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Report

Capsules with Prolonged Action. II. Capsule Filling by a Gelation Process[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 coacervation 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

[1] Part I, *Pharm. Ztg.* (in press).

[2] Dedicated to Prof. Dr. Elsa Ullmann on the occasion of her 75th birthday.

[3] Part of the thesis of B. Stockebrand, Marburg, 1985.

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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 I (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.

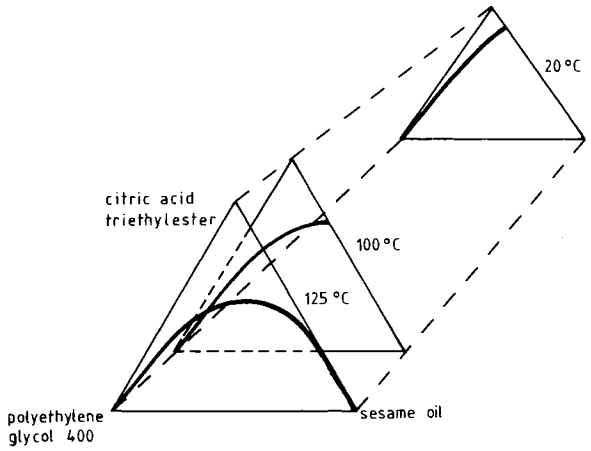

Fig. 1. Phase diagram for mixtures of polyethylene glycol 400, sesame oil, and citric acid triethyl ester at 125, 100, and 20°C. Above the bold line, one phase; below, two phases.

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 50°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-

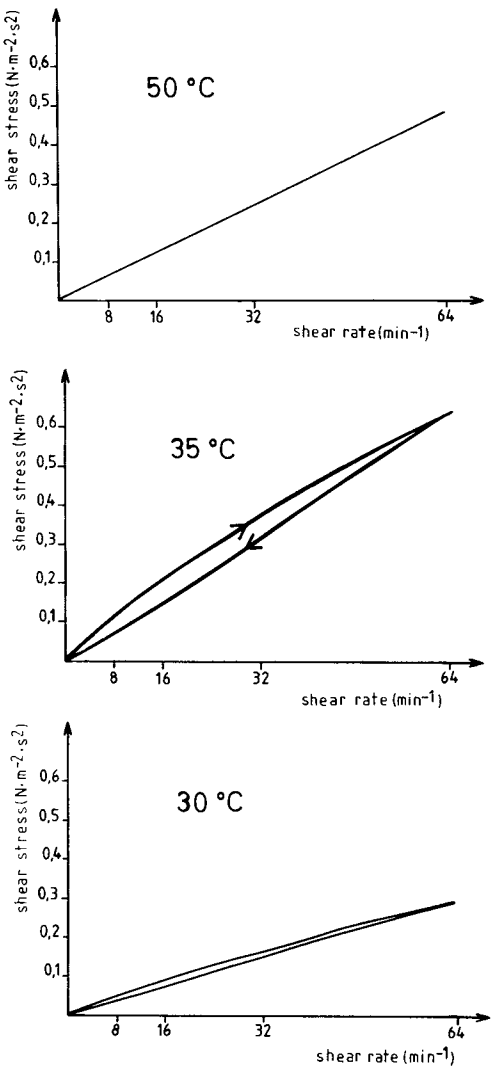

Fig. 2. Flow curves of a mixture containing 3.5% ethylcellulose, 22.0% polyethylene glycol 400, 10.0% sesame oil, and 64.5% citric acid triethyl ester (Citroflex-2). Temperatures: top, 50°C; middle, 35°C; bottom, 30°C. Shear rate was raised from 0 to 64 min^{-1} over a period of 3 min; cooling of the mixtures in steps of 5°C while shearing with 8 min^{-1}.

deine was dissolved in the carrier system in one formulation. For codeine a 4- to 8-μm fraction was used, and for theophylline a 80- to 100-μm fraction was used. Tables II and III show the detailed composition of the capsules.

After the dissolution of the capsule shell a film consisting of ethylcellulose is formed around the gel solid through the action of water. The codeine passes this barrier via diffusion. After 2 hr the main part of the polyethylene glycol has leached out, and a part of the Citroflex-2 also. This process leads to a new capsule consisting mainly of ethylcellulose and sesame oil that contains the remaining codeine, Citroflex-2, and water. A difference in the release of crystalline and dissolved codeine can be seen in Fig. 3. The formulation containing the dissolved drug (C I) starts to deliver the drug faster in the beginning. Crystalline codeine

