International Journal of Pharmaceutics, 16 (1983) 65–77
Elsevier

Preparation and in vitro dissolution tests of egg albumin microcapsules of nitrofurantoin

H.W. Jun and J.W. Lai

Department of Pharmaceutics, College of Pharmacy, University of Georgia, Athens, GA 30602 (U.S.A.)

(Received May 18th, 1982)
(Accepted January 13th, 1983)

Summary

Egg albumin microspheres of nitrofurantoin with and without ethylcellulose coating have been prepared by the methods of heat coagulation and phase separation. The effects of experimental conditions on the properties of beads and drug release rate were studied. In vitro dissolution tests in pH 7.2 phosphate buffer showed that release rate of nitrofurantoin from albumin beads was significantly reduced as compared to the nitrofurantoin powder. Ninety percent of the drug dissolved from the nitrofurantoin powder in about 1 h, while approximately 2 h were needed for half of the drug to be released from the albumin beads. The release of nitrofurantoin from ethylcellulose-coated microcapsules followed an apparent zero-order rate, although the drug was not completely released from the beads during the 8 h dissolution time. The constant rate of drug release from the coated beads suggests that the release of the drug was largely controlled by the permeability of nitrofurantoin through the coating.

Introduction

Many controlled-release dosage forms are designed to release the drug at a predetermined rate, thus maintaining relatively constant drug levels in the plasma for an extended period of time. A number of benefits may result from the use of such formulations. Reduction of frequency of dosing, lowered adverse effects and improved patient compliance have been considered as the primary advantages with the use of controlled-release dosage forms (Rogers et al., 1981).

Frequently, controlled-release formulations have been achieved by dispersing the drug in polymer matrices where the polymer is to act as a rate-controlling barrier

(Kydonieus, 1980). When a lipophilic polymer entraps a core of suspended drug, the core serves as a reservoir from which the drug molecules permeate through the barrier membrane. This system is often called a reservoir system and is thought to be a desirable formulation since the release rate can be maintained constant as long as the source of constant thermodynamic activity is preserved within the system (Baker et al., 1974). Constant release rates have been demonstrated with different versions of the reservoir system such as sandwich-type laminates (Cowsar et al., 1980; Olanoff et al., 1979), implantable microspheres (Abrahams et al., 1975; Shippy et al., 1973), medicated intrauterine devices (Baker et al., 1979). However, a reservoir system of the microcapsule for oral use has rarely been reported in the literature. Recently, albumin microspheres, which have been investigated as a drug carrier in chemotherapy (Ishizaka et al., 1981), were shown to be non-swelling when dispersed in aqueous medium. This non-swelling property is one of the important requirements for maintaining the constant geometric surface area of the reservoir-type controlled-release dosage forms. Beside the non-swelling property, using albumin microspheres as the core material has the advantage of biocompatibility.

The purpose of the present study was: (a) to investigate the feasibility of formulating controlled-release microspheres of a reservoir-type using egg albumin as the core matrix; (b) to coat the albumin microspheres with ethylcellulose using an organic phase separation method; and (c) to investigate the in vitro release rates of nitrofurantoin from the egg albumin microspheres and the ethylcellulose coated microcapsules. Nitrofurantoin was chosen as the model drug from the considerations of its short biological half-life (Cadwallader et al., 1976) and its known gastric irritation (Paul et al., 1967). Better antimicrobial effects by maintaining constant urine levels, and reduction of emesis and other gastrointestinal distress have been cited as the advantages which may result from sustained-release nitrofurantoin preparations (Urquhart, 1981).

Materials and Methods

Materials

The following chemicals were used as received from the suppliers: nitrofurantoin microcrystals (Sigma Chemicals), egg albumin (Fisher Scientific), dextrose monohydrate powder (J.T. Baker), polyethylene (Eastman Chemicals), ethylcellulose (45 cps, ethoxy content 48.4%, Sigma Chemicals), sorbitan trioleate (Atlas Chemicals), and mineral oil U.S.P. (Chevron Oil).

