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Oral Sustained-release Drug Delivery Systems using Polycarbonate Microspheres Capable of Floating on the Gastric Fluid

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—Polycarbonate microspheres loaded with aspirin, griseofulvin and *p*-nitroaniline were prepared by a solvent evaporation technique. High drug loading (> 50%) was achieved by this process. Drug-loaded microspheres were found to float on simulated gastric fluid and intestinal fluid. Drug-release studies were carried out in these fluids at 37°C. Increasing the drug to polymer ratio in the microspheres increased both their mean particle size and the release rate of the drugs. It was concluded that sustained delivery of drugs could be effected using this matrix.

The most convenient and commonly employed route of drug delivery has historically been by oral ingestion. An oral sustained release formulation is subjected to frequently changing environments in the gastrointestinal tract. During its transit it passes from the strongly acidic gastric part to the weakly alkaline intestinal part of the digestive system. Also, as the stomach emptying time varies from patient to patient, there is variation in the amount of drug absorbed. These drawbacks put constraints on the design of an oral sustained release system. Various attempts have been made to prolong the retention of the dosage form in the stomach. One such method used empty globular shells with a lower density than that of gastrointestinal fluid, enabling the shell to float on the fluid and prolonging the residence time in the stomach. Such type of systems have been tried with polymers such as polystyrene, but incorporation of the drug in these systems is difficult (Watanabe et al 1975). Another type of delivery system contains multilayered polymer films having drug in the matrix along with sealed air pockets (Mitra 1984). Yet another type of formulation is the drug hydrocolloid mixture (Sheth & Tossounian 1979; Bolton et al 1989) which on contact with gastrointestinal fluid will swell to form a soft gelatinous mass on the surface. This enlarged particle has a density less than one and floats on gastrointestinal fluid. Gel-type matrices incorporating light oil along with drug were also of recent interest due to their floating characteristics (Bolton & Desai 1989).

Aspirin is the most widely used drug in the treatment and control of rheumatoid arthritis. However, side-effects such as gastrointestinal irritation and gastric bleeding have been reported at high doses or due to particles lodging in the mucosa (Hoon 1974). Low dosages for prolonged periods may thus be advisable to reduce the gastrointestinal irritation (Levy et al 1960). Controlled release systems which can float on the gastrointestinal fluid are reported to increase the residence time in the stomach thereby providing therapeutic dosages for prolonged periods. In this paper we report a method for preparing polycarbonate microspheres containing high drug payloads, which can float on gastric and intestinal fluids for delivering drugs such as aspirin and griseofulvin.

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.

Materials and Methods

Materials

Bisphenol A-carbon dioxide based polycarbonate resin, and polyvinyl alcohol (PVA, mol. wt 125 kDa) were purchased from BDH Chemicals, Poole, UK. Aspirin was prepared from salicylic acid and recrystallized twice before use (Vogel 1978). *p*-Nitroaniline was prepared by the nitration of aniline and was purified by recrystallization (Vogel 1978). Griseofulvin was obtained from IDPL, Baroda, India, and was used as received. Simulated gastric and intestinal fluids (without enzymes) were prepared according to the US Pharmacopeia. All other reagents used were of analytical or equivalent grade.

Methods

Preparation and characterization of hollow polycarbonate microspheres. Hollow polycarbonate microspheres were prepared by a solvent evaporation process from a dichloromethane solution of the polymer from an aqueous dispersion medium containing NaCl, PVA and methanol. Of the various polymeric stabilizers examined (polyacrylamide, polyvinyl pyrrolidone, polymethacrylic acid and PVA) for stabilizing the polycarbonate solution droplets, PVA gave the best stabilization effect. The presence of at least 10% methanol was necessary to prevent the PVA from precipitating into the NaCl solution. Incorporation of NaCl to the extent of 20% in the aqueous phase was found to be necessary to prevent the dispersed phase from settling due to the high density of dichloromethane, thereby making the dispersion and stabilization of the droplets by stirring difficult. The preparation of the drug-loaded microspheres was carried out as follows. Typically, 50 mL of a 20% solution NaCl containing 0·04% PVA and 10% methanol was placed in a 100 mL beaker. A 25% solution of

