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RESEARCH PAPER

Development of Hollow Microspheres as Floating Controlled-Release Systems for Cardiovascular Drugs: Preparation and Release Characteristics

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ABSTRACT

Hollow microspheres of cellulose acetate loaded with four cardiovascular drugs (nifedipine [NFD], nicardapine hydrochloride [NCD], verapamil hydrochloride [VRP], and dipyridamole [DIP]) were prepared by a novel solvent diffusion-evaporation method. The oil-in-water emulsion prepared in an aqueous solution of 0.05% poly(vinyl alcohol) medium with ethyl acetate, a water-soluble and less toxic solvent, was used as the dispersing solvent. The yield of the microspheres was up to 80%. The microspheres had smooth surfaces, with free-flowing and good-packing properties. Scanning electron microscopy (SEM) confirmed their hollow structures, with sizes in the range 489–350 μm. The microspheres tended to float over the gastric media for more than 12 h. The drug loaded in hollow microspheres was in an amorphous state, as confirmed by differential scanning microscopy (DSC). The release of the drugs was controlled for more than 8 h. The release kinetics followed different transport mechanisms depending on the nature of the drug molecules.

Key Words: *Cardiovascular drugs; Floating hollow microspheres; Release characteristics; Transport mechanisms.*

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INTRODUCTION

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem, the oral controlled-release (CR) formulations have been developed as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation.

An incomplete release of the drug and shorter residence time of the dosage forms in the upper GIT, a prominent site for the absorption of many drugs, will lead to lower bioavailability (1). Therefore, prolonged gastric retention is important in achieving control over the GRT because this helps to retain the CR system in the stomach for a longer and predicted time. In addition, this improves the bioavailability of the basic drugs that have poor solubility in higher pH (2). Several techniques (3–6) have been adopted for this purpose. However, the development of bioadhesive systems is one such method by which the CR system adheres to gastric mucosa to improve the GRT. However, there are some inherent problems associated with such systems since they will deliver a large amount of drug at a particular site of the GIT, thereby leading to local irritation (3).

Another approach to improve the GRT is to incorporate the drug into a floating device that is less dense than the gastric fluid. Floating single-unit dosage forms, also called hydrodynamically balanced systems, have been extensively studied (6). These single-unit dosage forms have the disadvantage of a release all-or-nothing emptying process (4). However, the multiple-unit particulate dosage forms pass through the GIT to avoid the vagaries of gastric emptying and thus release the drugs more uniformly. The uniform distribution of these multiunit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation than the use of single-unit dosage forms (7). Surprisingly, however, less attention has been focused on the development of floating microspheres (8–11).

In continuation of our ongoing program of research on the CR of cardiovascular drugs (12–15), we now present the development of floating microspheres for the delivery of cardiovascular drugs such as dipyridamole (DIP) and verapamil hydrochloride (VRP), which are weakly basic in nature and demonstrate poor bioavailability in the small intestine. To improve the bioavailability, floating single-unit dosage forms containing VRP (tablet and capsules) with release over more than 24 h have been reported (16). Warren et al. (17) produced the pellets by an extrusion/spheronization method using different acidic modifiers to manipulate the pH of the microenvironment to improve the release of DIP. It thus becomes important to develop floating microspheres for the release of basic drugs. Nicardapine hydrochloride (NCD) and nifedipine (NFD) were also incorporated into the floating microspheres, even though these drugs have uniform absorption in the GIT. NCD has a short half-life of 1 h. The short-acting NFD should be used with caution to avoid the risk of death from myocardial infarction. This necessitates the development of CR systems for these drugs. Their GRT can be increased by loading NFD or NCD in floating microspheres, which are useful in the effective management of hypertension with a single dose.

EXPERIMENTAL

Materials

Cellulose acetate (received from Gujarat State Fertilizers Corp., Vadodara, India), ethyl acetate, acetone, methanol, poly(vinyl alcohol) (PVAL) with a molecular mass of 125,000, sodium lauryl sulfate (SLS) (s.d. Fine Chemicals, Mumbai, India), nicardapine hydrochloride and dipyridamole (both from Sigma Aldrich, St. Louis, MO), and verapamil hydrochloride and nifedipine (both received as gift samples from Lincoln Pharmaceuticals, Ahmedabad, India) were used in this research. All other reagents were analytical-grade samples that were used without further purification.

