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Controlled Release of Oral Drugs from Cross-linked Polyvinyl Alcohol Microspheres

B. C. THANOO, M. C. SUNNY AND A. JAYAKRISHNAN

Polymer Chemistry Division, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Satelmond Palace Campus, Trivandrum 695 012, India

Abstract—A new technique for the preparation of cross-linked polyvinyl alcohol (PVA) microspheres containing various drugs is described. An aqueous solution of PVA containing various concentrations of glutaraldehyde was dispersed as droplets in liquid paraffin using a suitable stabilizing agent. Cross-linking of PVA droplets with glutaraldehyde was induced by an acid catalyst (HCl) which was produced by the addition of small quantities of benzoyl chloride into the dispersion medium. Microspheres containing drugs such as aspirin, griseofulvin and nicotinic acid were prepared by carrying out the cross-linking reaction in the presence of such drugs. The drug release studies were carried out in simulated gastric and intestinal fluids without enzymes at 37°C. It was observed that increase in the cross-linking density of the microspheres reduced the drug release rate considerably, suggesting that the release profiles could be controlled by changing the cross-linking density. It was also observed that a higher rate of release was obtained from smaller beads.

Polyvinyl alcohol (PVA) and its copolymers have found applications in the controlled release of pharmaceuticals (Yamauchi et al 1979; Basmadjian & Sefton 1983). Despite their higher water content, PVA hydrogels have been reported to be useful for the release of both hydrophobic and hydrophilic drugs (Zentner et al 1979). PVA-based systems have also been investigated for the controlled release of macromolecules such as polypeptides. Colombo et al (1985) used PVA-based matrices having a thin layer of PVA cross-linked by UV irradiation on the surface for sustained drug delivery. These sytems showed a remarkable zero order release behaviour. PVA has been used in combination with other excipients and drugs to prepare compressed tablets as well as swelling controlled-release systems (Carstensen et al 1981). PVA in the form of cross-linked films have been investigated for the controlled release of oral drugs such as theophylline (Korsmeyer & Peppas 1981). We have recently reported on the preparation and properties of barium sulphate- and methyl iothalamate-loaded PVA microspheres as radiopaque emboli for endovascular embolization (Thanoo et al 1991). This paper reports on the preparation of cross-linked PVA microspheres containing drugs and the release of the drugs into simulated gastric and intestinal fluids in-vitro.

Materials and Methods

Materials

Cold water-soluble PVA (average mol. wt 10 000 Da), glutaraldehyde (25% aqueous solution) and dioctylsulphosuccinate were obtained from Sigma Chemical Company, USA. Benzoyl chloride, liquid paraffin (heavy: viscosity 90 cP at 30°C and light: viscosity 18 cP at 30°C) and nicotinic acid were obtained from SD Fine Chemicals, Bombay, India, and were used as received. Aspirin was prepared from salicylic acid, recrystallized twice (Vogel 1978). Griseofulvin was obtained from IDPL, Baroda, India, and was used after recrystallization from dichloroethane. All the drugs were used in micronized form having particle size less than 63 μm. Solvents such as petroleum ether and methanol were of analytical or equivalent grade.

Correspondence: A. Jayakrishnan, Polymer Chemistry Division, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Satelmond Palace Campus, Trivandrum 695 012, India.

Methods

Preparation of microspheres. A 30% solution of PVA was prepared in double-distilled water. The required amount of the drug and glutaraldehyde solution was mixed with 6·5 g of the PVA solution. The flowable pasty mass was dispersed in 50 mL dispersion medium, which was a mixture of 37·5 mL of liquid paraffin light and 12·5 mL of liquid paraffin heavy containing 0·02 g of dioctylsulphosuccinate in a 100 mL round-bottomed flask. The system was kept stirred at 400 ± 20 rev min^{-1} with a motor-driven half-moon paddle stainless steel stirrer at 30°C. After dispersing for 2 min, 1 mL benzoyl chloride was added slowly over a period of 1 min. The stirring was continued for 30 min and the hardened microspheres were filtered off and washed several times with petroleum ether. After removing traces of petroleum ether under vacuum, the beads were washed twice with a 15% solution of sodium bisulphite and thrice with a limited quantity of cold water to remove the unreacted glutaraldehyde. The presence of unreacted glutaraldehyde, if any, was further checked using HPLC (Waters, Model 440, USA) with a UV detector at 254 nm. Microspheres (100 mg) were extracted with 10 mL of methanol for 24 h. The methanol extract was analysed for the presence of glutaraldehyde using a μ-Bondapak C-18 column with 1:1 methanol/water as the mobile phase at a flow rate of 1 mL min^{-1}. The beads were finally air dried and desiccated for the release studies and scanning electron microscopy (SEM).