Preparation of albumin microspheres

Albumin microspheres containing nitrofurantoin were prepared by a modification of the methods used by Ishizaka et al. (1981) and Goett et al. (1953). The specified amount of distilled water (Table 1) was placed in a 1000 ml tall beaker. The egg albumin was weighed and dissolved in the distilled water by mild agitation with a glass rod. For the formulations in which albumin was partly replaced by a water-soluble additive, the additive was first dissolved in distilled water before albumin

TABLE 1

COMPOSITION OF EGG ALBUMIN MICROSPHERE FORMULATIONS AND CONTENT OF NITROFURANTOIN ASSAYED

Formulation code	Albumin (g)	Dextrose (g)	Nitrofurantoin (g)	dH_2O (ml)	Nitrofurantoin content % (w/w)
A	24.0	–	8.0	24	24.56 ± 0.10
B	24.0	–	16.0	24	38.44 ± 0.12
C	24.0	12.0	12.0	27	26.08 ± 0.06 26.44 ± 0.17 [a]
D	24.0	6.0	10.0	27	25.61 ± 0.19

[a] From a second batch.

was added. Nitrofurantoin was then dispersed in the albumin solution with gentle agitation until a uniform dispersion was obtained. 250 ml of mineral oil containing 0.6 ml of sorbitan trioleate was then poured into the beaker containing nitrofurantoin suspended in the albumin solution while the mixture was continuously agitated with a 3-blade stirrer. The speed of stirring was then increased and maintained at about 300 rpm for 10 min. A hot water bath was introduced and the temperature of the system was kept at 50°C for 5 min. With continuous stirring, the temperature of the system was raised to 75°C at a speed of 1–2°C per min and held there for 10 min. The heating of the mixture at this temperature resulted in the coagulation of albumin, entrapping nitrofurantoin particles in the albumin matrices. The temperature was then quickly brought down to about 10°C by packing ice into the water bath. After 10 min, 100 ml of cold isopropanol was added to the beaker and the dispersion continuously stirred for another 10 min. The albumin microspheres formed were then filtered out and washed 3 times with 200 ml portions of *n*-hexane. The products obtained were dried under vacuum at ambient temperature for about 12 h.

Encapsulation of albumin microspheres with ethylcellulose

Coating of albumin microspheres with ethylcellulose was obtained by a modification of the organic phase separation method used by John et al. (1979). Compositions of the coating solution used are shown in Table 2. The specified amount of ethylcellulose and polyethylene was weighed and placed in a 250 ml tall beaker. 100 ml of cyclohexane was then added and stirring was initiated. The top of the beaker was covered with a piece of aluminum foil to minimize solvent evaporation. While stirred at about 100 rpm, the system was heated using a water bath to dissolve both ethylcellulose and polyethylene. Temperature was held at about 75°C for 5 min to ascertain complete solution of both polymers. 5 g of albumin microspheres to be coated were then poured into this hot polymer solution. Care was taken not to spill the microspheres onto the wall of the beaker and to the shaft of the stirrer. Any microspheres adhering to these sites were swept into the solution using a spatula. Stirring speed was then increased and kept at 300 rpm for about 20 min. Heating was discontinued and the system allowed to cool gradually while stirring was

TABLE 2

COMPOSITION OF ETHYLCELLULOSE COATING SYSTEM [a] AND CONTENT OF NITROFURANTOIN ASSAYED FROM COATED BEADS

Formulation code	Core formulation [b] code	Ethylcellulose (mg)	Polyethylene (mg)	Nitrofurantoin content % (w/w)
P	A	150	300	24.3 ± 0.09
Q	C	150	300	25.5 ± 0.06
R	C	250	500	25.1 ± 0.18
S	C	300	600	26.0 ± 0.10
T	C	400	800	25.1 ± 0.10
U	D	150	300	25.2 ± 0.13

[a] Per 100 ml of cyclohexane.
[b] 5 g each.

maintained. When the temperature was down to 35°C, 100 ml of *n*-hexane was added and the system was further cooled to 5–10°C by packing ice into the water bath. Stirring was stopped after 20 min of cooling in ice. The liquid was decanted and microcapsules were washed 3 times with 100 ml portions of *n*-hexane. Finally, the coated microcapsules were separated using filter paper (Whatman no. 1, W and R Balston, U.K.) and were dried under vacuum at room temperature for at least 12 h.

Assay of nitrofurantoin in microspheres and microcapsules

In order to determine the percentage of drug-released during the dissolution study, the total drug contents in microspheres and microcapsules were determined using the U.S.P. XX method for the dissolution test of nitrofurantoin tablets.

About 1.5 g of microspheres or microcapsules were weighed and finely triturated using a motar and pestle. Triplicate samples of the triturates equivalent to about 50 mg of nitrofurantoin were accurately weighed and transferred to 500 ml volumetric flasks. 25 ml of dimethylformamide was then added to each flask. The flasks were then secured on a mechanical shaker (Lab-Line Junior Orbit Shaker, Lab-Line Instruments) and swirled at a speed of 300 rpm for 30 min. Thereafter, 350 ml of 0.05 M pH 7.2 phosphate buffer was added to each flask and shaken at the same speed for another 30 min. After dilution with the pH 7.2 phosphate buffer to 500 ml, a 10 ml sample taken from an aliquot which had been filtered through 0.45 μm membrane filter (Millipore, Type HA, 0.45 μm, Millipore) was transferred to a 100 ml volumetric flask and diluted to the volume with the buffer. The absorbance of the resulting solutions was determined at 367 nm using a spectrophotometer (Cary 118 Spectrophotometer, Varian Instruments) with pH 7.2 phosphate buffer as the blank.

