*International Journal of Pharmaceutics*, 13 (1983) 23–34
Elsevier Biomedical Press



# Polyacrylamide microbeads, a sustained release drug delivery system

M. El-Samaligy and P. Rohdewald

*Faculty of Pharmacy, Cairo University, Cairo (Egypt) and Institut für Pharmazeutische Chemie der Westfälischen, Wilhelms-Universität, Münster (F.R.G.)*

(Received February 18th, 1982)
(Modified version received June 1st, 1982)
(Accepted June 7th, 1982)

## Summary

Using tetracycline-HCl and theophylline as model drugs, polyacrylamide microbeads were prepared by w/o emulsion polymerization technique. Furthermore, drug-loaded polymer microbeads were prepared in the presence of different concentrations of gelatin, which were further cross-linked for different time intervals. The prepared microbeads were characterized through particle size analysis, electron microscopy, and in vitro dissolution. Relatively spherical free-flowing populations of microbeads were obtained. The presence of gelatin during the polymerization processes led to larger particles proportional to its concentration in the aqueous phase. The dried microbeads showed smooth pored or fissured surfaces. In aqueous media, they attained equilibrium hydration within 10 min, with 73.5% v/v water uptake forming spongy spheres. The products showed slower dissolution rates with higher gelatin concentrations and extended cross-linking.

## Introduction

Polyacrylamide microcapsules with a high degree of cross-linking have been widely used as matrices for covalent immobilization of enzymes and macromolecules (Ekman and Sjöholm, 1975; Johansson and Mosbach, 1974; Lukasheva et al., 1980; Gloger, 1979). The entrapment of proteins in the polymer network has found wide applications in the quantitative investigations of drug plasma protein binding (Kober et al., 1978; Ekman and Sjöholm, 1978). Prepared through micellar polymerization technique, polyacrylamide nanocapsules were used as parenteral ultrafine

0378-5173/83/0000-0000/$03.00 

drug carrier (Kopf et al., 1977; Couvreur et al., 1977; Speiser, 1976), and as antigen adjuvants (Kopf et al., 1976; Birrenbach and Speiser, 1976). Recently, polyacrylamide was also utilized as a base for medical films for angina treatment (Babayan et al., 1979) ophthalmic medication (Khristenko et al., 1979; Noritdinov, 1980), as well as for insulin-containing implants (Davis, 1978). In addition to the use of acrylates as artificial bones, artificial teeth, and as drug coating materials, polyacrylamide is literally stated to be orally safe as long as it is used monomer-free (Lazareva, 1967; Friedentkhal et al., 1977).

In the present study, the possibility of using polyacrylamide microbeads, with or without cross-linked gelatin, for the preparation of sustained release dosage forms was explored.

## Experimental

*Materials and methods*

Tetracycline-HCl, anhydrous theophylline, Arlacel A, gelatin, type II, from Swin skin, Sigma Chemicals, F.R.G. Acrylamide and N,N'-methylene bisacrylamide (Fluka AG, F.R.G.). Other chemicals were of analytical grade; all chemicals were used as provided without further purification.

*Formulation*

Using either tetracycline-HCl or theophylline as model drugs, drug-loaded polyacrylamide (PAA) microbeads, polyacrylamide microbeads containing 0.8 g gelatin (PAA–gelatin), as well as polyacrylamide microbeads containing different concentrations (0.8 or 1.6 g) of gelatin and cross-linked for different time intervals (2 or 8 h) were prepared.

*Preparation of polyacrylamide microbeads*

Two grams of either tetracycline-HCl or theophylline were dissolved or suspended in a solution of 1.5 g of acrylamide and 0.5 g of N,N'-methylene bisacrylamide in 20 ml of 0.005 M sodium phosphate buffer, pH 7.4. After the addition of the catalyst (0.5 of a 50% aqueous solution of ammonium persulfate), the solution was poured into a mixture of 100 ml toluene, 25 ml chloroform and 0.4 g Arlacel A. The mixture was treated for 10 s with a homogenizer, then the w/o emulsion was continuously stirred with a magnetic stirrer (1200 rpm). One ml of the accelerator (N,N,N',N'-tetramethyl ethylenediamine) was then added and dry nitrogen was bubbled through the solution. After complete polymerization (about 30 min), the nitrogen supply was discontinued, and the phases were allowed to separate. The beads were washed with 10 ml of 0.005 M sodium phosphate buffer containing 5% Tween 20, then with 10 ml of absolute alcohol, centrifuged and dried in a dissicator over $P_2O_5$.