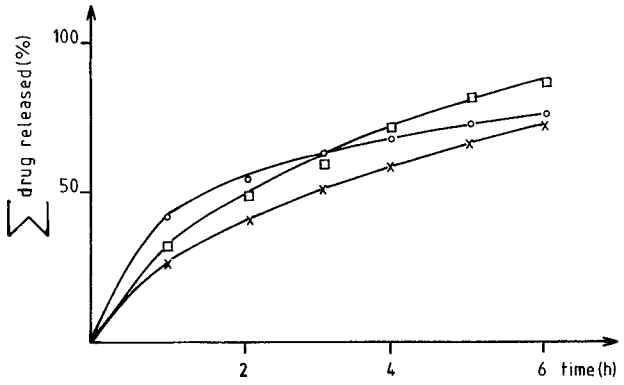

Fig. 3. Release of codeine from capsule formulations (Table II). (—○—) formulation C I; (—□—) formulation C II; (—×—) formulation C III. USP paddle method with 900 ml distilled water; Speed of the stirrer, 100 rpm. Values are means of four investigations per formulation, relative standard deviation being less than 5% for each value.

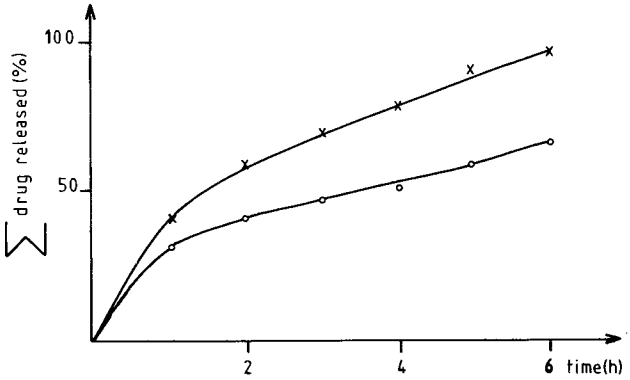

Fig. 4. Release of theophylline from capsule formulations (Table III). (—○—) Formulation T I; (—×—) formulation T II. USP paddle method with 900 ml distilled water; speed of the stirrer, 100 rpm. Values are means of four investigations per capsule, relative standard deviation being less than 8% for each value.

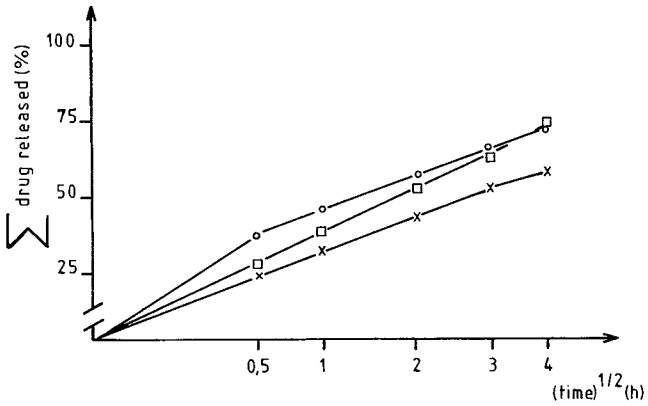

Fig. 5. The release of codeine from the capsules (Table II). The summarized amount of the drug is plotted versus the square root of time. (—○—) Formulation C I; (—□—) formulation C II; (—×—) formulation C III. Formulations C II and C III show a matrix-type release pattern that leads to a straight line from the beginning to the fourth hour of *in vitro* testing.

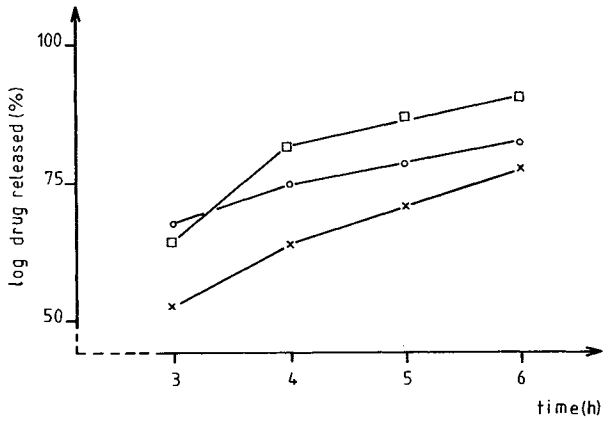

Fig. 6. The release of codeine from the capsules (Table II). The logarithm of the summarized amount of the drug is plotted against the time. (—○—) Formulation C I; (—□—) formulation C II; (—×—) formulation C III. The straight lines indicate that the release was controlled by membrane diffusion after the fourth hour.

seems to need time for dissolution in the matrix material first (C III). After 3 hr the fastest release can be observed from formulation C II because of the low amount of ethylcellulose.