The quantitative recovery of nitrofurantoin from the microspheres and microcapsules as shown in Tables 1 and 2 shows that the drug remained stable during the preparation and assay procedures.

Preparation of standard calibration curve

A standard curve was prepared in a similar fashion by dissolving nitrofurantoin powder in dimethylformamide and making subsequent quantitative dilutions with the pH 7.2 phosphate buffer. The amount of nitrofurantoin present in microspheres or microcapsules was calculated using the standard calibration curve.

Dissolution studies

An apparatus similar to the U.S.P. XX paddle method was used for testing the dissolution of nitrofurantoin from the formulations. Instead of the stirring paddle, a 3-blade stainless steel propeller, 5 cm in diameter, was employed. A known amount of nitrofurantoin powder or microsphere formulations was allowed to sink to the bottom of the container before rotation of the propeller was started. Other features of dissolution conditions were the same as specified in the U.S.P. XX monograph on the dissolution test for nitrofurantoin tablets. The temperature of the water bath was maintained at 37 ± 0.5°C. Dissolution medium was 900 ml U.S.P. pH 7.2 phosphate buffer prewarmed to 37°C before starting dissolution test. The motors were equipped with speed-regulation devices (Constant Speed and Torque Control Unit, Model 4425, Cole-Parmer Instruments) and stirring speed maintained at 100 rpm. All the samples tested for dissolution had microspheres in the size range of 350–500 μm. Triplicate samples from each batch containing 100 mg nitrofurantoin were weighed and transferred to prewarmed dissolution medium in each vessel. Two ml samples are taken every 30 min for the first 2 h and hourly until 8 h using a needle and syringe. An equal volume of fresh buffer solution was added to the dissolution media in order to maintain constant volume. The samples were filtered through a 0.45 μm membrane filter (J.T. Baker). After appropriate dilution with pH 7.2 phosphate buffer, the absorbance was measured at 367 nm using the buffer as the blank. The amount of drug released was then calculated using the standard calibration curve.

Results and Discussion

Preparation of egg albumin microspheres

The reports in the literature on the preparation of albumin microspheres were mostly focused on their potential use for parenteral routes (Widder et al., 1979; Kramer, 1974). Therefore, the size of the microspheres prepared was intentionally small (~ 1 μm). Also in these studies, cotton-seed oil was used as the external phase in which an aqueous albumin solution was dispersed for subsequent coagulation. In the present study, mineral oil was chosen as the external phase. By using mineral oil, it was found that microspheres of larger size were produced. The size of the particles also depended upon the concentration of surfactant added in the external phase and the speed of agitation during the formation of the albumin beads. However, particles having an average size of about 400 μm were chosen because they were found most suitable for the subsequent coating with ethylcellulose. During coating, smaller particles tended to aggregate together in such a way that the process became

ineffective. Therefore, the conditions used were cautiously maintained to produce particles in the range of 350–500 μm.

The rate of heating was the most important factor for the preparation of optimal albumin microspheres. Rapid heating seemed to facilitate aggregation of the particles formed. In extreme cases, the entire system became a thick semisolid mass to the point that stirring was impossible. Therefore, it was necessary that heating was carefully controlled. After the initial heating of the system at 50°C for 5 min, the temperature was raised to 75°C at the rate of 1°–2°C per minute and held at this temperature for 10 min. The microspheres thus obtained were found to be spherical and free flowing. In every formulation, about 30–40% of the particles fell in the 350–500 μm range. Table 3 shows the particle size distribution in weight percent of a typical batch of the microsphere formulations.

In an attempt to increase the release rate of nitrofurantoin from the albumin microspheres, dextrose, which was shown to enhance diffusion of the drug in the polymer matrix (Allen et al., 1977) was added to some of the formulations. Albumin beads containing up to 25% (w/w) dextrose were successfully prepared, but the beads containing more than 30% dextrose were too fragile to be properly handled during the process.

Encapsulation of albumin microspheres with ethylcellulose

A number of procedures for the coating of small particles using ethylcellulose are available in the literature (Bakan et al., 1976; Somerville, 1980). Among these, the organic phase separation method of John et al. (1979) was found simple and readily adaptable to the coating of albumin microspheres. This process was particularly useful because the conditions which initiate phase separation (i.e. precipitation of ethylcellulose on the beads) were readily achievable and reproducible. The temperature effect was also constant throughout the coating system, thus making the beads to be more uniformly coated.