*Preparation of gelatin–polyacrylamide microbeads*

The same procedure was followed after dissolving either 0.8 g or 1.6 g gelatin in the aqueous phase together with the drug and monomer. Cross-linking of the

product was done after complete polymerization by addition of 3 ml of 25% glutaraldehyde solution, the system was left in the refrigerator for 2 or 8 h. Phase separation, washing and drying were carried out as stated before.

*Investigation of the microbeads*

*(a) Electron microscopic scanning*

The microbeads were fixed to a metallic plate by spraying the powdered product on a very thin adhesive layer attached to the metallic slide. The samples were coated with carbon-gold layers (about 50 nm thick) under vacuum before they were photomicrographed.

*(b) Particle size analysis*

The dimensions of the microbeads were measured from the scanning electron micrographs; at least 150 particles were randomly measured. Furthermore, dry microbead specimens were measured with an optical microscope, left for 30 min in aqueous dispersion to swell and particle size measurements were done for the completely hydrated microbeads.

*(c) In vitro dissolution*

The in vitro release of the drugs from the microbeads was studied by the beaker method, in both 0.1 N HCl and phosphate buffer of pH 7.2. To avoid the effect of variation of the surface area exposed to the dissolution media, specific bead size ranges of the prepared products were utilized for the dissolution experiments. Tetracycline-HCl microbeads in the mesh size range of 100–400 μm, and theophylline microbeads of 300–600 μm mesh size range were used for dissolution investigations.

To 1000 ml of dissolution medium in a beaker, maintained at 37°C, 500 mg of the medicated microbeads were added. The system was magnetically stirred at a rate of 100 rpm. Aliquot samples were withdrawn at fixed time intervals for analysis. The samples withdrawn were replaced by the same volume of dissolution fluid. Total drug content was measured from the 24 h sample analysis.

Tetracycline-HCl and theophylline were determined spectrophotometrically at 360 nm and 270 nm, respectively. Dissolution results were computed from calibration curves for either of the drugs in the respective dissolution media.

## Results and discussion

Nearly homogeneous microbead populations were harvested in each case of the formulations stated. The scanning electron micrographs in Fig. 1 show in different magnifications of the plain polyacrylamide microbeads (A), as well as microbeads containing tetracycline HCl (B). The plain microbeads were generally spherical with porous smooth surfaces, while the medicated microbeads showed irregularly cracked surfaces due to the embedded drug particles. It is also of interest to note the