polycarbonate was made in dichloromethane by dissolving the polymer in the solvent overnight by continuous stirring using a magnetic pellet in a stoppered Erlenmeyer flask. While the solution in the beaker was kept stirred using a stainless steel half-moon paddle stirrer at 350 (±10%) rev min^{-1}, 5 mL of the polycarbonate solution was mixed with the required amount of the micronized drug (< 63 μm, 240 mesh) and the flowable pasty mass was introduced into the dispersion medium and the stirring continued at 30°C until all the solvent had evaporated (3–4 h). The microspheres were filtered, washed several times with cold water and dried in an air oven at 60°C to constant weight.

Scanning electron microscopy (SEM) was on a Jeol JSM-35C instrument. Microspheres were fixed on aluminium stubs using a double-sided tape, sputter-coated with gold and examined in the microscope. Size distribution of the microspheres was determined by sieving the particles in standard test sieves (Filterwel, Bombay, India).

Determination of in-vitro drug release. In-vitro release studies of aspirin, griseofulvin and *p*-nitroaniline from the microspheres were carried out at 37°C using simulated gastric and intestinal fluids. Into a 1000 mL Erlenmeyer flask containing 500 mL simulated fluid was introduced 100 mg of the drug-loaded microspheres. The flask was shaken in a bath incubator shaker at 37°C and 3 mL samples were withdrawn at specific time intervals. The drugs were assayed spectrophotometrically at 277 nm for aspirin, 377 for *p*-nitroaniline and 291 for griseofulvin. To maintain a constant volume, an amount of dissolution medium equal to the volume of the aliquot withdrawn was added immediately after removal of each sample. Values reported are the average of three determinations. The solubilities of each drug in the simulated fluids were also determined by spectrophotometry.

Results

The microspheres obtained were spherical and hollow as evidenced by SEM. Fig. 1 A, shows the photomicrograph of the unloaded spheres; B, spheres loaded with 50% aspirin; C, the surface morphology of the drug-loaded spheres at higher magnification showing the drug crystals on the surface. Fig. 1D, is the SEM of a thin cross-section of the microsphere demonstrating its hollow nature. Table 1 shows the drug entrapment efficiency of the microspheres. The drug incorporation efficiency in the case of aspirin was found to be high if the initial loadings were high. Thus, 60% initial loading resulted in microspheres with 52% of the drug, whereas with