After the albumin beads were briefly suspended in the hot ethylcellulose solution of cyclohexane heated at 80°C, the system was allowed to cool slowly. During the

TABLE 3

TYPICAL SIZE DISTRIBUTION OF ALBUMIN BEADS CONTAINING NITROFURANTOIN

Sieve number (passed/retained)	Arithmetic mean size of openings (μm)	Weight retained on smaller sieve (g)	% retained on smaller sieve
-35	500	2.6	9.3
35-45	425	10.8	38.4
45-60	300	8.3	29.5
60-80	213	3.8	13.5
80-100	163	1.4	5.0
100-140	127	1.1	4.0
140-	105	0.1	0.3
		28.1 g	100%

2-h cooling period, ethylcellulose precipitated out from the solution and coated the suspended particles. The polyethylene added to the solution was to further lessen the solubility of ethylcellulose in cyclohexane, thus facilitating the coating of the particles at a higher temperature where the viscosity of the solution was still low enough to allow particles to be more uniformly coated. Particles coated with ethylcellulose without polyethylene tended to stick together during the cooling process. The aggregation of the particles often occurred at places such as the edges of the solvent level, the bottom center of the beaker, and around the stirrer blades. These places were probably areas where the effect of agitation was relatively small. The problem of aggregation was, however, mostly corrected by using larger particles (~ 400 μm), continuous stirring during the cooling as well as the addition of polyethylene in the system.

Another problem was encountered during the drying process of the coated beads. In preliminary studies, after the coating system was cooled to room temperature, the beads were washed with cyclohexane and then isolated by filtration. The coated beads thus obtained tended to aggregate and also adhere to the filter paper during drying under vacuum. Apparently, the ethylcellulose coating was not completely solidified before vacuum drying. A faster hardening of the coating could be achieved by quickly cooling the system in an ice water bath. However, direct cooling of the beads in cyclohexane using an ice-water bath before filtration was not feasible since the freezing point of cyclohexane is only about 6.5°C (Windhalz, 1976) and cooling in ice could freeze the entire system. Therefore 100 ml *n*-hexane which has a freezing point of -95°C was added to the system prior to the cooling in ice. After the cooling, the coated beads were washed several times with *n*-hexane.

In vitro dissolution studies of uncoated microspheres

The dissolution rates of nitrofurantoin from the different egg albumin formulations were measured for a period of 8 h using the pH 7.2 phosphate buffer as a dissolution medium. Fig. 1 shows the dissolution profiles of nitrofurantoin powder and two uncoated albumin microsphere formulations. Both of these albumin formulations contained only the drug and egg albumin as the carrier matrix without dextrose. The two, however, differed with respect to the drug content (24.6% versus 38.5%). It was found that the release rate of the drug from the albumin beads was considerably reduced as compared to the powder. 90% of the drug dissolved from the nitrofurantoin powder in about 1 h, while approximately 2 h was needed for half of the drug to be released from the microspheres. As shown in Fig. 1, the slower dissolution rate of the nitrofurantoin powder after the first hour was probably due to non-sink conditions of the medium. A slower rate of dissolution observed for the beads containing a larger amount of drug, Formulation A as compared to Formulation B might also be caused by the solubility effect of the drug in the dissolution medium. For other dissolution studies, however, the drug content in each formulation was kept at 25% (w/w) in order to minimize the possible effect of drug content on dissolution.

All of the dissolution profiles in the present study represent the average of triplicate determinations on separate occasions. The results were found to be closely

Fig. 1.

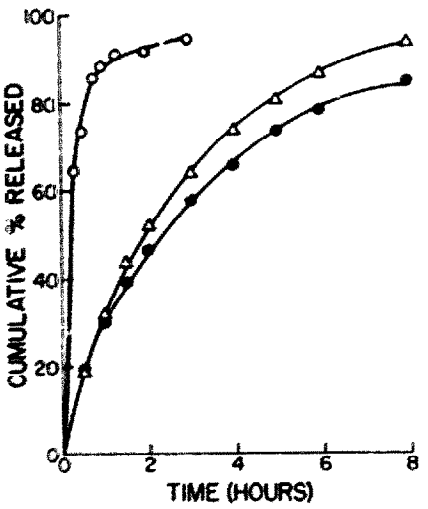

Fig. 2.

