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Clofibrate Microcapsules: Preparation and Release Rate Studies

P. L. MADAN *¶x, DEVENDRA K. MADAN ‡, and J. C. PRICE §

Abstract □ Microencapsulation of clofibrate and dissolution characteristics of clofibrate microcapsules were investigated. Spherical droplets of clofibrate, prepared by a capillary jet method, were encapsulated in gelatin by simple coacervation, using sodium sulfate as the coacervating agent. The microcapsules, which were hardened up to 8 hr with formaldehyde, were recovered as discrete, free-flowing particles. Dissolution of clofibrate from the microcapsules was not adequately described by either square root of time or Langenbucher kinetics but followed predominantly zero-order release patterns at all hardening times. A linear correlation was found between the hardening time and the $t_{50\%}$ release time.

Keyphrases □ Clofibrate—microcapsules prepared, release rate studied □ Microcapsules—clofibrate, preparation described, release rate studied □ Dosage forms—microcapsules, clofibrate, preparation described, release rate studied □ Release rate—clofibrate from microcapsules □ Hypocholesterolemic agents—clofibrate, microcapsules, preparation described, release rate studied

Clofibrate USP, a liquid hypocholesterolemic agent with an unpleasant odor and taste, is administered at rather frequent time intervals (1). Because of these properties, microencapsulation of the drug may result in a more acceptable and effective dosage form.

Simple coacervation with gelatin has been known for many years (2) and has been studied as a means of encapsulation for various pharmaceuticals and chemicals (3). Only a few reports of the dissolution characteristics of such microcapsules are available (4–7), possibly because of the difficulty of obtaining discrete, free-flowing, and reproducible microcapsules.

This study reports the microencapsulation of clofibrate by simple coacervation with gelatin and the effect of hardening time on the dissolution of the microcapsules.

EXPERIMENTAL

Materials—All materials were of USP or reagent grade and were used without further purification. The gelatin[1] used had the following specifications as provided by the manufacturer: type, B-lime treated; bloom, 275; viscosity, 63.9 mpoises; pH (of solution of gelatin), 5.70; moisture, 10.5%; and isoionic point, 4.9.

Production of Monodisperse Spheres—The method employed for the production of monodisperse spheres of clofibrate[2] liquid was similar to that reported earlier (8). The apparatus is shown in Fig. 1. A fine capillary tube, C, was attached to an aspirator bottle, R, which served as the reservoir for the liquid to be encapsulated. The internal diameter of the capillary tube was such that air pressure had to be applied to force the liquid through the capillary. A filter, F, was fitted between the capillary and the aspirator bottle to prevent obstruction by particulate matter.

By varying the internal diameter of the capillary and/or air pressure, the diameter of the droplets produced could be changed. To attain uniformity of droplet production, all experiments were conducted under identical conditions, using the same capillary tube and forcing clofibrate from the capillary tube under identical air pressure.

The droplets leaving the capillary tube were allowed to fall into the gelatin solution. This solution was continuously stirred to prevent coalescence of clofibrate droplets.

Microencapsulation Procedure—Simple coacervation was used to achieve microencapsulation (2), and all experiments were conducted under identical conditions with the same or similar equipment. Coacervation was carried out at 40 ± 1°. The gelatin solution was prepared by soaking 10 g of gelatin in 100 ml of distilled water, allowing it to hydrate for about 12 hr, and then warming to 40° to effect solution. Then 40 ml of clofibrate in the form of monodisperse spheres was added to the gelatin solution, and the mixture was stirred continuously at 30 rpm to prevent coalescence of clofibrate droplets.

After stirring for about 5 min, a 20% (w/w) solution of sodium sulfate, also at 40°, was added to the mixture. Stirring was continued for 15 min more to ensure complete encapsulation, and the formation of coacervate-coated spheres was verified microscopically. The product was then poured into 500 ml of a 7% (w/w) sodium sulfate solution at about 4° to gel the liquid shell of the microcapsules. The mixture was maintained at less than 10° and stirred continuously for 30 min to complete the gelling process.