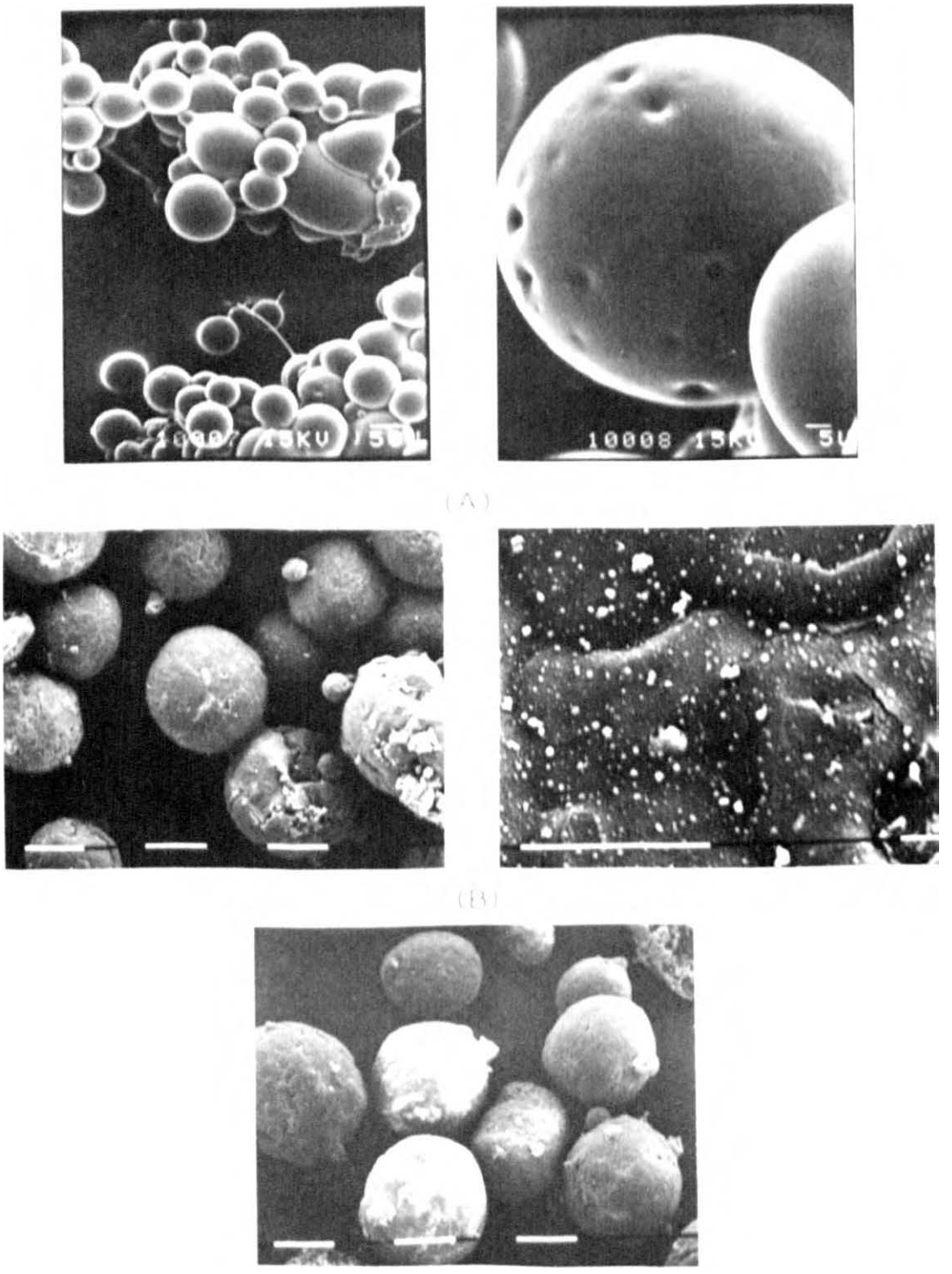


Fig. 1. Scanning electron micrographs of polyacrylamide microbeads. A: plain polyacrylamide microbeads. ×100; ×800. B: tetracycline-HCl–polyacrylamide microbeads. ×150; ×5000. C: tetracycline-HCl–polyacrylamide-cross-linked gelatin microbeads. ×150.

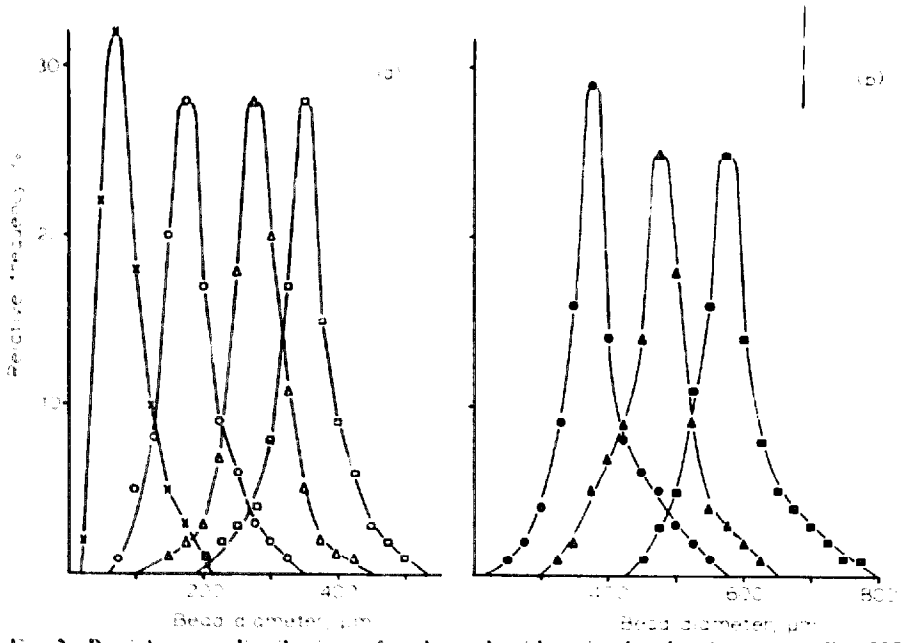

Fig. 2. Particle size distribution of polyacrylamide microbeads. A: tetracycline-HCl–polyacrylamide microbeads. B: theophylline–polyacrylamide microbeads. ×, plain polyacrylamide microbeads; ○, PAA microbeads; △, PAA–c.-l. gelatin microbeads (0.8 g gelatin); (□) PAA–c.-l. gelatin microbeads (1.6 g gelatin).

presence of minute drug particles on the surface of the medicated microbeads.