Methods

Preparation of Hollow Microspheres

Cellulose acetate hollow microspheres loaded with NFD, NCD, VRP, and DIP were prepared using an oil-in-water (o/w) emulsification method. Briefly, 3 g of the polymer was dissolved in 45 ml of ethyl acetate (EtAc) and 5 ml of acetone in a cold water bath. The NFD (5% w/w based on the dry mass of polymer) was added directly in the polymer solution, and NCD (5%), VRP (20%), and DIP (10%) in w/w units were dissolved into 5 ml methanol and later added to the polymer solution. The resulting solution was added slowly over a period of 1 min to 150 ml of water containing 0.05% (w/v) PVAL as otherwise the sudden addition leads to the formation of large polymer precipitates, thus reducing the yield of the microspheres.

To obtain better entrapment efficiency of VRP and DIP (both have pH-dependent solubility), phosphate

buffer solution at pH 8.8 containing 0.05% PVAL was used. The emulsion was continuously stirred at a speed of 500 rpm using a Eurostar (IKA Labortechnik, Staufen, Germany) at room temperature for 24 h. The floating microspheres were collected by decantation, while the nonfloating microspheres were discarded along with any polymer precipitate. Microspheres were then dried overnight at 40°C. The microspheres were weighed and stored in a desiccator until further analysis.

Micromeritic Properties of Hollow Microspheres

The microspheres are characterized by their micromeritic properties, such as particle size, tapped density, compressibility index, true density, and flow property. The size was measured using an optical microscope under regular polarized light, and the mean particle size was calculated by measuring 200–300 particles with the help of a calibrated ocular micrometer. The tapping method was used to calculate tapped densities and percentage compressibility index using

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}} \quad (1)$$

$$\% \text{ Compressibility index} = \left[1 - \frac{V}{V_0}\right] \times 100 \quad (2)$$

Here, V and V_0 are, respectively, the volumes of the sample after and before the standard tapping.

Density of hollow microspheres is determined by immersing the microspheres in 0.02% Tween 80 solution for 3 days in a metal mesh basket. The microspheres that are sunk after this process are used for density measurement as carried out by the displacement method.

The angle of repose ϕ of the microspheres, which measures the resistance to particle flow, was calculated as (18)

$$\tan \phi = 2H/D \quad (3)$$

where $2H/D$ is the surface area of the free-standing height of the microsphere heap that is formed after making the microspheres flow from the glass funnel.

Scanning Electron Microscopic Study

Scanning electron microscopic (SEM) studies were performed to confirm the hollow nature of the microspheres. SEM photographs were taken on a JSM 6400 scanning electron microscope (Nihon Denshi Co., Ltd., Japan) at the required magnification and at room temperature. Before scanning, the microspheres were sputtered with gold to make the surface conductive. A 5 kV voltage used was with the secondary electron image (SEI) as a detector.

Estimation of Drug Loading

Drug loading in hollow microspheres was carried out by dissolving the microspheres in a small amount of dichloromethane in a separating funnel and extracting the drugs into suitable aqueous media (i.e., 0.1 N HCl for VRP and DIP and 0.1% Tween 80 solution for NFD and NCD) by evaporating dichloromethane. The estimation of drugs was carried out using an ultraviolet-visible (UV-Vis) spectrophotometer (Secomam, Anthelie, France).

Differential Scanning Calorimetric Study

Differential scanning calorimetric (DSC) analyses were performed on cellulose acetate, VRP, NFD, blank microspheres, and the drug-loaded microspheres using a DuPont-2000 microcalorimeter (DE., USA). Samples were continuously heated at the rate of 10°C/min under a constant flow of nitrogen gas.

Drug Release

Drug release from the hollow microspheres is complicated because the hollow microspheres float and hence adhere to the inside surfaces of the dissolution basket while the dissolution experiments are in progress, which leads to the nonparticipation of the hollow microspheres or their surface in the release study. Hollow microspheres have the propensity to exhibit a buoyancy effect in vivo, but the development of a dissolution method as a quality control tool with the simulated buoyant condition is difficult.

