Report

Capsules with Prolonged Action. II. Capsule Filling by a Gelation Process\textsuperscript{1–3}

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A new formulation for manufacturing sustained-release soft gelatin capsules was investigated. It consists of a gel solid formed by ethylcellulose and sesame oil and 20 to 35\% polyethylene glycol 400 for the enhancement of drug release. Citric acid triethylester (Citroflex-2) makes it possible to combine sesame oil with polyethylene glycol. By recording the rheological behavior at various temperatures, the thixotropic properties of the mixture that leads to the gel-forming process were ascertained. The ideal temperature for filling into soft gelatin capsules can also be determined by this method. The release profile of codeine dissolved or suspended in the mixture shows the typical matrix-type release. In contrast, a high amount of theophylline suspended in the carrier system yields an erodible matrix with an almost-constant release rate.

KEY WORDS: soft gelatin capsules; sustained release; gel formation; ethylcellulose; polyethylene glycol; citric acid triethylester; diffusion model.

INTRODUCTION

Among the publications dealing with sustained-release dosage forms, there are only a very few on the development of sustained-release soft gelatin capsules. The Scherer rotary die method of manufacturing soft gelatin capsules has enabled this dosage form to be produced for many purposes. However, there are two main disadvantages that may cause problems in the development of a sustained-release form. These are, first, the fact that only liquids, pastes, and suspensions can be filled and, second, that all substances must be compatible with the capsule shell.

Widmann et al. (1) investigated a liquid system consisting of a solution of shellac or polyvinylacetate in polyethylene glycol together with other components controlling the delivery of drugs. After the dissolution of the capsule shell the polyethylene glycol is leached out and an insoluble matrix is formed. The delivery process is controlled by the diffusion of the drug within the matrix (2). While the diffusional path becomes longer, the release rate decreases very quickly. Another disadvantage can be seen in the fact that a liquid filling, which can form a lot of drops or remain as a whole after dissolution of the shell, causes problems with the reproducibility of drug release.

D’Onofrio et al. (3) reported on a microencapsulation procedure that allows an oil slurry of microcapsules to be filled into soft gelatin capsules. A fraction of acetylsalicylic acid crystals was coated with ethylcellulose in a system consisting of ethyl acetate and light liquid paraffin. After co-acervation the ethyl acetate was removed and the remaining oil slurry was filled into soft gelatin capsules. The authors were able to demonstrate that the release rate of aspirin was dependent on the thickness of the microcapsule shells.

In order to avoid the disadvantages of the shellac--polyethylene glycol system, an attempt was made to develop a liquid filling that forms a gel solid within the capsule soon after the filling process. With regard to a maximum temperature of 35°C that is practicable for manufacturing soft gelatin capsules, no hot melt system can be used. Therefore, this paper deals with a thixotropic system that is able to be filled into soft gelatin capsules by the Scherer rotary die method. The release rate should be controlled by the amounts of the carrier substances.

Thixotropic systems are well known in filling operations of hard gelatin capsules. However, formulations based on fats and waxes as used for hard capsules are of limited value in the design of a soft capsule filling because of their high melting range. Therefore, a thixotropic system based on ethylcellulose and nonaqueous solvents was developed in this study.

MATERIALS AND METHODS

Materials

Ethylcellulose (Ethocel premium grade) with an ethoxyl content of 48.0 to 49.5\% was used; the viscosity of a 5\% (w/w) solution in toluene--ethanol (80:20, w/w) was 10 and 20 cps, respectively (Dow Chemical Inc.). Sesame oil was pharmaceutical grade (Mainland, D-Frankfurt). Citric acid
triethyl ester (Citroflex-2) was 99.9% (Pfizer Corp., D-Wiesbaden). Polyethylene glycol 400 was pharmaceutical grade (Hoechst AG, D-Frankfurt). Codeine and theophylline were Ph.Eur. grade (Boehringer Ingelheim GmbH, D-Ingelheim). Filtration of samples was carried out with filtration set GSWP 02500, 0.22 μm (Millipore, D-Eschborn), and 5-ml plastic syringes (Braun, D-Melsungen).