Fig. 2 shows the size distribution curves of the polyacrylamide microbeads, as well as of those treated with glutaraldehyde. In comparison to the plain polyacrylamide microbeads, the presence of drugs and gelatin increases the particle size and

TABLE 1

AVAILABLE DRUG CONTENTS AND PARTICLE SIZE MEASUREMENTS OF POLYACRYLAMIDE MICROBEADS PREPARED BY DIFFERENT FORMULATIONS

| Drug | Formula | | Drug content ± S.D. (%) | Mean particle size [a] ± S.D. (μm) |
|---|---|---|---|---|
| Tetracycline-HCl | PAA-microb. | | 28.56 ± 1.8 | 182.50 ± 49.0 |
| | PAA-gelatin microb. | | 25.40 ± 2.1 | |
| | | 0.8 g gel, c.-l. 2 h | 20.38 ± 1.6 | 279.00 ± 47.8 |
| | PAA-cross-linked | 0.8 g gel, c.-l. 8 h | 19.72 ± 1.5 | |
| | Gelatin microb. | 1.6 g gel, c.-l. 2 h | 19.24 ± 1.1 | 353.25 ± 56.2 |
| | | 1.6 g gel, c.-l. 8 h | 18.68 ± 1.4 | |
| Theophylline | PAA microb. | | 37.26 ± 2.3 | 385.75 ± 56.3 |
| | PAA-gelatin microb. | | 34.62 ± 1.8 | |
| | | 0.8 g gel, c.-l. 2 h | 31.32 ± 1.7 | 471.75 ± 56.3 |
| | PAA-cross-linked | 0.8 g gel, c.-l. 8 h | 29.86 ± 2.1 | |
| | Gelatin microb. | 1.6 g gel, c.-l. 2 h | 30.41 ± 1.8 | 585.50 ± 64.4 |
| | | 1.6 g gel, c.-l. 8 h | 28.51 ± 1.6 | |

[a] Mean particle diameter of plain polymer microbeads = 82.25 ± 27.5 μm.

particle size distribution of the medicated products. Furthermore, increasing the concentration of gelatin led to large particle diameters and a widening of the bead size distribution (Table 1). Both findings could be expected from emulsions of larger globules due to increased viscosities. On the other hand, cross-linking does not influence particle size or particle size distribution of the microbeads, because cross-linking is carried out on already polymerized microbeads. It was also noticed that polyacrylamide-theophylline microbeads are generally larger than those containing tetracycline-HCl. Such findings may be attributed to the fact that the former was suspended in the aqueous phase while the latter was dissolved before the polymerization process. So, the suspended theophylline particles hindered the rate of globular subdivision, thus leading to relatively larger microbeads. Water influx experiments showed that equilibrated hydration was attained throughout the first 10 min with a water uptake of about 73.5% (±28) of the initial volume of the dried particles. The wet particles under the optical microscope showed a spongy structure but still retained their original form.

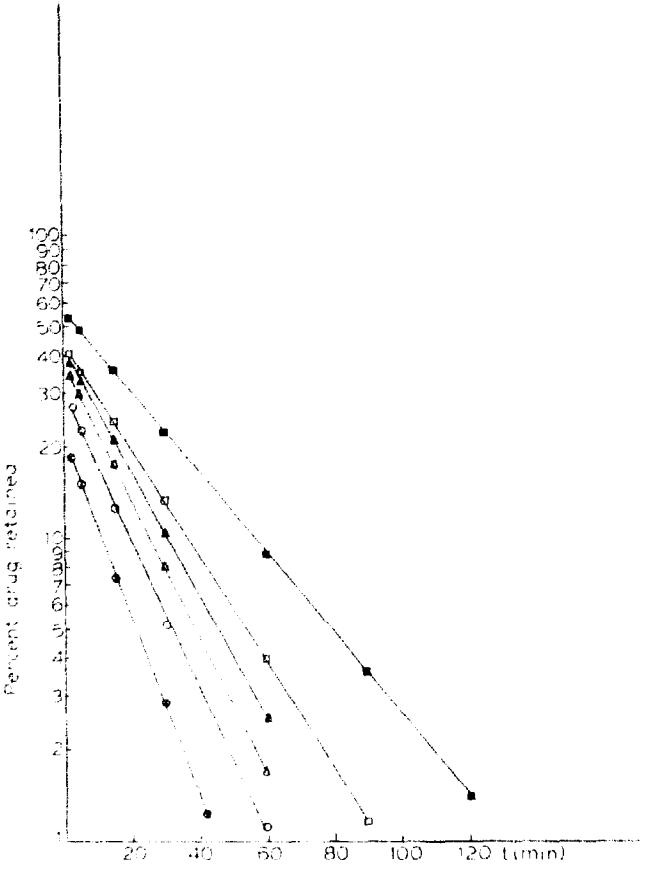


Fig. 3. First-order plot of tetracycline-HCl dissolution in 0.1 N HCl solution at 37°C by the beaker method from its PAA microbeads, ○; PAA-gelatin microbeads, ⊕; PAA–c.-l. gelatin, 0.8 g, microbeads (2 h, c.-l.), △; (8 h, c.-l.), ▲; and PAA–c.-l. gelatin, 1.6 g, microbeads (2 h, c.-l.), □; (8 h, c.-l.), ■.