Recovery of Microcapsules—For this investigation, it was essential to obtain microcapsules in the form of a free-flowing powder. The method of Madan *et al.* (8) was modified slightly and, instead of 70% 2-propanol at room temperature, an equal volume of chilled 2-propanol was added to the product to dehydrate and to flocculate the coacervated droplets. The microcapsules were allowed to settle,

[1] P. Leiner and Sons, America Inc., St. Claire Shores, Mich.

[2] Ayerst Laboratories, Rouses Point, N.Y.

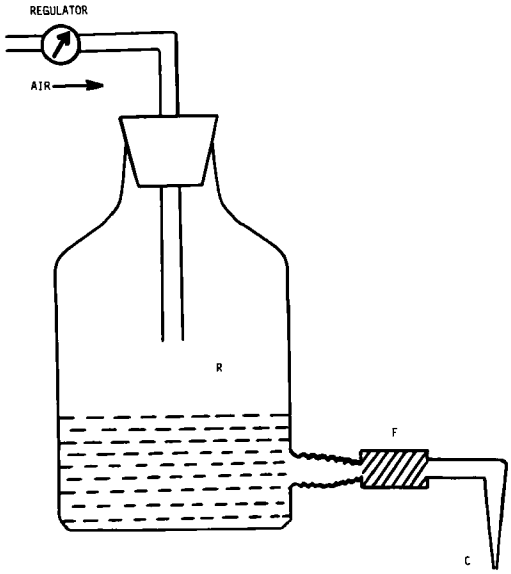

Figure 1—*Schematic diagram of the apparatus used for the production of clofibrate droplets.*

and the mother liquor was decanted. The product was washed with chilled 2-propanol (10 ml/g of microcapsules) and allowed to air dry at room temperature to yield free-flowing, discrete microcapsules.

Evaluation of Microcapsules—The microcapsules were hardened by immersing in a 10% solution of formaldehyde in 2-propanol for 0, 1, 2, 4, and 8 hr. Ten milliliters of hardening solution was used for each gram of microcapsules. The modified flask method (9) was used to evaluate the ability of dried microcapsules to resist release of the encapsulated drug. Six hundred milliliters of the dissolution medium (30% 2-propanol solution) at 37 ± 0.5° was stirred at 50 rpm using a constant-speed motor[3].

Dissolution was followed by examining triplicate samples containing approximately 30 mg of drug. In each case, microcapsules were placed on the surface of the dissolution medium and allowed to settle. At appropriate intervals, samples of the dissolution medium were withdrawn using a pipet fitted with a cotton plug. A constant volume of the dissolution medium was maintained by the addition of an equal volume of the dissolution medium after each 5-ml sample was withdrawn. The cotton plug was added to the dissolution mixture. Concentrations were determined spectrophotometrically at 226 nm.

Assay Procedure for Total Clofibrate Content of Microcapsules—Triplicate samples of approximately 30 mg of the microcapsules were accurately weighed and placed in a 150-ml homogenizing flask containing 50 ml of 30% 2-propanol. The samples were completely ruptured with a blender[4] operating at its maximum speed. In each case, two samples were blended for 10 min, and complete rupture was assured by blending a third sample for 15 min with no observed

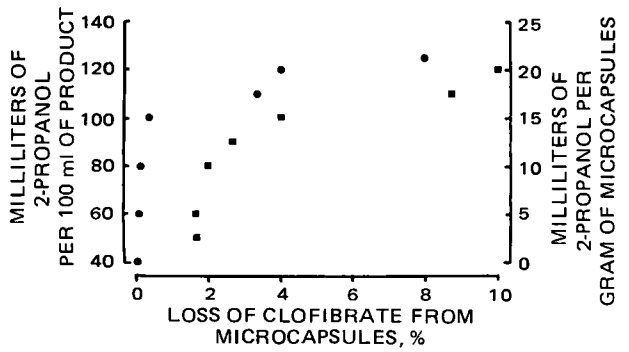

Figure 2—*Percent loss of clofibrate from the microcapsules during 2-propanol treatment. Key: ●, 2-propanol used for flocculation and dehydration; and ■, 2-propanol used for washing microcapsules.*

[3] Synchron model K12Rc 5-712.
[4] Model 45, Virtis Research Equipment, Gardner, N.Y.

