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CLOFIBRATE MICROCAPSULES: III. MECHANISM OF RELEASE

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ABSTRACT

The mechanism of release of clofibrate from microcapsules prepared in a gelatin-sodium sulfate system has been investigated. A theoretical model was developed to explain the release pattern of the drug from the microcapsules. It was shown that the release of the drug followed four stages giving individual zero-order profiles. The overall release from the thin-walled microcapsules showed greater deviation from the zero-order kinetics but followed the square-root of the time plots. Microcapsules

having thicker walls approximated overall zero-order release but deviated from the square-root of time plots. The effect of hardening on the release profiles and possible explanations for the differences observed in the release of clofibrate from the thin-walled and thick-walled microcapsules are discussed.

INTRODUCTION

Clofibrate USP is a liquid hypocholesterolemic agent which possesses an unpleasant odor and taste, and 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 microencapsulation for various pharmaceuticals and chemicals (3-6). Only a few reports of the dissolution characteristics of such microcapsules are available (1,7), possibly because of the difficulty of obtaining discrete, free-flowing, and reproducible microcapsules (8).

A recent investigation reported the microencapsulation of clofibrate by simple coacervation in a gelatin-sodium sulfate system (1). The microcapsules, which were hardened up to 8 hours 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, however, found between the hardening time and $t_{50\%}$ release time.

Another recent investigation reported the effect of wall thickness on the release characteristics of clofibrate from the microcapsules (9). The wall thickness of the microcapsules was calculated by recovering the wall material from the microcapsules and using the relationship between two concentric spheres. The wall thickness of the microcapsules was found to be related to the surface area of the clofibrate droplets being encapsulated. Thinner walled microcapsules gave faster release and showed greater deviation from zero order kinetics but followed the square root of time plots. Microcapsules having thicker walls approximated zero order release but deviated from square root of time plots.

This investigation discusses the mechanism of release of clofibrate from the microcapsules encapsulated by simple coacervation in a gelatin-sodium sulfate system.

EXPERIMENTAL

Materials:

All materials used were of USP or reagent grade and were used without further purification. The gelatin used had the following specifications as provided by the manufacturer:[1]

Type:	Type B-Lime Treated
Bloom:	275

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

Viscosity:	63.9 mps
pH (of solution of gelatin)	5.70
Moisture:	10.5%
Isoionic Point:	4.9

Production of Monodisperse Spheres:

The method used for the production of monodisperse spheres of clofibrate liquid was similar to that reported in the earlier investigations (1,9). In order to attain uniformity of droplet production, all experiments were conducted under identical conditions using same capillary and forcing clofibrate from the capillary under same air pressure.

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

Microencapsulation Procedure:

Simple coacervation was used to achieve microencapsulation (1). All experiments were conducted under identical conditions using same or similar equipment. Coacervation was carried out at 40° using a water bath maintained at $40\pm1^{\circ}$. Gelatin solution was prepared by soaking 10 g of gelatin in 100 ml of distilled water, allowing it to hydrate overnight and then warming to 40° to effect solution. Forty milliliters of clofibrate liquid in the form of monodisperse spheres was then 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 minutes, a 20% w/w solution of sodium sulfate, also at 40°, was added to the mixture. Stirring was continued for 15 more minutes 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 more minutes to complete the gelling process.

Recovery of Microcapsules:

For the purposes of this investigation it was essential to obtain microcapsules in the form of a free-flowing powder. The method of Madan et al. (8,10) was modified slightly as reported in the earlier investigations (1,9) and chilled isopropanol was added to the product to dehydrate and flocculate the coacervated droplets. The microcapsules were allowed to settle, and the mother liquor was decanted. The product was washed with chilled isopropanol, and allowed to air dry at room temperature to yield microcapsules as discrete particles in the form of a free-flowing powder.

Dissolution Studies:

The microcapsules obtained were first hardened by immersing portions of microcapsules in a 10% solution of formaldehyde in isopropanol for 0, 1, 2, 4, and 8 hours. Ten milliliters of the hardening solution was used for each gram of the microcapsules. The hardening solution was later tested to determine if any clofibrate had leaked out during hardening treatment.