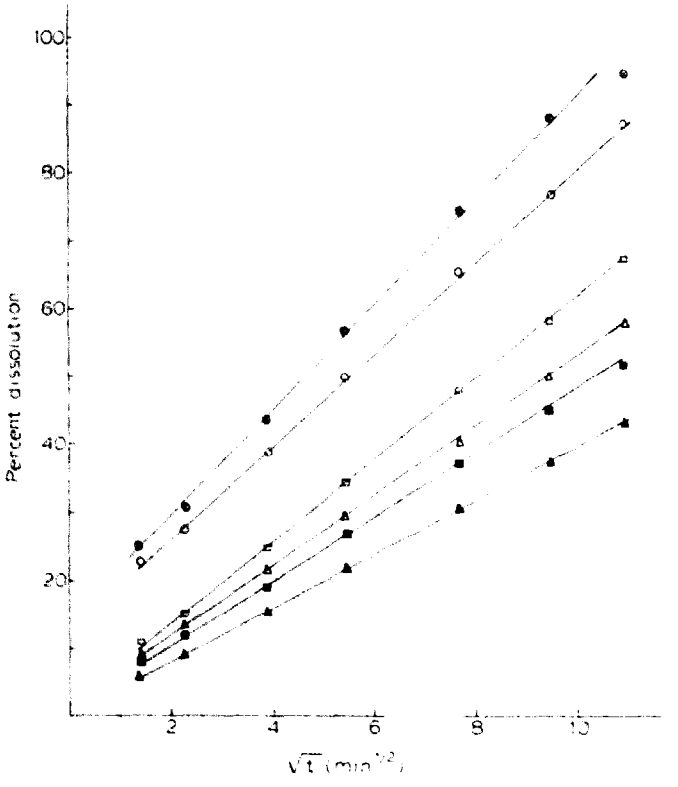


Fig. 4. Square-root of time plot of tetracycline-HCl dissolution from its polyacrylamide microbeads in phosphate buffer solution of pH 7.2 at 37°C by the beaker method. Key as under Fig. 3.

The variation in the total drug content (Table 1) demonstrated whether the drug was dissolved (tetracycline-HCl) or suspended (theophylline) in the aqueous phase before the polymerization process. The drug content in theophylline microbeads was generally about 10% higher than the corresponding tetracycline-HCl products, due to the higher solubility of tetracycline-HCl in either the cross-linking solution or in the washing liquids. The presence of gelatin decreased the microbead drug content as a function of gelatin concentration.

The results of the in vitro drug dissolution studies are shown in Figs. 3–6. In both drugs investigated there was a high drug dissolution during the first 5 min, followed by a relatively delayed release which differed according to the formulation product investigated. This behaviour is characteristic for most monolithic dissolved or suspended devices (Kim et al., 1980), due to the rapid dissolution of the minute drug particles dried on the microbead surface (Fig. 1B). In addition, drug diffusion through pores and cracks, detected on the microbead surface, might contribute to drug mass transfer during the first stages of drug dissolution. It is of interest to note that the presence of non-cross-linked gelatin in the microbead formulation products showed enhancing drug dissolution effects to the polyacrylamide matrices in both acidic and alkaline dissolution media. Such a finding may be explained as being due to the channelling action of the rapidly dissolved gelatin through the polymeric devices. On the other hand, hardening of the products through glutaraldehyde