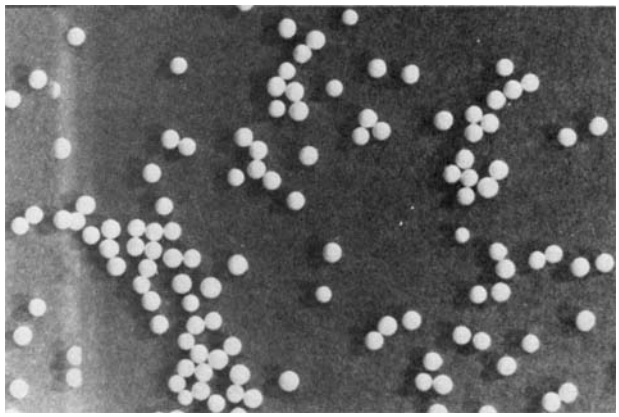

Figure 3—*Photomicrograph of clofibrate microcapsules as discrete particles.*

increase in drug content. Filtered aliquots of the mixture were then assayed spectrophotometrically.

RESULTS AND DISCUSSION

Preparation of Uniform Drug Particles—Uniform spheres of clofibrate with a mean diameter of 190 ± 10 μm were obtained when the rate of production was restricted to 100–120 particles/min. The resulting particles were essentially monodisperse and ideally suited to encapsulation and dissolution studies. Greater production rates were attempted, but they resulted in coalescence of the droplets in the gelatin dispersion.

Preparation and Recovery of Microcapsules—The usual methods of recovery by decantation and filtration or centrifugation resulted in rubbery masses which dried to hard lumps impossible to separate into individual particles. However, discrete microcapsules were successfully obtained using a chilled solution of 50% 2-propanol to dehydrate the coacervate droplets. At lower concentrations, the coacervate tended to agglomerate; at higher concentrations, an increased loss of clofibrate occurred due to leaching. The effect of the 2-propanol treatment on the loss of clofibrate from the microcapsules is summarized in Fig. 2.

Figure 3 shows a photomicrograph of clofibrate microcapsules recovered as discrete particles in the form of a free-flowing powder.

Dissolution Studies—Since clofibrate is insoluble in water (10), conventional dissolution media such as 0.1 *M* hydrochloric acid and simulated gastric fluid could not be used. The selection of a suitable dissolution medium was, therefore, based on the following criteria: (*a*) solubility of the drug, (*b*) suitability of the dissolution medium as the solvent for spectrophotometric assay, and (*c*) noninterference with the hydration of the microcapsule shell.

The USP spectrophotometric assay for clofibrate (10) uses methanol as the solvent. Neither methanol nor ethanol, in any dilution, can be employed as a dissolution medium for gelatin–acacia microcapsules because the strong dehydrating properties of these alcohols does not permit the hydration of the capsule walls. Bensusan (11) showed that soluble collagens are precipitated by aliphatic alcohols in the order methanol > ethanol > 1-propanol > 2-propanol. Thirty percent 2-propanol in water proved to have sufficient solvent property to permit dissolution without the risk of saturation and also allowed the complete hydration of the microcapsules. Microscopic examination revealed that the hydration of the microcapsules in 30% 2-propanol solution was almost identical to that in water.

The dissolution rate profiles of the microcapsules are shown in Fig. 4. Each point represents an average of at least three experiments. Most of the points had a range of less than 5%; a few points exceeded 5% but were within a 10% range.