Particle size analyses of the microspheres were carried out

by fractionation using standard test sieves (Filterwel, Bombay, India).

Swelling studies of the microspheres having different cross-linking densities were carried out in water, and in simulated biofluids. Drug-loaded microspheres (100 mg) were equilibrated in 50 mL of the fluids at 37°C for 24 h. After equilibration, the fluids were removed using a Pasteur pipette, the microspheres were blotted on filter paper and weighed. From the weights of the swollen beads and the weight of the dry beads, the equilibrium fluid content (EFC) was estimated using the following equation:

$$\text{EFC}(\%) = \frac{\text{Wt. of swollen beads} - \text{Wt. of dry beads}}{\text{Wt. of swollen beads}} \times 100 \quad (1)$$

The kinetics of swelling of the microspheres with two different cross-linking densities, with and without the drug, was examined. Fifty milligram portions of the spheres were kept in 10 mL of the fluids at 37°C. At various time intervals the fluids were removed as before and the weight of the swollen beads determined. Swelling attained at various times was calculated as before.

Release studies. In-vitro release studies of the drugs from the microspheres were carried out at 37°C in simulated gastric and intestinal fluids without enzyme according to the US Pharmacopeia. One hundred milligrams of the microspheres was added to 500 mL of the fluid in a 1 L Erlenmeyer flask. The flask was shaken in a bath incubator shaker at 37°C at 50 cycles min^{-1}. Aliquots of 0·5 mL were withdrawn at specified time intervals and analysed spectrophotometrically at 277 nm for aspirin, 291 for griseofulvin and 261 for nicotinic acid in a UV-Vis spectrophotometer (Shimadzu, UV 240, Japan). To maintain a constant volume, an amount of dissolution medium equal to the volume of the sample withdrawn was added immediately. Values reported are the average of three determinations. The drug-loading efficiency of the microspheres was determined by spectroscopically estimating the drug content in 20 mg of the microspheres by extraction with 200 mL of methanol.

Results and Discussion

Acid-catalysed cross-linking of PVA with glutaraldehyde is an instantaneous reaction leading to the gelling of the polymer. Incorporation of the drug before cross-linking leads to the drug-loaded matrix which has been prepared in the form of sheets and other moulded forms (Korsmeyer & Peppas 1981). A matrix for an oral or injectable sustained-release formulation should preferably be in the form of microparticles or microspheres. The method reported here appears to be eminently suitable for the preparation of PVA microspheres containing various drugs in a simple and efficient manner. The cross-linking of PVA using glutaraldehyde is an acid catalysed reaction. Addition of concentrated HCl or passing HCl vapours through the dispersion did not produce microspheres which were discrete and non-aggregatory in character. Such attempts led to instantaneous gelation of the dispersed phase without the formation of microspheres. Therefore, the cross-linking reaction was attempted using benzoyl chloride as the catalyst. Advantage

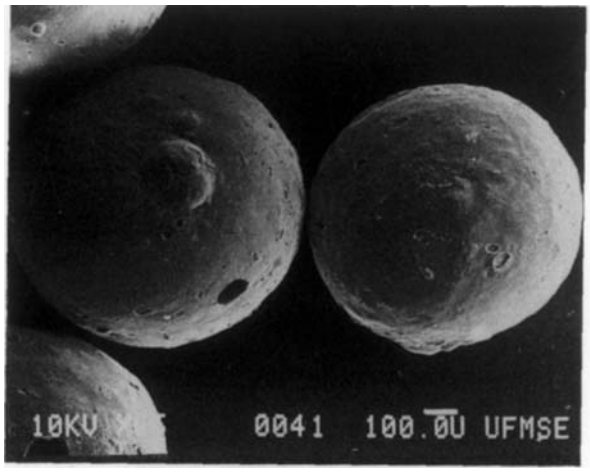

FIG. 1. Scanning electron microscopy of 30% aspirin-loaded PVA microspheres.

was taken of the solubility of benzoyl chloride in the dispersion medium and its instability on contact with the polymer droplets. Liberation of HCl occurred when the acid chloride came in contact with the surface of the aqueous polymer droplets which led to cross-linking of the polymer. The benzoic acid formed as a byproduct of the reaction remained almost completely in the oil medium due to its insolubility in the aqueous phase.