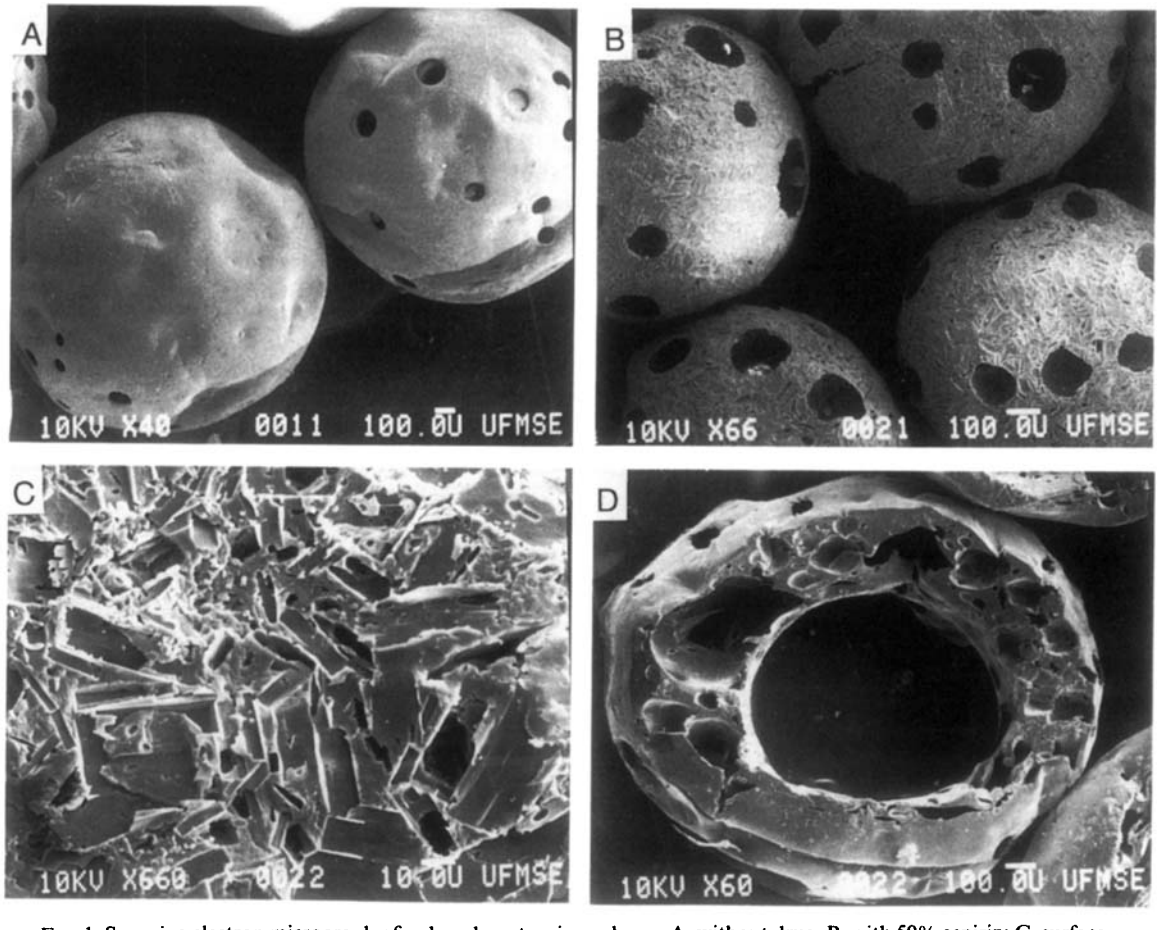

FIG. 1. Scanning electron micrograph of polycarbonate microspheres. A, without drug; B, with 50% aspirin; C, surface morphology of 50% aspirin-loaded microspheres; D, cross-section demonstrating the hollow nature of the spheres.

Table 1. Entrapment efficiency of aspirin and *p*-nitroaniline in polycarbonate microspheres.

Drug	Theoretical content (%)	Actual content (%)	Incorporation efficiency (%)
Aspirin	60	52	87
	50	41	82
	40	30	75
	30	14	45
Griseofulvin	50	49	98
p-Nitroaniline	50	49	98

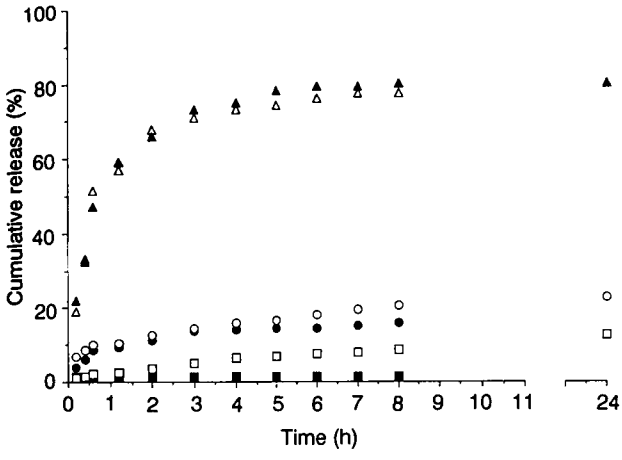

FIG. 2. The release profiles of drug-loaded microspheres in simulated gastric (▲, ○, □) and intestinal (△, ●, ■) fluids. Microspheres used had 50% loading and bead size of 710-850 μm. Aspirin ▲, △; *p*-nitroaniline ○, ●; griseofulvin □, ■. Values are average of three determinations, standard deviations are not shown but were within 5-12%.