The formulations with theophylline show a release pattern that differs from that of the codeine capsules. In contrast to the formation of an ethylcellulose shell, a complete erosion of the matrix can be observed. A high amount of drug and polyethylene glycol is causing this phenomenon. The erosion proceeds with the leaching out of both substances, thereby destroying the gel solid. From this behavior a relatively constant release profile is obtained (Fig. 4).

DISCUSSION

This investigation focuses on the important role played by the citric acid triethyl ester in the sustained-release formulations proposed here. This substance enables a homogeneous mixture between sesame oil and polyethylene glycol 400. Without Citroflex-2 there would be no coherence and miscibility between the other components. Furthermore, the substance is soluble in water to some extent, and therefore, it enhances the delivery of drugs. From the flow curves it can be seen that the mixture is able to form a thixotropic system that leads to a gel solid. Naturally, the decreasing temperature is important for the gel formation; more important, however, is the desolvation of the ethylcellulose by polyethylene glycol at a certain temperature. This effect is generally known in polymer chemistry (10). The flow curves also reveal the suitable time for filling the mixture into soft gelatin capsules. A mixture may not be filled below its temperature of maximum thixotropy because of the separation process. In that case the shear stress during the filling process would destroy the gel.

Table I. Usable Amounts of Components for Filling into Soft Gelatin Capsules

Component	Range (%)
Ethylcellulose	2–5
Polyethylene glycol 400	16–35
Sesame oil	5–20
Citric acid triethyl ester	40–77

The release profiles of two codeine capsules have the typical shape of a matrix-type release pattern (2,11). However, only during the first 3 hr of *in vitro* testing can a linear dependence to the square root of time be observed (Fig. 5).

The capsules which lead to a straight line in Fig. 5 contain the drug in a suspended form. The release profile of capsule C I shows a high value in the first hour. In other words, the formulation with the dissolved codeine possesses a share of the drug that is not retained by the gel system. Indeed it was found that about 4% of the drug could be assayed in the capsule shell after washing in methylene chloride and dissolving the gelatin in water. The migration of compounds of the capsule filling into the shell was studied by Armstrong *et al.* (12). It was established that the extent of the migration is directly dependent on the partitition coefficient of the shell and the oily filling. It is obvious that especially the dissolved drug has the possibility to diffuse into the capsule shell during the drying process, and therefore a higher delivery during the first hour can be noted.

In the later phase of *in vitro* testing the delivery of the suspended codeine is faster. After the fourth hour there is also a change in the release kinetics, which now follow a first-order type (Fig. 6). This is due to the change of the shape of the gel solid. It has become a capsule consisting of ethylcellulose and sesame oil; and the release through this barrier is controlled by membrane diffusion. The release of suspended codeine is faster than that of the dissolved drug.

Table II. Composition of the Codeine Capsules

Compound	Formulation			mg per capsule		
	C I	C II	C III	C I	C II	C III
Ethylcellulose[a]	5	2	5	15	6	15
Polyethylene glycol 400	20	20	20	60	60	60
Sesame oil	10	10	10	30	30	30
Citric acid triethyl ester	65	68	65	195	204	195
Codeine				30[b]	30[c]	30[c]
Total weight of filling				330	330	330

[a] Nominal viscosity was 20 cps.
[b] Dissolved in the carrier system.
[c] Suspended in the carrier system.

Table III. Composition of the Theophylline Capsules

Compound	Formulation (%)		mg per capsule	
	T I	T II	T I	T II
Ethylcellulose	2 (20 cps)	2 (10 cps)	9	9
Polyethylene glycol 400	35	35	157.5	157.5
Sesame oil	5	5	22.5	22.5
Citric acid triethyl ester	58	58	261	261
Theophylline[a]			300	300
Total weight of filling			750	750

[a] Suspended in the carrier system.

It can be supposed that the codeine crystals leave behind a porous ethylcellulose membrane after their dissolution in the matrix. The fact that in the late step of in *vitro* testing the ethylcellulose capsule is completely filled with water confirms that even thick ethylcellulose walls can have a high permeability for water (9).

Regarding the composition of the formulations T I and T II (Table III), the amount of drug is 45%. When the amounts of theophylline, polyethylene glycol 400, and Citroflex-2 are added, the capsules contain about 90% substances that could be leached out. This leads to a stepwise erosion of the whole matrix and a nearly constant release of the drug (Fig. 4). Ethylcellulose with 10-cps nominal viscosity has a lower average molecular weight than the 20-cps type, and therefore, the erosion takes place faster. Regarding the list of available types of ethylcellulose, there might be a possibility of selecting the types according to special requirements.

ACKNOWLEDGMENTS

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