The use of several methods has been described in the literature (6), but in the present study, we used the standard USP paddle method. The microspheres were placed in a nonreacting mesh that had a smaller mesh size than the microspheres. The mesh was tied with a nylon thread to avoid the escape of any microspheres, and the glass marble was used in the mesh to help induce any possible sinking of the microspheres in the dissolution medium. The dissolution medium used was 900 ml of 0.1 N HCl for DIP and VRP and 0.1 N HCl with 0.1% SLS for NFD and NCD. At specified time intervals, 10-ml aliquots were withdrawn and analyzed by UV-Vis spectrophotometer at the respective λ_{max} values for DIP (283 nm), VRP (278 nm), NFD (238 nm), and NCD (250 nm).

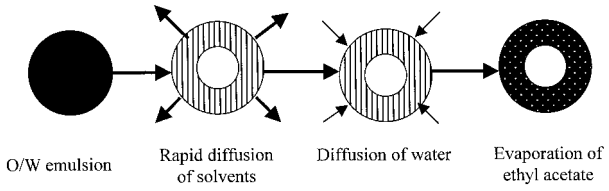


Figure 1. Mechanism of formation of hollow microspheres.

RESULTS AND DISCUSSION

The gastric retention time of the dosage form will decide the activity of the oral CR formulations. This has prevented the development of CR formulations that release for more than 12 h. On the other hand, there are some drugs that have better bioavailability only in the upper GIT. Thus, there is a need to increase the gastric residence time so that irregular absorption of such drugs can be avoided.

To increase the GRT of the drugs, we developed hollow microspheres with a floating property so that they can be retained in the upper GIT for a longer time and thus help in prolonged drug action exceeding 12 h. In addition, these will increase the bioavailability of the highly basic drugs like VRP and DIP, which have better bioavailability in the upper GIT.

In the present study, a novel solvent diffusion and evaporation method was employed using less-toxic solvents like ethyl acetate, acetone, and methanol. The mechanism of formation of hollow microspheres is shown schematically in Fig. 1. When the polymer solution is first poured into an aqueous phase to make an o/w emulsion with a phase ratio of 1:3, all the methanol or acetone will diffuse along with a small amount of ethyl acetate, which has a limited water solubility of 8.1% v/v. Ethyl acetate diffuses until it reaches an equilibrium concentration in the embryonic microspheres. Since 150 ml of queous phase was used to prepare the hollow microspheres, about 13 ml of ethyl acetate was diffused out to saturate the aqueous phase along with methanol and acetone. Such a quick leaching out of the organic solvents into the aqueous phase is responsible for inducing an interfacial polymer deposition, leading to the formation of hollow microspheres (19,20). The aqueous phase will also diffuse into the embryonic hollow microspheres simultaneously because the solubility of water in ethyl acetate is 3.65% v/v which acts as a poor solvent for the polymer. This further enhances polymer precipitation and thereby hardens the microspheres.

The present method is quite different from that reported by Kawashima et al. (9) for the production of hollow microspheres, by which rapid diffusion of ethanol precipitated the polymer, and the dichloromethane that remained with the microspheres was removed by evaporation at 40°C. Even though rapid removal of the solvent from the organic phase occurred during the emulsification procedure, not much of the polymer precipitates was formed. Hence, the microspheres were formed with yields up to 80% w/w (see Table 1).