The hardened, dried microcapsules were then evaluated for their ability to resist release of the encapsulated drug using the modified flask method described in previous reports (1,9). The method consisted of a 1000 ml, three necked round-bottomed flask, with a 6 cm hole cut in the center to accommodate the entrance of a 5 cm propeller. A 600 ml quantity of the dissolution medium (30% isopropanol solution in water), preheated to 37° was added to the flask immersed in a water bath maintained at 37±0.5°. A three blade, 5 cm diameter, polyethylene propeller was inserted through the center opening of the flask and immersed in the dissolution medium to a depth of 27 mm. The propeller was centered and used at a stirring rate of 50 rpm using a constant speed motor.[2]

Dissolution was followed by examining triplicate samples containing approximately 30 mg of the drug. In each case the microcapsules were placed on the surface of the dissolution medium and allowed to settle. At appropriate time 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. In each case, the cotton plug was added to the dissolution mixture. Concentrations were determined spectrophotometrically at 226 mu after appropriate dilutions were made.

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[2] SYNCHRON constant speed motor Model K12Rc 5-712.

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% isopropanol. The samples were then completely ruptured using a Virtis blender[3] at its maximum speed. In each case, two samples were blended for 10 minutes and complete rupture was insured by blending a third sample for 15 minutes with no observed increase in drug content. Complete collection from the flask assembly was insured by washing with 50 ml of 30% isopropanol in water. Aliquots were then filtered and diluted to an appropriate volume for spectrophotometric assay at 226 mu.

RESULTS AND DISCUSSION

Preparation of Uniform Drug Particles:

Preparation of clofibrate droplets by the capillary drop method resulted in uniform spheres with a mean particle diameter of 190 ± 10 u when the rate of production was restricted to 100 to 120 particles per minute. The resulting particles were essentially monodisperse and ideally suited to encapsulation and dissolution studies.

Preparation and Recovery of Microcapsules:

Some new techniques, other than those previously described (1,8-10) were attempted to obtain the microcapsules in an

[3]Model 45, Virtis Research Equipment, Gardner, New York.

acceptable form, i.e., discrete, free-flowing particles. None of the new techniques were as successful as the one described in earlier investigations. The only successful method of obtaining the microcapsules as discrete particles in a non-aggregated form was the isopropanol-treatment technique (1, 8-10).

Dissolution Studies:

In all cases studied the release of clofibrate from the microcapsules was linear over the major part of the dissolution process (1). The non-linearity observed in the end portions of the graph has already been explained in the previous reports (1) on the basis of a model depicting the various stages of the dissolution process.

In order to study the mechanism of release of clofibrate from the microcapsules, several release mechanisms were examined (1), but none of these models could explain the mechanism of release satisfactorily. For example, neither the square-root of time plots nor the Langenbucher cube-root dissolution plots yielded linear graphs. These graphs were curvelinear at all hardening times studied. It therefore follows that the release of clofibrate from the microcapsules does not follow the conventional classical approaches proposed. This may be because the matrix of clofibrate microcapsules perhaps does not necessarily behave similar to those used for explaining the classical mechanisms reported for the release of medicaments from solid matrices or from uniform non-disintegrating granules.

Re-examination of these plots reveals that what appears to be a curvelinear graph may in fact be composed of segments of various linear portions, each with a differing slope. For example, the square-root of time plot (Fig. 1) shows that each release curve may be drawn as segments of linear portions. The release from the unhardened microcapsules is thus shown as