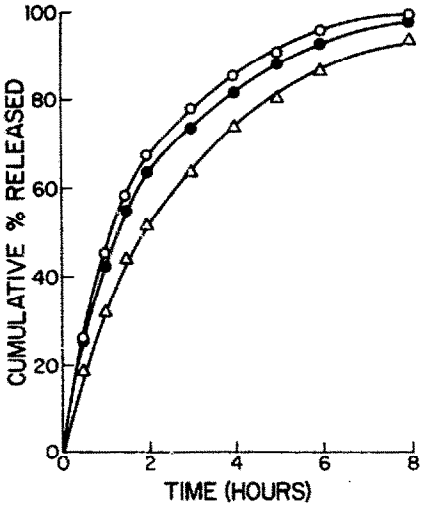

Fig. 1. In vitro dissolution profiles of nitrofurantoin (NFT) in pH 7.2 phosphate buffer: ○, NFT powder; △, formulation A; ●, formulation B.

Fig. 2. In vitro release rates of nitrofurantoin from albumin microspheres: △, formulation A; ○, formulation C; ●, formulation D.

reproducible and the percent standard deviation for each data point was less than 4%.

Encapsulation of albumin microspheres with a barrier membrane was considered necessary to achieve a rate of zero-order release. Therefore, the microspheres were coated with ethylcellulose. In this case the release of the drug from the coated beads should be viewed as a two-step process: the diffusion of the drug through the matrix and subsequent release of the drug through the coating. However, in order to maintain constant release rate, the transfer of the drug from the matrix core toward the coating should be faster than drug release through the coating. Therefore, dextrose was added to some of the formulations to enhance drug diffusion through the albumin matrices. Fig. 2 shows that albumin microspheres containing dextrose exhibited faster drug release than the reference product and the effect of dextrose on dissolution rate seemed to be positively related to the amount of dextrose in the formulation. The presence of hydrophilic dextrose could have aided permeation of water through the albumin matrices, thus enhancing the internal diffusion of nitrofurantoin.

As shown in Figs. 1 and 2, all the formulations tested exhibited dissolution profiles of parabolic shape, suggesting that the microsphere formulations might conform to Higuchi's matrix dissolution model (Higuchi, 1963) which offers a linear correlation between the cumulative amount released and square-root of time. Figs. 3 and 4 are the plots showing the cumulative percent of drug released as a function of the square-root of time for the different formulations. These plots show that a linear correlation only occurs during an earlier portion of the curves. After about 50% of the drug was released, a negative deviation from linearity was observed for these

Fig. 3.

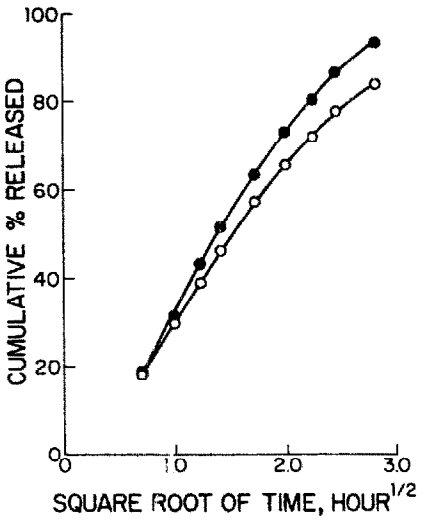

Fig. 4.

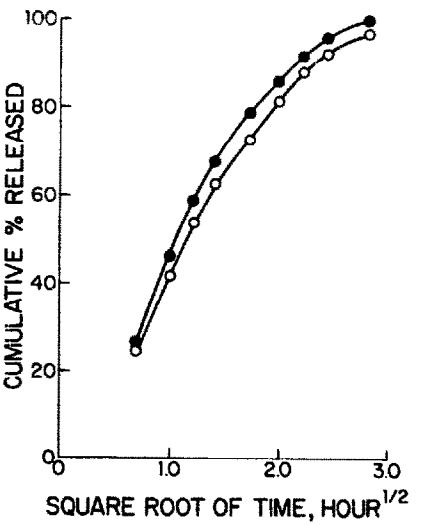

Fig. 3. Release rates of nitrofurantoin from albumin microspheres without dextrose as a function of square-root of time: ○, formulation A; ●, formulation B.