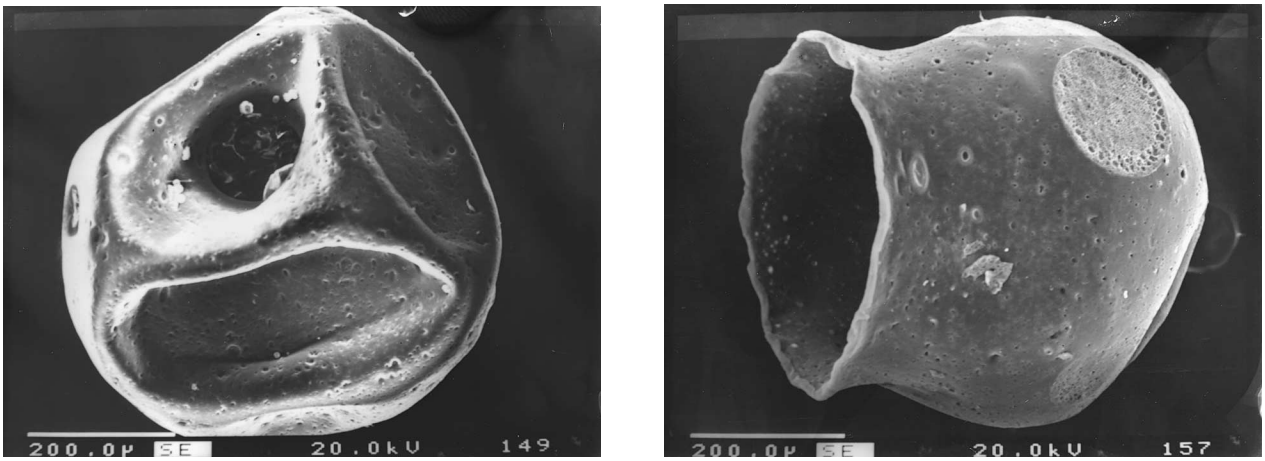
Mean particle size of the hollow microspheres ranged between 350 and 489 μm. Larger particles were produced due to the rapid polymer precipitation, leading to hardening and avoiding further particle size reduction during solvent evaporation. Another possibility is that, by rapidly removing the solvent, the inward shrinking of the polymer could be avoided; this can be achieved by slowly removing the solvent (13). Of the four formulations prepared, the microspheres loaded with VRP had the largest size (see Table 1), possibly due to their higher drug loading. The SEM photographs (Fig. 2a) show that the microspheres had smooth surfaces with inward dents due to the collapse of the wall of the microspheres during the in situ drying process. Thus, the rate of solvent removal

Table 1

Micromeritic Properties of the Drug-Loaded Hollow Microspheres

Formulation	Yield[a] (%)	Size (μm)	ϕ (degree)	*I* (%)	Tapped Density (g/cm^3)	True Density (g/cm^3)
VRP	78.3	489	23.2 ± 0.30	12.5 ± 1.2	0.185 ± 0.02	0.851 ± 0.06
DIP	80.6	365	27.5 ± 0.51	13.6 ± 2.1	0.161 ± 0.04	0.745 ± 0.06
NFD	70.1	380	23.2 ± 0.53	12.9 ± 0.9	0.136 ± 0.02	0.811 ± 0.11
NCD	69.2	350	23.1 ± 0.33	8.3 ± 2.1	0.160 ± 0.04	0.910 ± 0.10

DIP, dipyridamole; *I*, compressibility index; NCD, nicardapine hydrochloride; NFD, nifedipine; VRP, verapamil hydrochloride.
[a] [Mass of hollow microspheres/(Mass of polymer + Mass of drug)] × 100.



(a) (b)

Figure 2. SEM photographs of hollow microspheres loaded with NFD showing (a) surface dents and (b) hollowness.

from the embryonic microspheres exerts an influence on the morphology of the end product (19).

SEM photographs also indicated the presence of minute pores on the surface of the hollow microspheres. Wagenkenecht et al. (21) have reported the production of highly porous cellulose acetate microspheres using ethyl acetate. Due to rapid diffusion of the solvent, there is a possibility of rupture of some of the hollow microspheres (Fig. 2b). The SEM photographs reveal the absence of crystals of the drugs on the surface of the hollow microspheres, indicating uniform distribution of the drugs in the walls of the hollow microspheres. The physical state of the drug in the microspheres has an influence on the release kinetics (12).

To understand the state of the drug, DSC was performed on pure drug, empty microspheres, and drug-loaded microspheres. From the DSC thermograms presented in Fig. 3, which are typical for NFD microspheres, it is observed when NFD is loaded in the microspheres it is molecularly distributed, as indicated by the absence of the melting endotherm of the drug at about 172°C in the drug-loaded microspheres.