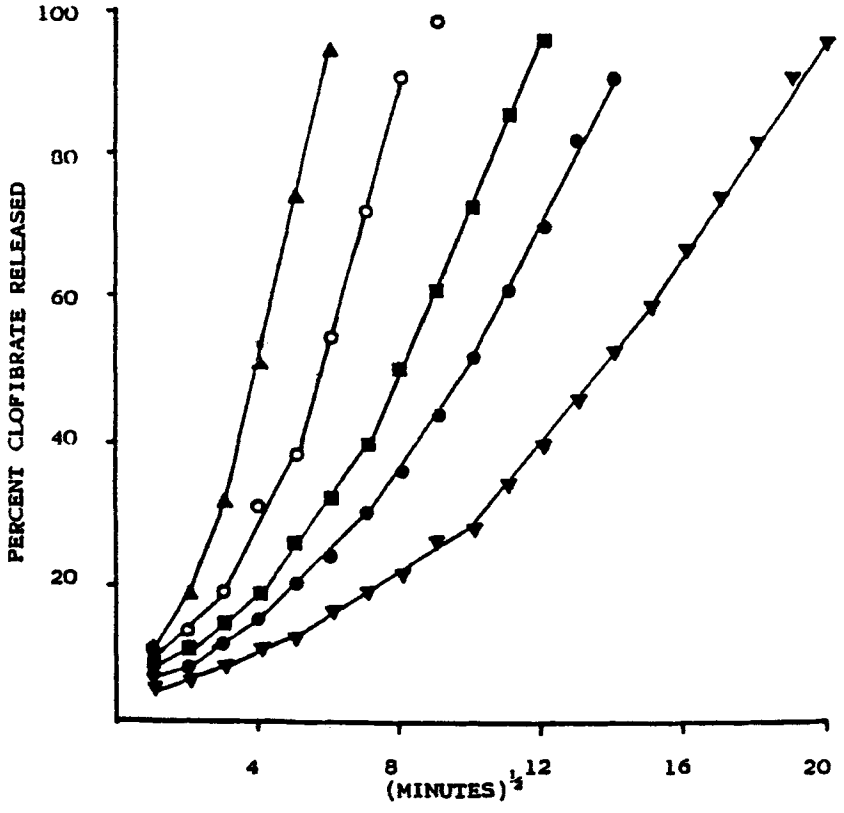

FIGURE 1

SQUARE-ROOT OF TIME PLOTS FOR MICROCAPSULES HARDENED FOR

▲ 0 hr., ○ 1 hr., ■ 2 hr., ● 4 hr., ▼ 8 hr.

comprising of three linear segments whereas the hardened microcapsules exhibit four linear segments. The slopes of the segments in each case show a progressive increase indicating the increase in release rate as a function of dissolution time.

Similarly, the Langenbucher cube-root dissolution plots also appear to be composed of linear segments (Fig. 2). But in this case the release from the unhardened microcapsules