The microspheres prepared had good spherical geometry as evidenced by SEM (Fig. 1). The selection of the dispersion medium is an important factor for obtaining spherical beads of optimum size without aggregation. Our previous experience (Thanoo et al 1991) showed that liquid paraffin with

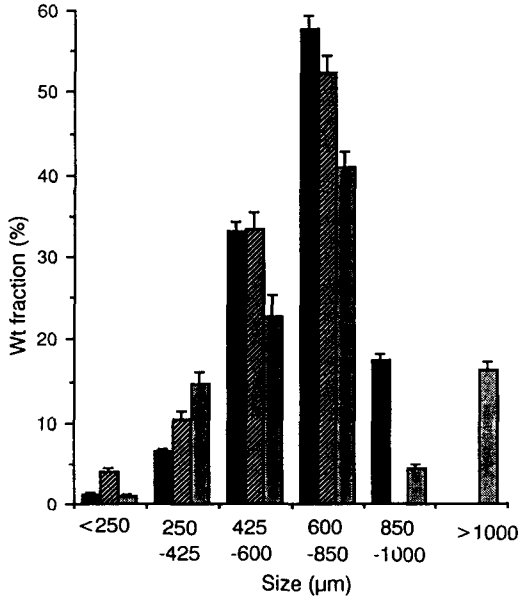

FIG. 2. Particle size distribution of PVA microspheres cross-linked with two different glutaraldehyde concentrations. ■ with 0·8 mL glutaraldehyde (unloaded), ■ with 2·4 mL glutaraldehyde (unloaded) and ▨ with 0·8 mL glutaraldehyde and 60% aspirin.

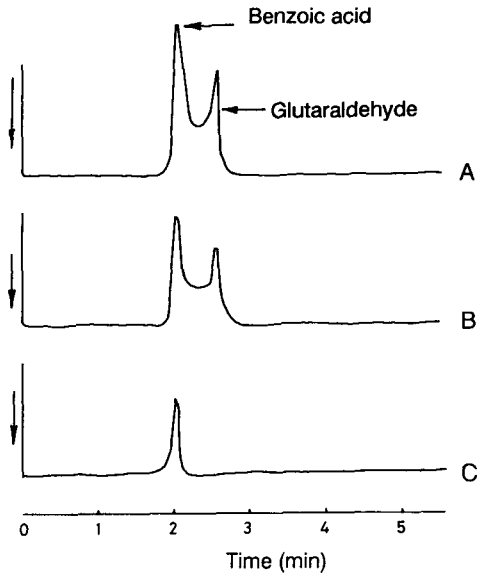

FIG. 3. HPLC of methanol extract of PVA microspheres before and after sodium bisulphite wash. A. Standard mixture of glutaraldehyde and benzoic acid in methanol. B. Microspheres washed only with water. C. Microspheres washed with sodium bisulphite.

dioctylsulphosuccinate as the suspension stabilizer yielded good spherical beads. The mixture of high and low viscosity paraffin oil in the ratio 1:3 by volume was found to give beads of which more than 50% fell within the size range of 0·5–1·0 mm in diameter. The particle size distribution of PVA microspheres cross-linked with two different concentrations of glutaraldehyde is shown in Fig. 2. While increase in the glutaraldehyde concentration by three times results in a slightly larger proportion of smaller particles in the case of unloaded beads, with 60% aspirin-loaded beads, a slightly larger proportion of bigger beads were obtained even at relatively low glutaraldehyde concentration. The decrease in size at higher glutaraldehyde concentrations may be explained by increased cross-linking density resulting in shrinkage of the particles. In the case of aspirin-loaded particles, the presence of a small portion of beads of more than 1·0 mm in diameter could be due to a viscosity effect in the dispersed phase owing to the presence of the drug. High viscosity liquid paraffin alone gave small beads (more than 50% below 300 μm) whereas low viscosity liquid paraffin alone led to the agglomeration of the particles.