As seen in Fig. 4, at between 10 and 85–90% release, the microcapsules yielded straight-line plots, characteristic of zero-order release irrespective of the effect of hardening. The first 5–10% clofibrate was released almost as soon as the dissolution determinations were started. This early rapid release was probably due to the clofibrate on or in the wall material of the microcapsules.

In a study dealing with the microencapsulation of sulfadiazine by a method similar to the one described here, Nixon and Walker (6)

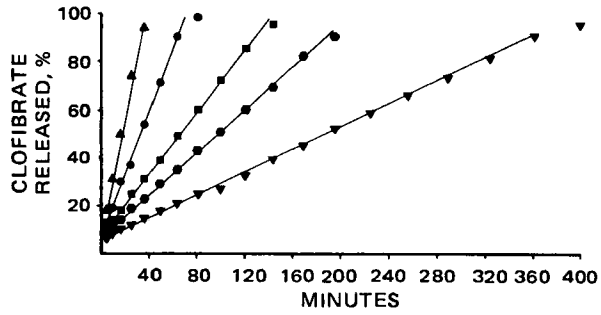

Figure 4—*Relase rate profiles of clofibrate microcapsules. Key: ●, microcapsules hardened for 1 hr; ■, microcapsules hardened for 2 hr; ●, microcapsules hardened for 4 hr; ▼, microcapsules hardened for 8 hr; and ▲, unhardened microcapsules.*

reported a similar initial rapid release. However, the results obtained in the present investigation differ in several respects. For example, Nixon and Walker (6) found that the initial rapid release approximated 25% of the core material dissolved followed by a gradual fall in the rate, with the last 20% being released very slowly. These authors found first-order release for the hardened material, but the unhardened microcapsules were better described when the percent sulfadiazine released was plotted on a probability scale as a function of the logarithm of time. They concluded that their dissolution data were not amenable to any one type of treatment.

It is possible that the nature of the core material may have been responsible for the differences observed between the present investigation and the one reported by Nixon and Walker (6). Microcapsules made from liquids usually contain only one droplet and tend to be spherical. In this investigation, the droplets were nearly monodisperse. In the case of solids, the individual microcapsules can be composed of a number of crystals, usually arranged toward the center of the microcapsule. On hardening, the wall material shrinks and the microcapsules tend to assume the shape of the solid crystals dispersed in them, thus resulting in a heterogeneous mixture.

Mechanism of Release of Clofibrate from Microcapsules—It was proposed previously (12, 13) that the release of medicaments from solid matrixes may be considered as taking place through a simple diffusional process or through leaching by dissolution into the permeating fluid. In either case, a plot of the residual fraction as a function of the square root of time should yield a straight line. Square root of time plots of the clofibrate release from microcapsules (Fig. 5) show a linear relationship only over the latter part of the dissolution. The initial portion of the graph shows that the first 5–10% clofibrate was released almost as soon as the dissolution determinations were started, while the next 25% clofibrate was released very slowly.

Here again, the results are somewhat different from those reported by Nixon and Walker (6). They found a linear relationship for the entire period with the hardened material, but the unhardened microcapsules tended to nonlinearity during the latter part of the dissolution.

Langenbucher kinetics (14) of uniform, nondisintegrating granules were also applied to the dissolution data. Figure 6 shows the cube root

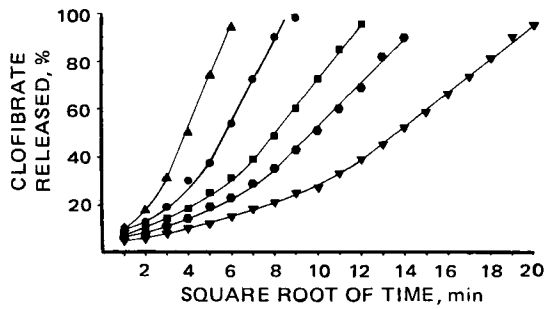

Figure 5—*Percent clofibrate released as a function of the square root of time. Key: ●, microcapsules hardened for 1 hr; ■, microcapsules hardened for 2 hr; ●, microcapsules hardened for 4 hr; ▼, microcapsules hardened for 8 hr; and ▲, unhardened microcapsules.*