Usually, the microparticulate drug delivery systems are formulated as single-unit dosage forms in the form of tablets or capsules. Such microparticulate systems should possess the required micromeritic properties. The flow property of the hollow microspheres was studied by calculating the angle of repose ϕ and compressibility index *I*. These data, along with the related parameters, are presented in Table 1. The values of ϕ ranged between 20° and 28°, indicating reasonable flow potential for the particles. These results are further substantiated by the values of *I*, which ranged between 8% and 14%, suggesting good flow characteristics of the microspheres (18). The better flow property indicates that the hollow microspheres produced are nonaggregated. The tapped density values ranged from 0.136 to 0.185 g/cm^3, while their true densities ranged between 0.745 and 0.910 g/cm^3.

Recently, Sah (20) developed poly(DL-lactide-*co*-glycolide) microspheres using a phase ratio of 1:10 and ethyl acetate as a solvent. The hollow microspheres formed were irregular in shape and were highly aggregated. By using a phase ratio of 1:2.5, spherical microspheres were formed, but these were not hollow in nature. In the present study, we have optimized the phase ratio to avoid aggregation and to create the hollow inner core in the microspheres.

To assess the floating properties, the microspheres were placed in 0.1 N HCl containing 0.02% v/v Tween 80 surfactant to simulate gastric conditions. The use of 0.02% Tween 80 was to account for the wetting effect of the natural surface-active agents, such as phospholipids in the GIT. Despite the solution being stirred for more than 12 h, the hollow microspheres still floated (see Fig. 4), indicating that the microspheres exhibit an excellent buoyancy effect. Density values of the microspheres ($<$1.000 g/cm^3) were less than that of the gastric fluid ($\sim$1.004 g/cm^3), further supporting the floating nature. The in vitro floating test was conducted on the drug-loaded microspheres. In all four formulations, about 80% of the microspheres floated; we did not observe a considerable effect of release of drug on the floating behavior.

