydrocolloids, requires a large fraction of water for full hydration, which in turn reduces the strength of the film. Therefore, Archibald et al.[11] presented a method for extracting a portion of water from the film-forming composition, leading to the production of a dried film with 8%–25% water. To avoid these water-related complications, as early as 2002, Brown proposed using polyvinyl alcohol (PVA) for the encapsulation process.[12] Although PVA is less hygroscopic than hydrocolloids or gelatin, it lacks the gelling properties. Therefore, Brown suggested using preformed rolls of almost water-free films that can be fed into the rotary die encapsulation.

In summary, the research of novel shell materials has brought to light the difficulties of replacing gelatin. In particular, the production step remains a technical challenge for alternative materials. Further, it remains uncertain as to whether such alternative soft capsules have any pharmaceutical advantages other than their nonanimal origin. This stresses the need for more pharmaceutical research in the area of identifying new shell materials. A particular rationale for new material is to obtain a robust drug product for the encapsulation of comparatively hydrophilic lipid-based formulations, such as self-microemulsifying drug delivery systems (SMEDDS). Such preconcentrates exhibit favorable dispersion behavior when in contact with water or gastrointestinal fluids, but it comes at the cost of employing large amounts of hydrophilic surfactant(s) and/or cosolvent(s). Thus, an optimal formulation is often incompatible with gelatin, so that current capsule technology actually limits the freedom to select the best system from a biopharmaceutical viewpoint. It would be desirable first to focus on the development of an optimal formulation with respect to drug absorption and stability and then still have a sufficient choice of a viable capsule technology.

This article describes a new soft capsule material that is extruded to films for the subsequent rotary die encapsulation process. The starch-based PVA (S-PVA) material combines the thermoplastic properties of starch with the characteristics of PVA. We expected this material to be specifically suited for encapsulation of hydrophilic lipid-based formulations.

More recently, there has been an increasing interest in "hydrophilic formulations" of poorly water-soluble drugs. These lipid-based formulations containing a high proportion of hydrophilic surfactant and cosolvent are classed as type IIIB and type IV of the lipid formulation classification system (LFCS) proposed by Pouton in 2006.[13] The addition of small amounts of water to these systems can lead to the loss of drug solubility in the formulation. SGCs bear a particular risk of drug crystallization in such a hydrophilic fill because of water uptake from the shell during production.[6,14]

The present work compared the encapsulation of a rather hydrophilic SMEDDS (type IIIB formulation) in starch-based PVA thermoplastic capsules (S-PVA-Cs) and SGCs. We aimed to determine whether the novel shell material is associated with less water exchange than gelatin, thus, preventing drug precipitation in the fill mass. Other potentially beneficial physical properties of the novel shell material were analyzed as well.

MATERIALS AND METHODS

Materials

Fenofibrate (Sigma–Aldrich, St. Gallen, Switzerland) was selected as a poorly water-soluble model drug. Solvents for Karl Fischer titrimetry [HYDRANAL®-Formamide dry, HYDRANAL®-Solvent, HYDRANAL®-Composite 5, and dimethyl sulfoxide (DMSO)] and ammonium acetate were

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