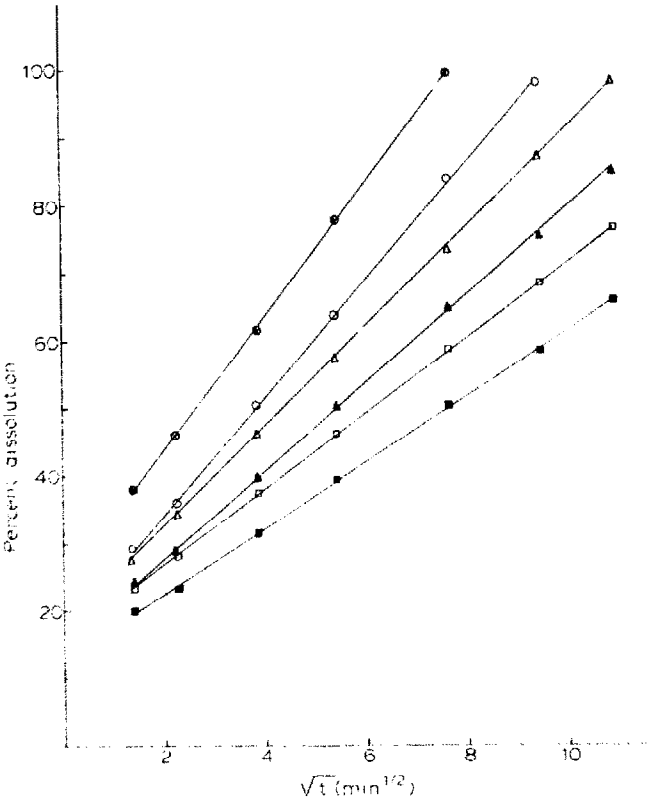


Fig. 5. Square-root of time plot of theophylline dissolution from its polyacrylamide microbeads in 0.1 N HCl solution at 37°C by the beaker method. Key as under Fig. 3.

cross-linking led to the gradual dissolution retardation as functions of dissolution medium, gelatin concentration, as well as hardening time.

It was found that the dissolution of tetracycline-HCl from the different microbead products was more delayed in phosphate buffer than in acidic dissolution medium (Figs. 3 and 4). This can be explained by the high solubility of the drug in acidic media. Comparatively, theophylline behaved in an opposite way, although slight differences could be detected between its dissolution in acidic and phosphate-buffered media.

It was also stated that in acidic medium, the release of either of the two drugs was retarded as a function of gelatin concentration, as well as its cross-linking time. In phosphate buffer, on the other hand, the dissolution pattern increased by increasing the cross-linked gelatin content of the beads. This finding may be explained to be due to the high channelling effect of the solubilized gelatin in basic medium. Furthermore, such a channelling effect was more apparent in the products with shorter cross-linking times, probably due to its rapid solubility in the dissolution medium.

In order to study the mechanism of release of both dissolved (tetracycline-HCl), or suspended (theophylline) drugs from their polymeric matrix microbeads, several release kinetic mechanisms were examined. Regarding tetracycline-HCl dissolution

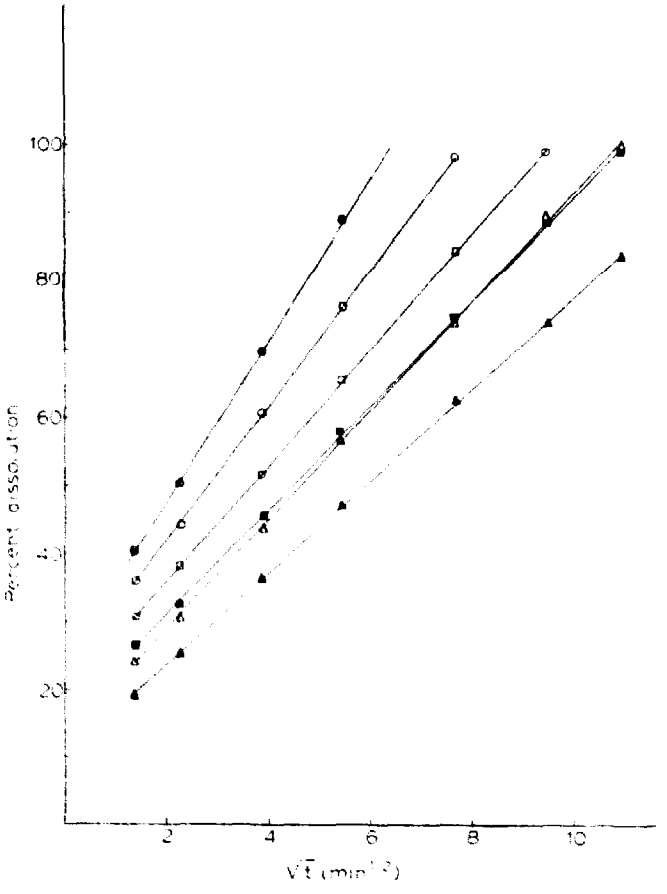


Fig. 6. Square-root of time plot of theophylline dissolution from its polyacrylamide microbeads in phosphate buffer solution of pH 7.2 at 37°C by the beaker method. Key as under Fig. 3.