Fig. 4. Release rates of nitrofurantoin from albumin microspheres containing dextrose as a function of square-root of time: ○, formulation C; ●, formulation D.

formulations. After reviewing the equation for Higuchi's model, it was found that the equation was originally derived for a planar matrix system, but not for the spherical formulation. On the other hand, the equation for drug release from a spherical matrix was proposed by Baker and Lonsdale (1974) as:

$$\frac{dM_t}{dt} = \frac{3C_s D}{r_0^2 C_0} \cdot \frac{(1 - M_t/M_\infty)^{1/3}}{1 - (1 - M_t/M_\infty)^{1/3}}$$

which on integration gives:

$$\tfrac{3}{2}\left[1 - (1 - M_t/M_\infty)^{2/3}\right] - M_t/M_\infty = \frac{3DC_s}{r_0^2 C_0} t$$

or

$$\tfrac{3}{2}\left[1 - (1 - F)^{2/3}\right] - F = Kt$$

where M_t is the amount released at time t, M_∞ is the total amount of the drug initially present in the matrix, r_0 is the radius of the bead, D is the diffusivity of the drug in the matrix, C_0 is the total concentration of drug initially present in the matrix, F is the fraction of drug released up to t, M_t/M_∞ and $K = 3DC_s/r_0^2 C_0 \cdot C_s$ is the solubility of the drug in the matrix.

In Table 4 are listed calculated $3/2[1-(1-F)^{2/3}]-F$ values for each formulation tested at each sampling time. Figs. 5 and 6 were obtained by plotting $3/2[1-(1-F)^{2/3}]-F$ as a function of time. On the bottom line of Table 4 are listed the correlation coefficients obtained by linear regression of $3/2[1-(1-F)^{2/3}]-F$ versus t for each formulation. Interestingly, a linear relationship was found for each of the formulations tested. This finding supports usefulness of the dissolution model of Baker and Lonsdale (1974) for testing release rate of nitrofurantoin from the present formulations.

Dissolution studies of ethylcellulose-coated albumin microspheres

In order to maintain a constant concentration gradient across a membrane which is necessary for zero-order release, the core matrix must continually and sufficiently provide the drug to the surface. Such a condition may exist only when the core contains a reservoir of excess drug and the transfer of the drug molecules through the matrix is faster than the release from the coated layer.

Initially 5 g of albumin microspheres of nitrofurantoin containing 15% and 25% dextrose were coated with 150 mg of ethylcellulose. The beads without dextrose was also coated in the same way. Fig. 7 shows the dissolution profiles of the coated microspheres with and without dextrose. The release rates of the drug from these formulations were found to be slower but considerably linear as compared to the uncoated beads. Apparently, the release of drug from the coated beads was mostly controlled by the permeability of nitrofurantoin through the coating. Fig. 2 also shows that coated beads containing 25% dextrose released the drug much faster than the two other formulations. However, the release rate from this preparation was slightly deviated from linearity after about 4 h of dissolution time. This apparent deviation of release rate after about 30–40% drug release from this formulation could result either from a change in the constant thermodynamic activity of the drug

TABLE 4

CALCULATED $3/2[1-(1-F)^{2/3}]-F$ VALUES AT EACH SAMPLING TIME FOR VARIOUS ALBUMIN FORMULATIONS

Time (h)	Formulation code			
	A	B	C	D
0.5	0.006	0.006	0.013	0.012
1	0.020	0.017	0.044	0.037
1.5	0.040	0.031	0.080	0.068
2	0.059	0.046	0.114	0.099
3	0.099	0.077	0.175	0.148
4	0.146	0.116	0.230	0.202
5	0.188	0.141	0.287	0.263
6	0.240	0.174	0.352	0.313
8	0.318	0.226	0.445	0.395
Correlation coefficient	0.999	0.999	0.999	0.998

Fig. 5.

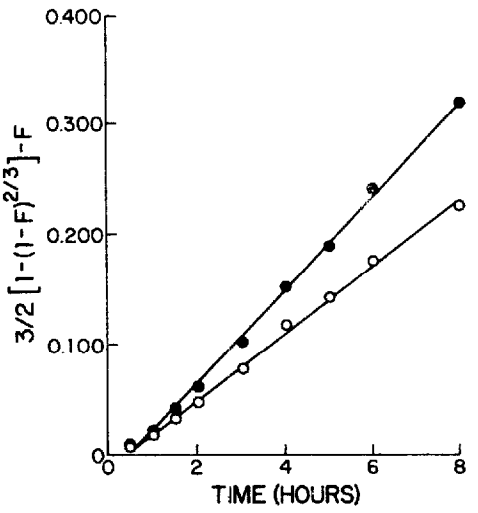

Fig. 6.