In view of the fact that the cross-linking was induced on the surface of the polymer droplets using benzoyl chloride, it was felt necessary to determine whether any residual glutaraldehyde was present unreacted in the beads. Fig. 3 shows the HPLC traces of the methanol extract of the microspheres. Microspheres washed using only cold water were found to contain trace amounts of glutaraldehyde. However, washing with a 15% solution of sodium bisulphite followed by water removed the glutaraldehyde completely. Similar results were obtained when the microspheres were washed with a 1% solution of glycine.

The incorporation efficiency of the three drugs investigated is shown in Table 1. In comparison with aspirin, the incorporations efficiency of the other two drugs is found to be low. In the case of nicotinic acid, this can be attributed to the higher aqueous solubility of the drug. During the cross-linking of PVA droplets, water is exuded from the droplets along with the drug thereby reducing the amount of drug entrapped in the beads. The poor loading of griseofulvin is

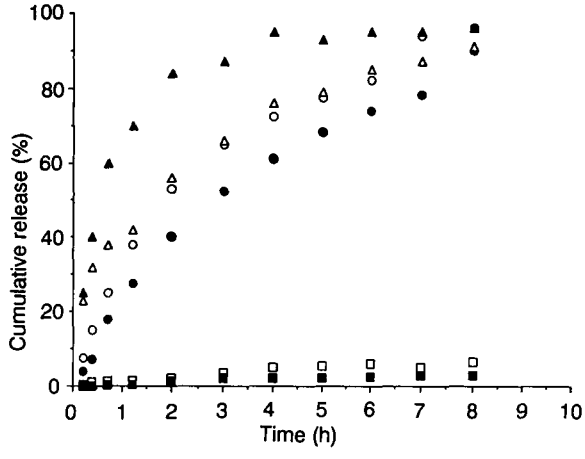

FIG. 4. The release profile of drugs from microspheres in simulated biofluids. Microspheres (710–850 μm) were cross-linked using 0·8 mL of 25% glutaraldehyde solution. Values are the average of three determinations. Standard deviations (not shown on the curves) were within 5–12%. Griseofulvin in intestinal (■) and gastric (□) fluid. Aspirin in intestinal (○) and gastric (●) fluid. Nicotinic acid in intestinal (△) and gastric (▲) fluid.

Table 1. Incorporation efficiency of drugs in PVA microspheres.

Drug	PVA* (g)	Glutaraldehyde** (g)	Drug (g)	Drug content (%) (theoretical)	Drug content (%) (actual)	Incorporation efficiency (%)
Aspirin	1·5	0·2	0·73	30·0	28·0	93·33
	1·5	0·1	1·60	50·0	42·0	84·00
	1·5	0·2	1·70	50·0	42·4	84·76
	1·5	0·3	1·80	50·0	41·5	83·00
	1·5	0·4	1·90	50·0	41·8	83·66
	1·5	0·6	2·10	50·0	42·0	84·00
	1·5	0·2	2·55	60·0	47·1	78·54
	1·5	0·2	3·97	70·0	46·6	66·57
Nicotinic acid	1·5	0·2	1·70	50·0	28·5	57·00
Griseofulvin	1·5	0·2	1·70	50·0	20·4	40·80

*Actual PVA content in 6·5 g of 20% solution. **Actual glutaraldehyde content in 25% solution.

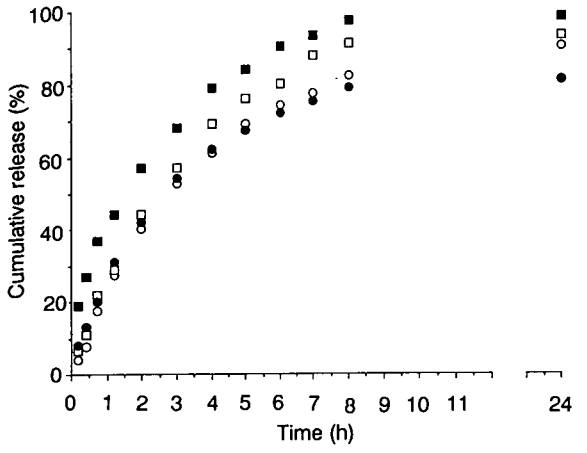

FIG. 5. The effect of aspirin content in microspheres on the release profile in gastric fluid. ● 30%, ○ 50%, □ 60% and ■ 70%. Microspheres (710–850 μm) were cross-linked using 0·8 mL 25% glutaraldehyde solution. Average of three determinations with standard deviations within 5–12%.