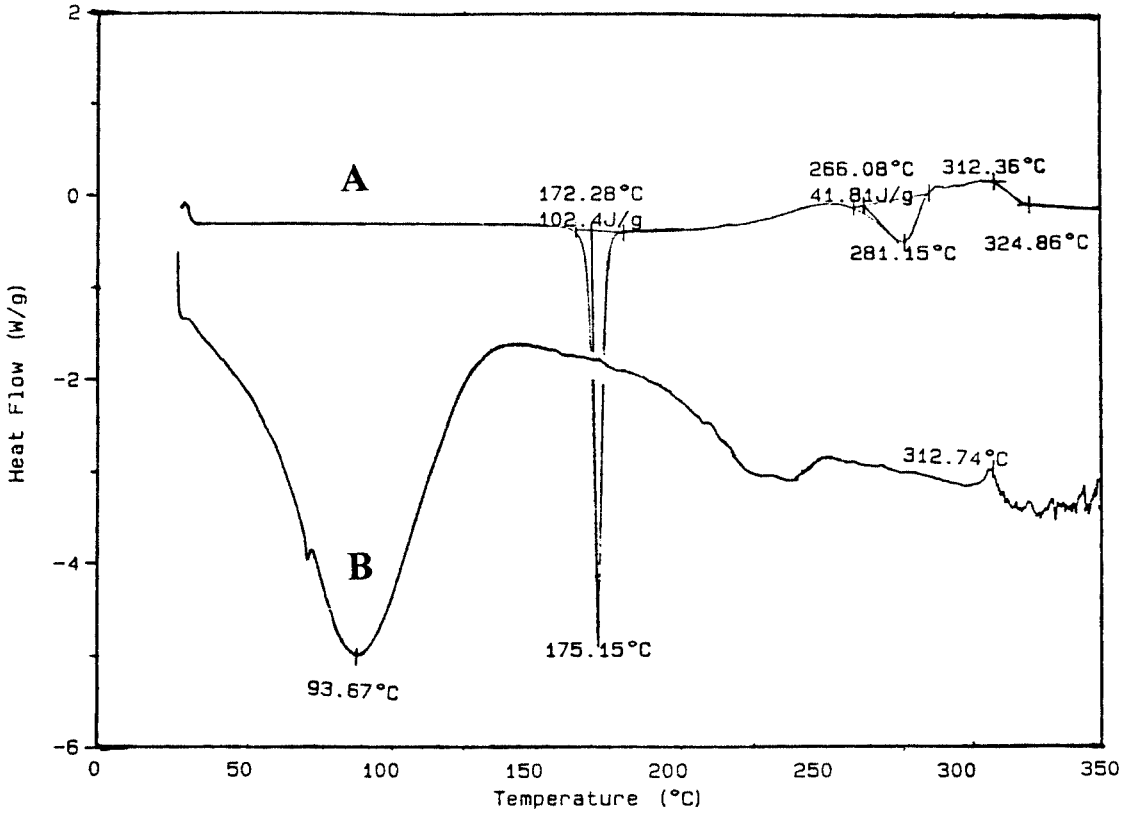


Figure 3. DSC thermograms of (A) NFD and (B) NFD-loaded hollow microspheres.

Drug-loading properties of the microspheres are given in Table 2. For NFD and NCD, we loaded with 5% drug based on the dry mass of the polymer. In our preliminary experiments, we found that, at higher drug loadings (>5%), crystal formation on the microspheres was observed. On the other hand, for DIP and VRP, the loadings were 10% and 20%, respectively, due to their limited solubility in ethyl acetate and the requirement of methanol as the cosolvent. The microspheres were loaded with drugs depending on their solubility behavior. In the case of drugs like NFD that are less water soluble, the encapsulation efficiency was 95%. In the case of NCD, which has partial solubility in water, the encapsulation efficiency was lowest (66%), probably because the drug might have leached out in the external phase during emulsification. Since VRP and DIP are highly basic drugs with a pH-dependent solubility, the pH of the external phase was adjusted to 8.8 while preparing these microspheres. This helps avoid any leaching of the drugs and leads to their higher encapsulation efficiencies of 89% and 79%, respectively.

Drug release profiles from the floating microspheres are presented in Figs. 5 and 6. Due to their floating nature, the microspheres were forcibly immersed into the dissolution media to avoid adherence to the surface of the dissolution jar, thus leading to nonparticipation in the dissolution process. The drug release was extended to more than 15 h. The release of VRP and DIP was relatively fast initially, showing a large burst release. This is attributed to the release of the drug from the surface of microspheres as the drug might have migrated to the surface along with water during the drying process. Subsequent release of drug was slower, and this continued up to more than 15 h. The release of DIP was fast when compared to VRP; that is, almost 60% of DIP was released within the first 20 min. Gursoy et al. (22) have also reported such a fast release of DIP from alginate-Eudragit microspheres. The release rates of NFD and NCD shown in Fig. 6 are slower than those of VRP and DIP. In the case of NFD, when the dissolution was conducted in 0.1% (w/v) of SLS solution of 0.1 N HCl, the release was very slow; that is, only 62% of the drug was released at the

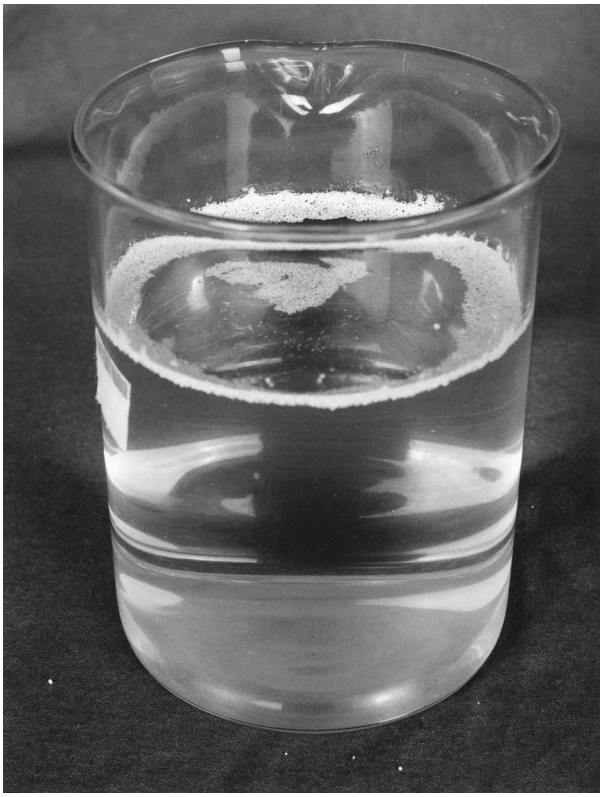


Figure 4. Floating behavior of hollow microspheres in 0.1 N HCl containing Tween 80 (0.02%) after stirring for 12 h.