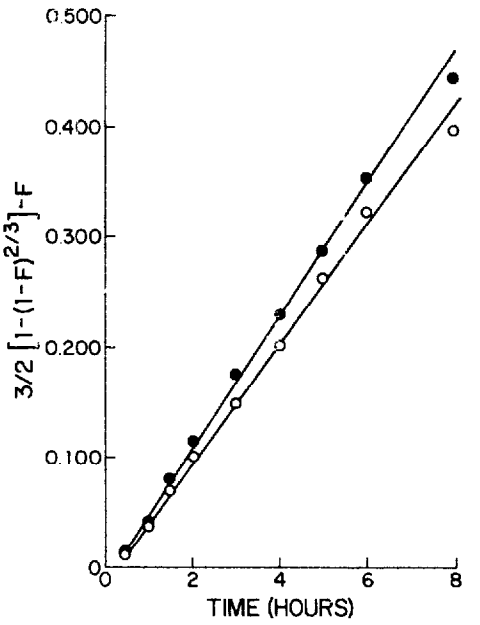

Fig. 5. Relationship between calculated value of $3/2[(1-F)^{2/3}]-F$ and time for albumin microsphere formulations containing no dextrose: ○, formulation A; ●, formulation B.

Fig. 6. Relationship between calculated values of $3/2[1-(1-F)^{2/3}]-F$ and time for albumin microsphere formulations containing dextrose: ○, formulation C; ●, formulation D.

within the matrix or due to the effect of non-sink conditions of the dissolution medium.

The effect of the coating thickness on the release of drug was examined by comparing dissolution rates of the microcapsules containing 25% dextrose which had been coated with different amounts of ethylcellulose. Fig. 8 shows the dissolution data for microspheres coated with 150 mg, 250 mg, 300 mg and 400 mg of ethylcellulose. All of the coated beads exhibited fairly linear release rate during the 8-h dissolution time. Fig. 8 also shows that the rate of release was inversely related to the amount of coating material used.

Fig. 9 was obtained by plotting the slopes of linear portion of the dissolution plots for the formulations of different coatings against the reciprocal amount of ethylcellulose used. It was found that the plot is fully linear with a correlation coefficient of 0.998. This suggests that the microspheres coated with ethylcellulose conform to the reservoir model. The observed constant rate of release of nitrofurantoin from the coated beads suggests that the beads were uniformly coated with ethylcellulose. The lack of intercept in the dissolution plots of these preparations also suggests that the coating remained intact during the dissolution testing. The uniformity and integrity of the coating were also shown by microscopic examination of the beads. A thin and even layer of the film surrounding the individual beads was clearly visible under the microscope (100 ×) both before and after subjecting the beads to dissolution testing. After washing the beads with a

Fig. 7.

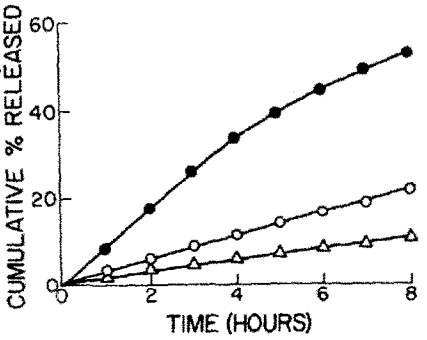

Fig. 8.

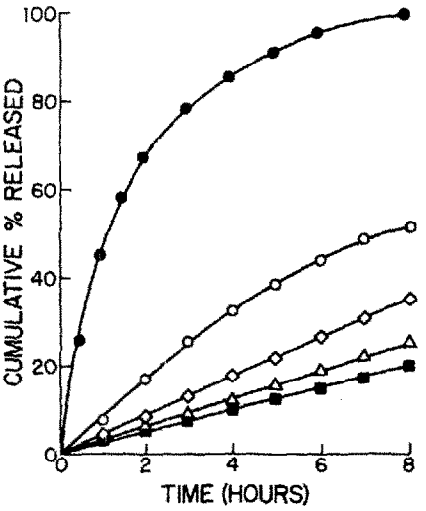

Fig. 7. In vitro release of nitrofurantoin from ethylcellulose-coated albumin beads containing different amount of dextrose: △, formulation P; ○, formulation U; ●, formulation Q.

Fig. 8. In vitro release of nitrofurantoin from coated and uncoated albumin beads: ●, formulation C; ○, formulation Q; ◇, formulation R; △, formulation S; ■, formulation T.

solvent which dissolves ethylcellulose, the film completely disappeared from the surface of the particles.