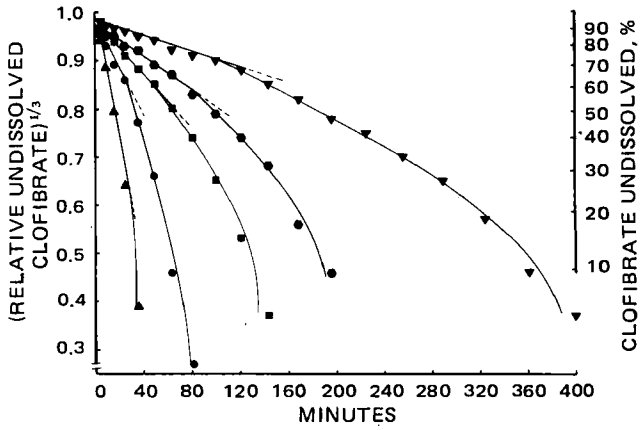

Figure 6—*Langenbucher cube root dissolution plot. Key: ●, microcapsules hardened for 1 hr; ■, microcapsules hardened for 2 hr; ●, microcapsules hardened for 4 hr; ▼, microcapsules hardened for 8 hr; and ▲, unhardened microcapsules.*

of the relative undissolved clofibrate plotted as a function of time. This treatment of the data appears to describe the dissolution of the microcapsules only in the initial portion (up to about 30–40% clofibrate released).

The predominantly zero-order release observed in the present investigation can be explained by the model shown in Fig. 7. As soon as the dissolution determinations were started, the dissolution medium (water–2-propanol) penetrated the microcapsule wall to dissolve some clofibrate. This result produced a saturated clofibrate solution within the microcapsule shell wall, thus setting up a concentration gradient between the microcapsules and the dissolution medium. As dissolution progressed, clofibrate solution diffused out slowly and therefore constituted a rate-limiting step. Since the concentration of solution inside the microcapsule shell remained constant (saturated), the diffusion rate of clofibrate out of the microcapsules would also be expected to remain constant, *i.e.*, follow zero-order dissolution, until the quantity of undissolved material was insufficient to produce a saturated solution.

Effect of Hardening Time—The effect of hardening time was studied over an 8-hr period, because hardening beyond 8 hr caused the loss of clofibrate from the microcapsules. No loss of clofibrate could be detected when the hardening time was 8 hr or less. Microscopic examination of those microcapsules hardened for more than 8 hr revealed numerous fractured and broken capsules, thus accounting for the loss of clofibrate. Prolonged hardening probably caused the walls to become brittle and subject to fracture, with subsequent loss of the liquid internal constituent.

The initial rapid release (Fig. 4) decreased with an increase in the hardening time, in contradiction to the rates reported by Nixon and Walker (6). The decrease in the initial rapid release with the corresponding increase in hardening time may be explained by the shrinkage of the wall material during the hardening process, thus leaving less room for clofibrate entrapped within the wall.

The release of clofibrate from the microcapsules was related directly to the hardening time. Figure 8 shows a linear relationship of the $t_{50\%}$ release time plotted as a function of hardening time.

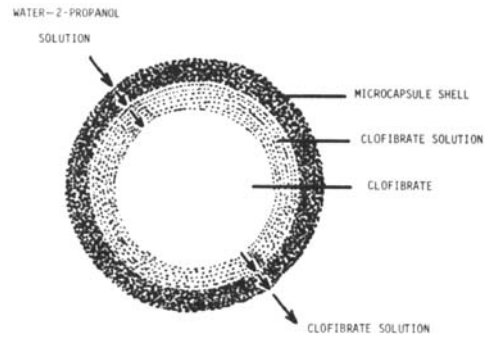

Figure 7—*Proposed model explaining the release of clofibrate from microcapsules.*