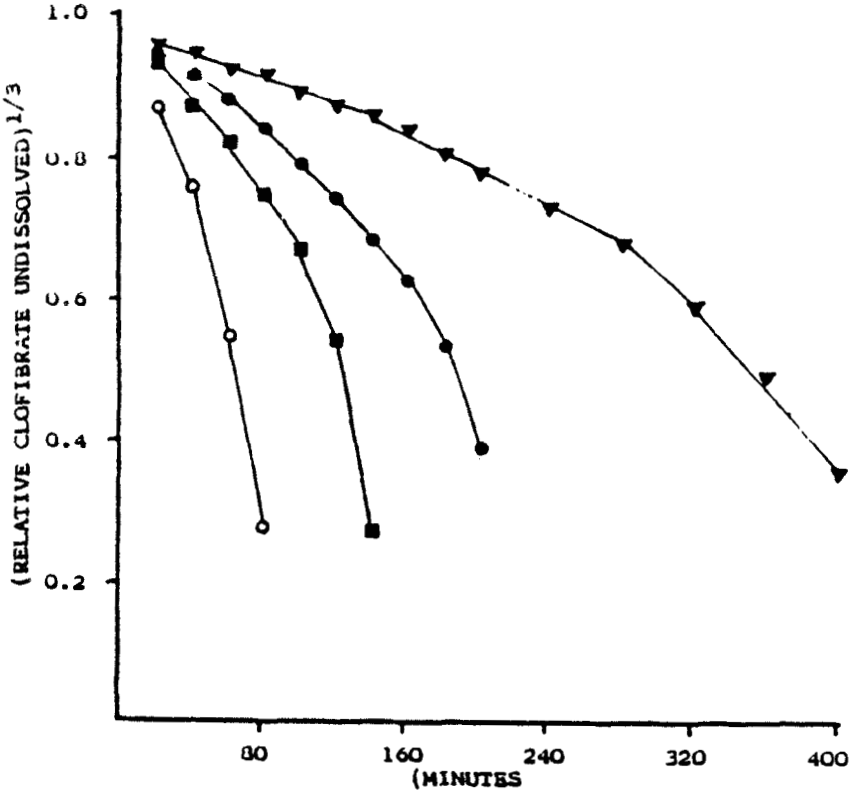

FIGURE 2

CUBE-ROOT DISSOLUTION PLOTS FOR MICROCAPSULES HARDENED FOR ○ 1 hr., ■ 2 hr., ● 4 hr., ▼ 8 hr.:

appears to be comprised of two segments and that from the microcapsules hardened for one hour shows three segments. Here also the number of segments increase as the hardening time is increased. The slopes of the segments in each case decrease with time. This is because in this case the plot follows amount remaining to be released.

It is clear from Figs. 1 and 2 that the matrix of clofibrate microcapsules differs from that proposed in the release of drugs from solid matrices or from uniform, non-disintegrating granules. In the latter cases the matrix is believed to be uniform or homogeneous in the sense that either it behaves as a single layer or each layer of the matrix is similar to the preceding as well as the following layer so far as the release characteristic of the drug is concerned. In the case of clofibrate microcapsules the matrix appears to be composed of various effective layers which seem to exhibit different release characteristics.

This concept can be supported by the following explanation. In preparing clofibrate microcapsules, sodium sulfate is added to the gelatin dispersion to create an insufficiency of water for the total system and thus cause (simple) coacervation. Since commercial gelatins are not homogeneous with respect to molecular weight or molecular weight distribution (11,12), addition of soium sulfate to the gelatin dispersion will cause selective fractionation of gelatin, i.e., the higher molecular weight gelatin molecules undergo coacervation first, followed by the next lower molecular weight fraction. The extent of fractionation will naturally depend upon the degree of hydration produced which is governed by the amount of

sodium sulfate added to the system. The microcapsules formed as a result of simple coacervation process therefore may consist of an essentially multilayered wall of various gelatin fractions. If one added sodium sulfate slowly and in small increments then it may be possible to produce a microcapsule having a shell wall that is composed of separate layers which are distinct from each other. On the other hand, addition of sodium sulfate either rapidly or in a lump-sum quantity may produce a shell wall which may or may not be so distinct because the fractionation in this case may not be well defined in terms of molecular weight or molecular weight distribution of gelatin. This would be true in all coacervation procedures utilizing gelatin or similar heterogeneous wall-forming materials.

Thus, the release pattern of clofibrate from the microcapsules will depend upon the nature of the microcapsule wall. In the present investigation it appears that the microcapsule wall is composed of various layers which possess different release characteristics. In order to check the reproducibility, microcapsules were prepared on several occasions using similar equipment and under identical conditions. The release characteristics were always found to be within narrow limits. Fig. 3 shows the square root of time plots of the release of clofibrate from the microcapsules hardened for 8 hours. Each point in the graph is the average and the vertical lines show the range of dissolution data obtained from every batch.

There is a distinct advantage in converting the curve-linear graph into the segmented linear graph. The slopes