In conclusion, the egg albumin beads of nitrofurantoin with and without ethylcellulose coating were prepared by the methods of heat coagulation and phase separation. The release of the drug from uncoated beads was significantly delayed as compared to the powder, and complied to the dissolution model for a spherical

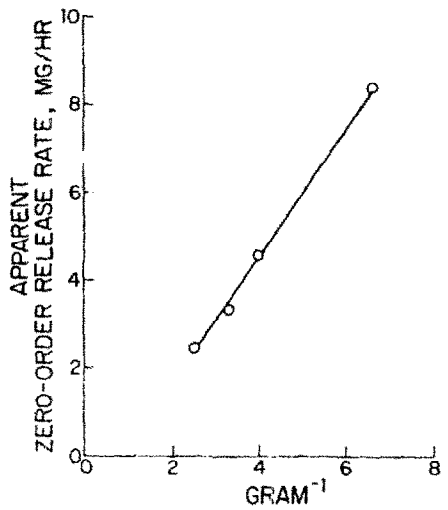

Fig. 9. Relationship between apparent zero-order release rate and the reciprocal amount of ethylcellulose used in coating.

matrix proposed by Baker and Lonsdale. The release rate of the drug from the coated beads was found to be considerably linear, although the drug was not completely released from the beads during the 8-h dissolution time. The constant rate of drug release from the coated beads suggests that the release of the drug was fully controlled by the diffusion of the drug through the coating. Dextrose in the albumin matrix increased the dissolution of nitrofurantoin from the coated beads.

References

Abrahams, R.A. and Ronel, S.H., Biocompatible implants for the sustained zero-order release of narcotic antagonists. J. Biomed. Mater. Res., 9 (1975) 355–366.

Allen, L.V., Yanchick, V.A. and Maness, D.D., Dissolution rates of corticosteroids utilizing sugar glass dispersions. J. Biomed. Mater. Res., 66 (1977) 494–496.

Bakan, J.A. and Anderson, J.L., In Lachman, L. et al. (Eds.), Theory and Practice of Industrial Pharmacy, Lea and Febiger, 1976, pp. 420–438.

Baker, R.W. and Lonsdale, H.K., In Tanquary, A.C. and Lacey, R.E. (Eds.), Controlled Release of Biologically Active Agents, Plenum Press, New York, 1974, pp. 15–71.

Baker, R.W., Tuttle, M.E., Lonsdale, H.K. and Ayres, J.W., Development of an estriol releasing intrauterine device. J. Pharm. Sci., 68 (1979) 20–26.

Cadwallader, D.E. and Jun, H.W., In Florey, K. (Ed.), Analytical Profiles of Drug Substances, Vol. 5, Academic Press, New York, 1976, pp. 345–374.

Cowsar, D.R., Tarwater, O.R. and Tanquary, A.C., In Andrade, J.O. (Ed.), Hydrogels for Medical and Related Applications, American Chemical Society, Washington, DC, 1976, p. 180.

Goett, E.J., Macdonough, Jr., E.J. and Malverne, J.S., U.S. Patent 2, 643, 209, June, 1953.

Higuchi, T., Mechanism of sustained-action medication. J. Pharm. Sci. (1963) 1145–1149.

Ishizaka, T., Endo, K. and Koishi, M., Preparation of egg albumin microcapsules and microspheres. J. Pharm. Sci., 70 (1981) 358–363.

John, M.P., Minatoya, H. and Rosenberg, F.J., Microencapsulation of bitolterol for controlled release and its effect on bronchodilator and heart rate activities in dogs. J. Pharm. Sci., 68 (1979) 475–481.

Kramer, P.A., Albumin microcapsules as vehicles for achieving specificity in drug delivery. J. Pharm. Sci., 63 (1974) 1646–1647.

Kydonieus, A.F., (Ed.), Controlled Release Technologies, Vol. 1, CRC Press, Boca Raton, FL, 1980.

Merck Index, 9th Edn., Windholz, M. (Ed.), Merck & Co., Rahway, NJ, 1976, p. 356.

Olanoff, L., Koinis, T. and Anderson, J.M., Controlled release of tetracycline I. J. Pharm. Sci., 68 (1979) 1147–1150.

Paul, H.E., Hayes, K.J., Paul, M.F. and Borgmann, A.R., Laboratory studies with nitrofurantoin. J. Pharm. Sci., 56 (1967) 882–885.

Rogers, J.D. and Kwan, K.C., In Urquhart, J. (Ed.), Controlled-Release Pharmaceuticals, APhA, Washington, DC, 1981, p. 95.

Shippy, R.L., Hwang, S.T. and Bunge, R.G., Controlled release of testosterone using silicone rubber. J. Biomed. Mater. Res., 7 (1973) 95–10.

Somerville, G.R. and Goodwin, J.T., In Kydonieus, A.F. (Ed.), Controlled Release Technologies, Vol. 2, CRC Press, Boca Raton, FL, 1980, pp. 155–164.

Urquhart, J., In Urquhart, J. (Ed.), Controlled Release Pharmaceuticals, APhA., Washington, DC, 1981, p. 1.

Widder, K., Flouret, G. and Senyei, A., Magnetic microspheres: synthesis of a novel parenteral drug carrier, J. Pharm. Sci., 68 (1979).