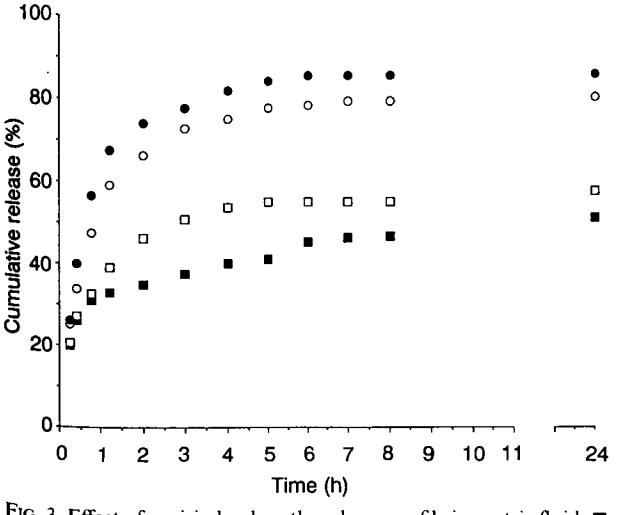

FIG. 3. Effect of aspirin load on the release profile in gastric fluid. ■ 30%-, □ 40%-, ○ 50%- and ● 60%-loaded beads. Bead size is 710–850 μm.

30% initial loading, only 14% of the drug was incorporated. High incorporation efficiencies were achieved for *p*-nitroaniline and griseofulvin.

The release patterns of the three drugs from simulated biofluids are given in Fig. 2. The release rate of aspirin is several times faster than either *p*-nitroaniline or griseofulvin. Both aspirin and *p*-nitroaniline showed nearly the same release rates in both fluids. The release pattern of aspirin from polycarbonate microspheres with different loadings of the drug (30–60%) is shown in Fig. 3. Increased release rate was observed with increased loading of the drug.

Table 2. Solubility of aspirin, *p*-nitroaniline and griseofulvin in similated gastric and intestinal fluids at 37°C.

	Solubility (mg mL^{-1})		
	Aspirin	*p*-Nitroaniline	Griseofulvin
Gastric fluid	2·94	0·43	0·091
Intestinal fluid	7·69	0·27	0·070

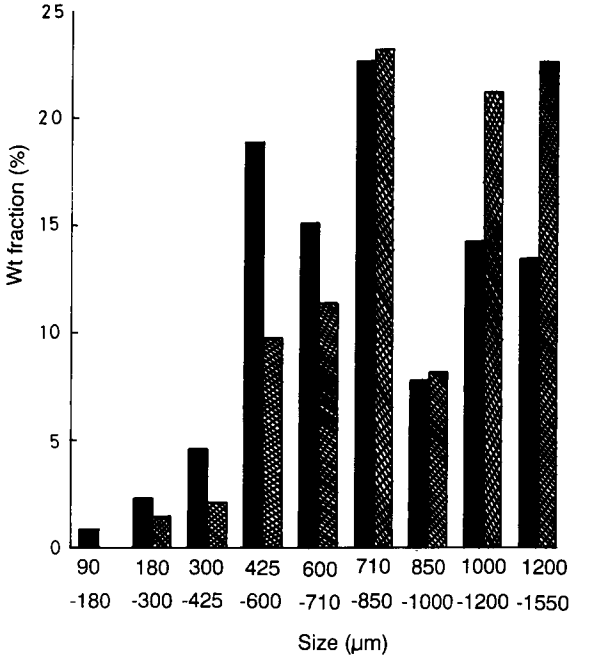

FIG. 4. Effect of aspirin content on the particle size distribution of polycarbonate microspheres. Left, 50%; right, 60%.

Table 2 shows the solubility of the three drugs in the simulated fluids.

The amount of drug initially incorporated was found to influence the particle size distribution of the microspheres. Fig. 4 shows the particle size distribution obtained with 50 and 60% aspirin. The formulation having 60% aspirin produced a larger proportion of bigger particles.

The effect of bead size on the release pattern of aspirin showed that, although a faster release was observed from the smaller particles initially (300–425 μm), the rate approached the rate of release from bigger particles (710–850 μm) in the final stage.