**In Vitro Test and Assay of Samples**

A paddle apparatus (USP XXI) with 900 ml distilled water was used at 100 rpm. After each hour 5-ml samples were withdrawn, filtered, and used for spectrophotometry. After the spectrophotometric assay the whole sample was replaced into the dissolution fluid. A PMQ II photometer (Zeiss, D-Oberkochen) was used, with 2.0-cm quartz cuvettes. The wavelength was 285 and 271 nm for codeine and theophylline, respectively.

**Rheology**

A Rotovisco RV 12 apparatus was used, with measuring system MV 1 (Haake, D-Karlsruhe). The shear rate was 0 to 64 rpm, raising over a period of 3 min. The temperatures began at 70°C, with cooling and measuring at each 5°C interval while cooling shearing with 8 rpm was continued. A PM 8120 plotter (Philips, D-Kassel) was used, with shear stress recorded at 50 mV/cm.

**Determination of Phase Diagrams**

The concentration of mixtures was with variation of the compounds in steps of 10%. Ten milliliters of the mixtures filled into small tubes was heated on the plate of a magnetic stirrer until a clear solution was obtained. The temperature at the beginning of opacity was recorded.

**Manufacturing of Capsules**

Ethylcellulose, polyethylene glycol 400, sesame oil, and citric acid triethyl ester were warmed together to achieve a clear solution. Codeine was dissolved at 60°C. For suspension formulations codeine and theophylline were suspended at 35°C. The mixtures were degassed by vacuum before filling into the capsules. The temperature was 30°C; the composition of the capsule shell was of glycerol, water, and gelatine.

**RESULTS**

**Phase Diagrams**

Ethylcellulose is able to form solid gels when it has been dissolved in fats or waxes at relatively low concentrations (4). In this investigation sesame oil was chosen for the oil component, but any similar oil could be used. In order to enhance the release rate of the drug it was necessary to have a component in the system that could easily be leached out. Several papers report that especially polyethylene glycols are able to give ethylcellulose layers a microporous structure (5–9). However, sesame oil and polyethylene glycols do not form a homogeneous mixture. To some extent a homogeneous mixture can be achieved together with a large amount of citric acid triethyl ester (Citroflex-2). Figure 1 shows the phase diagram of the system polyethylene glycol 400, sesame oil, and Citroflex-2.

At 20°C the homogeneous phase is very small since only 7% Citroflex-2 can be dissolved in sesame oil. Ethylcellulose at concentrations of up to 5% does not influence the position of the phase separating lines.

Upon cooling to near 25°C a solid gel is formed, if the mixture contains at least 2% ethylcellulose and the composition of the mixture lies in the nonhomogeneous area. This is due to a partial desolvation of the ethylcellulose by the polyethylene glycol 400. Mixtures without polyethylene glycol do not give a solid gel when the amount of ethylcellulose lies between 2 and 5%.

In Table I the lower and upper concentration of each component is shown. The maximum amount of ethylcellulose is limited by the resulting viscosity suitable for the capsule filling process. Polyethylene glycol 400 should be present at a concentration of about 16% to achieve a gel but a concentration above 35% will desolvate the ethylcellulose so that the whole system could break down. The amounts of sesame oil and Citroflex-2 are less important; about 5% sesame oil is required to form a gelling system together with the ethylcellulose.

**Rheology**

The demonstration of the flow curves shows the formation of the gel in Fig. 2. The rheological behavior of a system consisting of 3.5% ethylcellulose, 22% polyethylene glycol 400, 10% sesame oil, and 64.5% Citroflex-2 shows a Newtonian behavior at a temperature of 30°C. At 35°C a distinct thixotropic behavior can be observed. At 30°C the thixotropic flow curve has changed to a nearly Newtonian type, indicating that the gel has been destroyed by the shearing procedure. This was visible by a flocculation of the system.

**Drug Release**

The release profiles of three codeine and two theophylline formulations are presented. Codeine capsules contained 30 mg of the drug, and theophylline capsules 300 mg. Theophylline was formulated only as a suspension, while co-