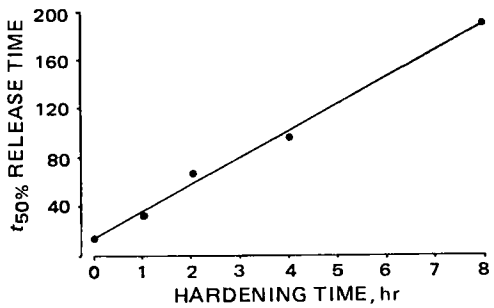

Figure 8—*The $t_{50\%}$ release time as a function of hardening time of the microcapsules.*

SUMMARY AND CONCLUSIONS

This study was undertaken to investigate the feasibility of microencapsulation of clofibrate, to collect the microcapsules in the form of a free-flowing powder, and to evaluate the dissolution characteristics of the microcapsules obtained. From the results, the following conclusions are drawn:

1. Microencapsulation of clofibrate can be successfully achieved by simple coacervation.
2. Free-flowing discrete microcapsules can be obtained by treatment with 2-propanol.
3. After an initial surge, dissolution of clofibrate from microcapsules under sink conditions followed apparent zero-order release rates until nearly 90% of the drug was released. The dissolution pattern observed can be explained by a model in which the capsule wall limits dissolution from a saturated solution of the clofibrate formed inside the microcapsule.
4. The release rates of the microcapsules were related directly to the hardening time of the microcapsules. A linear correlation was found between the hardening time and the *in vitro* $t_{50\%}$ release time of the microcapsules.
5. Hardening of microcapsules up to 8 hr did not result in a loss of clofibrate, but longer hardening times caused rupture of some of the microcapsules with subsequent loss of clofibrate.

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Synthesis of Potential Mescaline Antagonists

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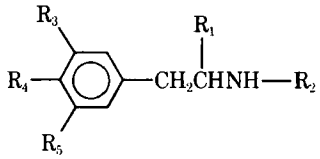
Abstract □ 1-[2-(3,4,5-Trimethoxyphenyl)ethyl]-3-pyrroline, 2-(3,4,5-trimethoxybenzyl)-1,2,3,6-tetrahydropyridine, *N*-*n*-propylmescaline, *N*-cyclopropylmethylmescaline, and *N*-allylmescaline were synthesized as potential mescaline antagonists. The ability of these compounds to antagonize mescaline-induced disruption of swim behavior is also given.

Keyphrases □ Mescaline antagonists, potential—synthesized and screened for effect on mescaline-induced CNS stimulation □ Antagonists, mescaline, potential—synthesized and screened for effect on mescaline-induced CNS stimulation □ CNS stimulation, mescaline induced—effect of various mescaline antagonists evaluated □ Structure–activity relationships—various mescaline antagonists screened for effect on mescaline-induced CNS stimulation

The method presently used to counteract the hallucinogenic effects of mescaline (I) and other hallucinogens is administration of drugs that indirectly counteract the hallucinogenic effects, such as tranquilizers and sedatives (1). The object of this research was to synthesize compounds that would antagonize the effects of mescaline through a direct competitive mechanism. The compounds would ideally have little or no effect of their own but, when given in conjunction with mescaline, would mitigate the central nervous system (CNS) stimulation.

It has been well documented that replacement of the



I: $R_1 = R_2 = H$, $R_3 = R_4 = R_5 = OCH_3$

II: $R_1 = CH_3$, $R_2 = R_3 = R_4 = R_5 = H$

III: $R_1 = CH_3$, $R_2 = H$, $R_3 = R_4 = R_5 = OCH_3$

IV: $R_1 = H$, $R_2 = n\text{-}C_3H_7$, $R_3 = R_4 = R_5 = OCH_3$

V: $R_1 = H$, $R_2 = CH_2$—  , $R_3 = R_4 = R_5 = OCH_3$

VI: $R_1 = H$, $R_2 = CH_2$—CH=CH_2, $R_3 = R_4 = R_5 = OCH_3$