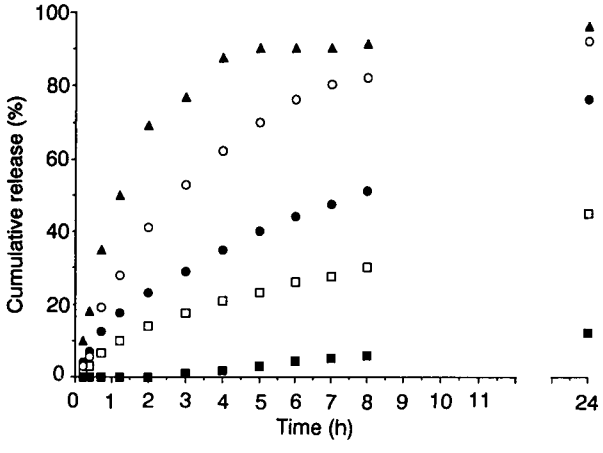

FIG. 6. Effect of cross-linking density on the controlled release of aspirin in gastric fluid. ▲ 0·4 mL, ○ 0·8 mL, ● 1·2 mL, □ 1·6 mL, ■ 2·4 mL 25% glutaraldehyde solution. Theoretical aspirin content is 50%. Average of three determinations with standard deviations within 5–12%.

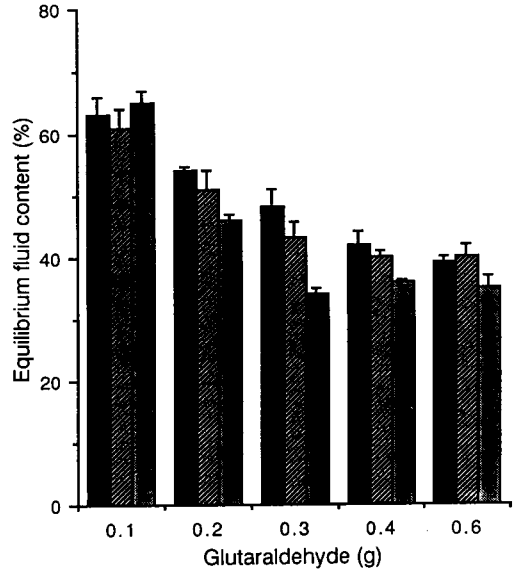

FIG. 7. Equilibrium fluid content of microspheres cross-linked using various concentrations of glutaraldehyde. ■ Water, ▩ gastric fluid, ▨ intestinal fluid.

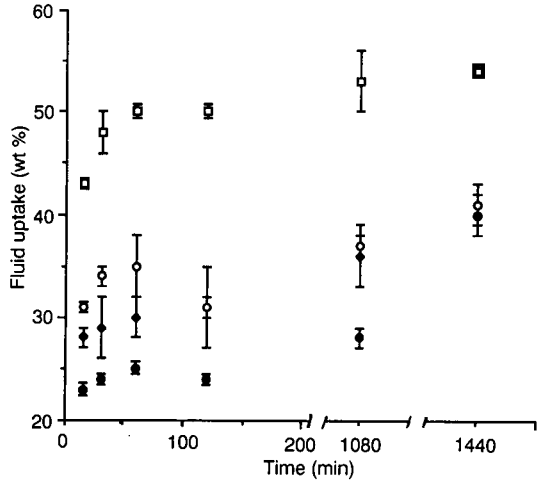

FIG. 8. Kinetics of swelling in gastric fluid of microspheres cross-linked using three different concentrations of glutaraldehyde. ■ 0·8 mL, ○ 1·6 mL, ● 2·4 mL, ◆ 60% aspirin-loaded microspheres cross-linked with 0·8 mL 25% glutaraldehyde.

possibly due to an opposite effect, its hydrophobicity favouring its migration into the paraffin medium as evidenced by the fact that considerable amounts of the drug remained in the dispersion medium as powder after cross-linking of the polymer droplets. Aspirin in different amounts (30–70%) was incorporated in the microspheres. The incorporation efficiency is found to be very good in the case of aspirin, presumably due to the optimum polarity of the drug. It is also seen that the incorporation efficiency is higher at lower drug loadings and is not affected by the changes in the cross-linking density of the microspheres.