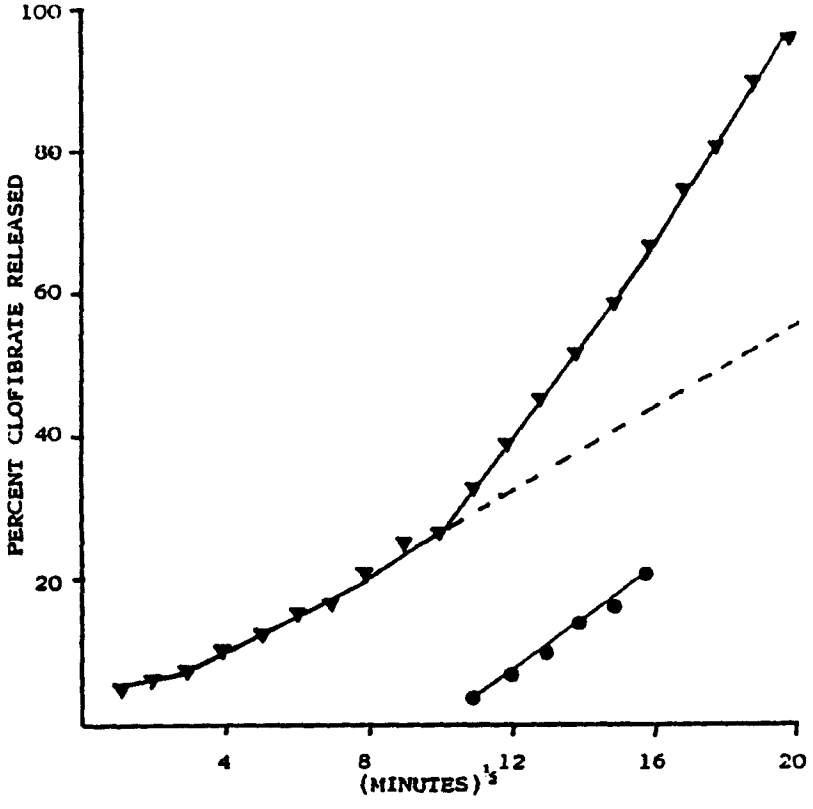

FIGURE 3

SQUARE-ROOT OF TIME PLOT FOR MICROCAPSULES HARDENED FOR 8 hrs.

of the linear segments of such graphs indicate the resistance to mass transfer through each effective layer of the microcapsule wall. These slopes can then be used to explain whether or not the process being examined is operative.

Tables I and II list the slopes of the linear segments calculated from Figs. 1 and 2 respectively. The slopes listed in Table I indicate that the release of clofibrate from each layer is an additive function which is not so

TABLE I

SLOPES OF LINEAR SEGMENTS FROM SQUARE-ROOT OF TIME PLOTS

SEGMENT	SLOPE OF THE LINEAR SEGMENT FOR THE MICROCAPSULES HARDENED FOR				
	0 hr	1 hr	2 hr	4 hr	8 hr
1	8	3	2	2	1
2	13	6	4	3	2
3	21	9	6	5	3
4		17.7	10.8	9.6	6.8

TABLE II

SLOPES OF LINEAR SEGMENTS FROM CUBE-ROOT DISSOLUTION PLOTS

SEGMENT	SLOPE OF THE LINEAR SEGMENT ($X10^{-4}$) FOR THE MICROCAPSULES HARDENED FOR				
	0 hr	1 hr	2 hr	4 hr	8 hr
1	-142.9	- 45.24	-25.56	-16.67	- 9.29
2	-227.3	- 83.33	-34.38	-22.81	-11.76
3		-121.88	-52.50	-26.09	-16.67
4			-69.57	-48.00	-22.86
5				-37.04	-26.32

in the case of slopes listed in Table II. For example the slope of the first segment plus the slope of the second segment yields the slope of the third segment. Similarly, the slope of the second segment plus the slope of the third segment yields the slope of the fourth segment, and so on. Clearly, this is the case for the slopes listed in

Table I (square-root of time plots) but not for those listed in Table II (cube-root plots).

The release of clofibrate from the microcapsules therefore appears to follow the diffusion or teaching model characteristic of the square-root of time plots. This can be further confirmed when one applies the sequential subtraction technique to obtain the slope of the adjacent segment. To do this, a straight line is fitted through the end portion of the graph and a plot is made of the difference between the ordiante values of the original data points and the resultant extrapolated straight line. The subtraction employed for one of the segments of the microcapsules hardened for 8 hours is shown in Fig. 3.

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