in 0.1 N HCl, the log percentage retained drug showed a linear relation with time (Fig. 3), hence an apparent first-order dissolution pathway was proved according to the equation:

$$\log Q_t = \log Q_0 - \frac{kt}{2.303}$$

where $Q_t$ is the amount of the drug retained undissolved at time t, $Q_0$ is the total drug content, and k is the first-order dissolution rate constant. Otherwise, theophylline in either of the dissolution media, as well as tetracycline-HCl in phosphate buffer of pH 7.2 showed linear relations between their percentage dissolution and the square-root of time, indicating a typical square-root of time dissolution pattern according to Higuchi equation (1963):

$$Q = \left[ \frac{D\varepsilon}{\tau}(2A - C_s)C_s t \right]^{1/2}$$

TABLE 2

DISSOLUTION MECHANISMS, DISSOLUTION RATE CONSTANTS (DRC[a]), AND TIME OF 50% DISSOLUTION ($t_{50\%}$ min) OF TETRACYCLINE-HCl AND THEOPHYLLINE FROM THEIR POLYACRYLAMIDE MICROBEADS IN DIFFERENT DISSOLUTION MEDIA

| Drug | Dissolution medium | Dissolution mechanism | | PAA Microb. | PAA-gel Microb. | PAA–Cross-linked Gelatin Microb. | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 0.8 g gel. | | 1.6 g gel. | |
| | | | | | | c.-l. 2 h | c.-l. 8 h | c.-l. 2 h | c.-l. 8 h |
| Tetracycline-HCl | 0.1 N HCl | First-order | DRC | 0.0566 | 0.0682 | 0.0527 | 0.0467 | 0.0405 | 0.0311 |
| | | | $t_{50\%}$ | 12.24 | 10.16 | 13.15 | 14.84 | 17.11 | 22.28 |
| | Phosph. Buffer | Square-root of time | DRC | 6.877 | 7.906 | 5.221 | 4.009 | 6.056 | 4.641 |
| | | | $t_{50\%}$ | 52.86 | 40.00 | 91.71 | 155.55 | 68.17 | 116.07 |
| Theophylline | 0.1 N HCl | Square-root of time | DRC | 8.470 | 9.626 | 7.293 | 6.404 | 5.526 | 4.802 |
| | | | $t_{50\%}$ | 34.85 | 26.98 | 47.00 | 60.69 | 81.87 | 108.42 |
| | Phosphate buffer pH 7.2 | Square-root of time | DRC | 9.884 | 12.050 | 7.960 | 6.785 | 8.309 | 7.934 |
| | | | $t_{50\%}$ | 25.59 | 17.22 | 39.46 | 54.31 | 36.21 | 39.71 |

[a] First-order dissolution rate constants are in ($min^{-1}$). Square-root of time dissolution rate constants are in ($\% \ min^{-1/2}$).

where Q is the amount of drug released per unit area at time t; D is the diffusion coefficient of the drug in the dissolution medium; $C_s$ is the solubility of the drug in the dissolution medium; $\varepsilon$ is the porosity of the matrix; $\tau$ is the tortuosity of the matrix; and A is the total amount of the drug present in the matrix. Considering the relatively constant surface area of the drug microbeads exposed to the dissolution medium, the percentage dissolution of the drug can simply be taken as representative of the amount of drug released per specific surface area, and hence as a function of Q. Taking k as the square-root of the time dissolution rate constant and representing the other variables, the equation can be simplified as:

$$\text{Percentage of dissolution} = k \cdot t^{1/2}$$

therefore,

$$k = \frac{\text{percentage of dissolution}}{t^{1/2}} \; \% \cdot \text{min}^{-1/2}$$

Thus, excluding the first drug flush, the dissolution kinetics of both drugs (except tetracycline-HCl in 0.1 N HCl) from such polymeric monolithic microbeads was found to follow the equation proposed by Higuchi (1963) describing the drug release from an insoluble matrix. Although this equation was developed for drug release from insoluble plastic matrices, it has also been applied to drug release from hydrophilic matrices (Lapidus and Lordi, 1968). Table 2 shows the dissolution mechanisms, the dissolution rate constants and the time of 50% dissolution of the model drugs from their polymeric devices in both acidic and alkaline dissolution media. The $t_{50\%}$ values computed showed that, in acidic dissolution medium, the retardation of drug dissolution is directly proportional to gelatin concentration and its cross-linking time. On the other hand, in phosphate buffer medium, increasing the gelatin concentration in the microbeads decreased the sustainment of drug release.

Based on the stated discussion, drug-loaded poly(acrylamide-N,N′-methylene bisacrylamide) microbeads, with a controlled particle size range, could be prepared. Being dense and free-flowable, they display promising characteristics for pharmaceutical solid dosage formulation purposes. In addition the cross-linked gelatin–polyacrylamide microbeads developed have potentials as time-release oral dosage forms.

**Acknowledgements**

M.E.-S. thanks the Alexander von Humboldt Foundation for his research fellowship. We are also very grateful to Prof. Dr. Blaschke and Frau Krug (Institut für Medizinische Physik, Münster) for the scanning electron micrograph preparations.