Fig. 4 shows the release profiles of the three drugs in simulated gastric and intestinal fluids. The release of nicotinic acid was found to be rapid in both fluids due to its enhanced aqueous solubility. Griseofulvin, the least soluble drug, is released slowly; less than 6% of the drug is released in 8 h. Aspirin showed moderate release rate and the rate is slightly faster in intestinal fluid than in gastric fluid. Aspirin is ionized at the alkaline pH of intestinal fluid (pH 7·5) facilitating increased solubility and a faster release rate.

The amount of drug initially present in the microspheres did not influence the rate of release to any significant extent. The release curves obtained with 30 and 50% aspirin-loaded beads in gastric fluid were superimposable, indicating very little effect of drug loading on the release profile (Fig. 5).

The rate of release of the drugs was found to be considerably influenced by the cross-linking density. Microspheres were prepared by using various concentrations of glutaraldehyde for cross-linking. Fig. 6 shows the effect of cross-linking density on the release of aspirin from microspheres. Almost 87% of the drug was released after 4 h from the microspheres cross-linked using 0·4 mL glutaraldehyde

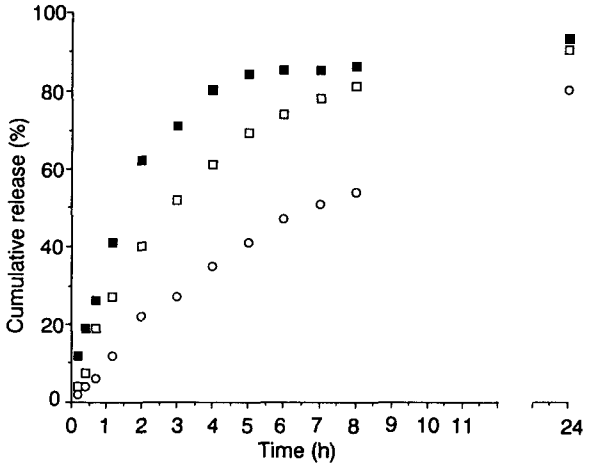

FIG. 9. Effect of microsphere size on the release of aspirin from 50%, loaded microspheres in gastric fluid. ■ 300–425 μm, □ 710–850 μm, ○ 1200–1500 μm. Microspheres were cross-linked using 0·8 mL 25% glutaraldehyde.

solution whereas only 2% was released after 4 h from microspheres cross-linked using 2·4 mL glutaraldehyde under identical conditions. Such wide variation in the release rate demonstrates that a desired degree of drug release may be achieved by changing the cross-linking density of the microspheres. More glutaraldehyde gave rise to a more cross-linked gel which retarded the diffusion of the drug into the medium. More cross-linking also resulted in a less hydrophilic, less swelling gel since most of the hydroxyl groups in the PVA would be utilized for the cross-linking reaction by acetal formation (Toyoshima 1973). This was further demonstrated by determining the equilibrium swelling of the beads in various fluids. Fig. 7 shows the equilibrium fluid content of the microspheres cross-linked with various concentrations of glutaraldehyde in three different media at 37°C. The equilibrium uptake of the three fluids decreased as the concentration glutaraldehyde is increased, but reaches a plateau at higher glutaraldehyde concentrations. Although with 1·6 and 2·4 mL glutaraldehyde in the reaction (equivalent to 0·4 and 0·6 g of glutaraldehyde), the equilibrium uptake of the three fluids was virtually the same, the release of aspirin from spheres cross-linked using 2·4 mL glutaraldehyde was slower compared with the release from beads cross-linked using 1·6 mL glutaraldehyde. This can be attributed to the differences in the kinetics of swelling observed for the microspheres with different cross-linking densities. While the equilibrium is attained with virtually the same fluid uptake at both cross-linking densities, the kinetics of swelling as shown in Fig. 8 demonstrated that for the first few hours, the fluid uptake at higher cross-linking density was relatively less. This may also have influence in controlling the release of entrapped drug.

The particle size of the microspheres also greatly affects the release pattern of the drug. The amount of aspirin released at various time intervals in gastric fluid from microspheres of different sizes is shown in Fig. 9. Smaller beads, due to increased area of contact with the dissolution medium, release drug faster compared with the bigger beads.

In conclusion, it appears that PVA microspheres cross-linked using glutaraldehyde are promising for the controlled release of oral drugs, particularly for drugs such as aspirin. As the cross-linking density of the microsphere has been found to greatly influence the drug release profile, the method possibly offers a unique opportunity to control the release of drugs at any desired rate by varying the cross-linking density of the spheres.

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