Discussion

Polycarbonate appears to be a suitable polymer for the

preparation of hollow spheres capable of floating on gastrointestinal fluids. We examined the possibility of preparing hollow spheres using polymers such as polymethyl methacrylate (PMMA) and polystyrene (PS) using various solvents (chloroform, dichloromethane, acetone), but only hard and solid spheres could be obtained. Polycarbonate in dichloromethane, however, was found to give hollow spheres which floated on water. Therefore, this polymer was chosen for the preparation of the hollow spheres. Why polycarbonate alone gives rise to hollow spheres is not clear. Determination of the density of the polymer gave a value of $1{\cdot}167 \pm 0{\cdot}05$ which was comparable with the density of PMMA and PS reported in the literature ($> 1{\cdot}0$). Mitra (1984) has claimed that floating-type dosage forms are not cleared into the small intestine from the stomach as quickly as other dosage forms. Therefore, oral sustained-release dosage forms using polycarbonate in the form of hollow microspheres were worthy of further investigation.

The microspheres obtained exhibited fairly good spherical geometry as evidenced by SEM. They appeared to be hollow in both the unloaded and loaded state, presumably because of the rapid escape of the volatile solvent from the polymer matrix. They were also found to be hollow in nature, as evidenced by the SEM, making them float on simulated biofluids.

The similar release rates in both fluids could be due to the fact that the solubilities of griseofulvin and *p*-nitroaniline in these media were not so different as to exert a significant effect on their release behaviour, which is believed to be diffusion mediated.

Although the solubility of aspirin is different in the two simulated fluids, nearly the same rate of release was observed. This may be attributed to the effect of a burst release; nearly 20% of the drug is released due to the burst effect. The burst effect is found to be the same in both fluids irrespective of the solubility since the concentrations of the drug present in the microsphere is very small with respect to the volume of the dissolution medium, thereby making the dissolution of aspirin rapid. The drug crystals seen on the surface of microspheres are believed to be responsible for the effect. However, the burst effect is less evident in the case of the other two solutes, because of the poor solubility of these drugs.

The rate of release of aspirin remains high with high drug loading and it decreases as the loading decreases (Fig. 3). With low drug payloads, the drug particles are widely distributed inside the matrix and separated from each other by the polycarbonate binder. The contact of drug particles with the dissolution medium therefore is less favourable for rapid dissolution of the drug from the matrix. In the case of high drug loads, the drug particles within the microspheres are in close proximity with each other which makes the contact of the particles with the dissolution medium more favourable. The dissolution produces channels throughout the matrix facilitating the rapid erosion of the drug. The higher surface concentrations of the drug is believed to exert little effect on the release profile as most of the surface drug is liberated during the initial burst.

The increased incorporation efficiency of aspirin with higher drug loading as compared with lower drug loading is possibly because a constant amount of aspirin is lost into the dispersion medium during the washing process at all drug concentrations.

Although the bead size was not found to be dramatically influenced by the concentration of the drug in the dispersed phase at the two aspirin loads examined (50 and 60%), the proportion of bigger particles was higher when higher drug concentrations were employed. With 60% aspirin-loaded beads, nearly 40% was within the size range of 1000–1500 μm whereas with 50% aspirin, only around 28% fell within this range. With both amounts, the fraction below 425 μm was small, whereas almost the same fractions were seen in the range of 700–1000 μm. The larger proportion of bigger particles seen at higher loading can be attributed to a viscosity effect in the dispersed phase at higher drug content.

A slightly increased release rate was observed initially from smaller particles as compared with bigger particles (data not given). The larger area of contact of the smaller particles with the dissolution medium is believed to be responsible for the faster rate of release. Since the release pattern of aspirin in both simulated fluids is similar, it can be predicted that oral administration of these microspheres will not markedly affect the release profile, whereas the poorly water soluble drugs, *p*-nitroaniline and griseofulvin will display slower release. Therefore polycarbonate as a matrix may be more favourable for the controlled release of drugs having moderate water solubility, between those of aspirin and *p*-nitroaniline.

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