## References


Babayan, E., Gerasimova, G., Davydov, A., Utyamyshev, R., Khromov, G., Metelitsa, V., Vikhert, A., Savvateev, K., Piotrovskii, V. and Novikova, E., Medicinal film with antianginal activity. Ger. Offen. Patent 2, 913, 752, (1979). Through Chem. Abstr., 92 (1980) 153166h.

Birrenbach, G. and Speiser, P., Polymerized micelles and their use as adjuvants in immunology. J. Pharm. Sci., 65 (1976) 1763–1766.

Couvreur, P., Tulkens, P., Roland, M., Trouet, A. and Speiser, P., Nanocapsules: a new type of lysosomotropic carrier. FEBS Lett., 84 (1977) 323–326.

Davis, B., Control of diabetes with polyacrylamide implants containing insulin. Experientia, 28 (1972) 348–349.

Ekman, B. and Sjöholm, I., Use of macromolecules in microparticles. Nature (London), 257 (1975) 825–826.

Ekman, B. and Sjöholm, I., Improved stability of proteins immobilized in microparticles prepared by modified emulsion polymerization technique. J. Pharm. Sci., 67 (1978) 693–696.

Friedentkhal, M., Josua, L., Siimer, E. and Kostner, A., Public health aspects of the use of enzymes immobilized in polyacrylamide gel in the food industry. Tr. Tallin. Politekh. Inst. 424 (1977) 73–80. Through Chem. Abstr., 89 (1978) 89106x.

Gloger, M., Determination of bound and active proteins, measurement of specific activities — considerations of particle size fractions. DECKEMA — Monogr., 84 (1979) 200–202. Through Chem. Abstr., 92 (1980) 126834t.

Higuchi, T., Mechanism of sustained-action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci., 52 (1963) 1145–1149.

Johansson, A. and Mosbach, K., Acrylic copolymers as matrixes for the immobilization of enzymes. Biochim. Biophys. Acta, 370 (1974) 339–347.

Khristenko, L., Salos, D., Pertsev, I. and Negrashi, A., Study of ophthalmological drug films. Farm. Zh (Kiev) 3 (1979) 51–54. Through Chem. Abstr., 91 (1979) 112398w.

Kim, S., Petersen, R. and Feijen, J., Polymeric drug delivery systems. In E. Ariens (Ed.), Drug Design, Vol. X, Academic Press, 1980, pp. 193–250.

Kober, A., Ekman, B. and Sjöholm, I., Direct and indirect determination of binding constants of drug–protein complexes with microparticles. J. Pharm. Sci., 67 (1978) 107–111.

Kopf, H., Joshi, R., Soliva, M. and Speiser, P., Studium der Mizellpolymerisation in Gegenwart niedermolekularer Arzneistoffe, 1. Herstellung und Isolierung der Nanopartikle, Restmonomerenbestimmung, Physikalisch-Chemische Daten. Pharm. Ind., 38 (1976) 281–284.

Kopf, H., Joshi, R., Soliva, M. and Speiser, P., Studium der Mizellpolymerisation in Gegenwart niedermolekularer Arzneistoffe, 2. Bindungsart von Inkorporierten Niedermolekularen Modellsubstanzen an Nanopartikle auf Polyacrylamid-Basis. Pharm. Ind., 39 (1977) 993–997.

Lapidus, H. and Lordi, M., Drug release from compressed hydrophilic matrices. J. Pharm. Sci., 57 (1968) 1292–1301.

Lazareva, G., Experimental data for a study of polyacrylamide, Brand AMF, used in hydraulic Engineering. Mater. Nauch. Prakt. Konf. Molodykh Gig. Sanit. Vrachei, 11th, (1967) 44–46. Through Chem. Abstr., 72 (1970) 35634y.

Lukasheva, E., Aisina, R., Kazanskaya, N. and Eremeev, N., Properties of α-chymotrypsin covalently incorporated into spherical microgranules made from polyacrylamide. Biokhymiya (Moscow) 45 (3) (1980) 449–454. Through Chem. Abstr., 92 (1980) 210968x.

Nuritdinov, V., Polyacrylamide as a base for medicinal eye films. Vestn. Oftal' mol 5 (1980) 59–61. Through Chem. Abstr., 94 (1981) 52832h.

Speiser, P., Nanocapsules as an ultrafine parenteral drug delivery system. 'Microencapsulation': New Tech. Appl., Proc. Int. Symp.-Microencapsulation, 3rd (1976) 245–255. Through Chem. Abstr., 91 (1979) 163004x.