end of 15 h. However, about 90% of NCD was released during the same period, probably due to the higher solubility of NCD (339.3 μg/ml) than that of NFD (70.7 μg/ml) in the dissolution media used.

The mechanism of drug release from the hollow microspheres was studied by fitting the release data to an empirical equation of the following type (23):

$$(M_t/M_\infty) = kt^n \quad (4)$$

Table 2

Drug-Loading Properties of Hollow Microspheres

Formulation	Theoretical Loading (%)	Loading (%)	Encapsulation Efficiency (%)
VRP	16.6	14.8 ± 0.96	89.1 ± 7.1
DIP	9.1	8.6 ± 0.51	79.0 ± 6.0
NFD	4.8	3.8 ± 0.23	94.5 ± 4.9
NCD	4.6	3.1 ± 0.50	65.5 ± 11.1

DIP, dipyridamole; NCD, nicardapine hydrochloride; NFD, nifedipine; VRP, verapamil hydrochloride.

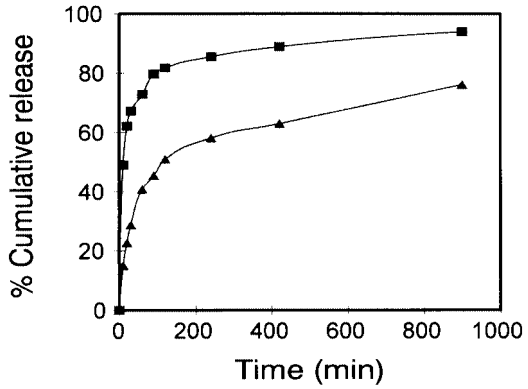


Figure 5. Percentage cumulative release of hollow microspheres loaded with ▲ VRP and ■ DIP.

The ratio M_t/M_∞ represents the fractional drug release at time t, k is a constant characteristic of the drug-polymer system, and n is the diffusional exponent. A value of $n = 0.5$ indicates that a Fickian mechanism is operative, while $n = 1.0$ indicates the presence of case II transport. The values of n ranging between 0.5 and 1.0 are due to the presence of anomalous transport (23). The limiting values of n are lower for the devices with different geometries. Values of $n = 0.45$–0.89 have been obtained for cylindrical geometry and 0.43–0.85 for the spherical particles (24); for polydisperse microspheres, the values of n could be as low as 0.3 and 0.45 for Fickian and case II transport, respectively (24).

In the present study, the statistically estimated values of n at the 95% confidence limit are presented in Table 3. For the DIP-loaded microspheres, $n = 0.29$, indicating

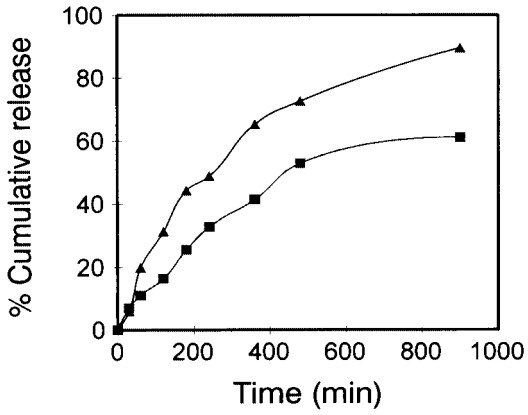


Figure 6. Percentage cumulative release of hollow microspheres loaded with ▲ NCD and ■ NFD.

Table 3

Release Kinetic Parameters[a] *of Hollow Microspheres*

Formulation	n	$k \times 10^2$ $(\text{min})^{-n}$	Correlation Coefficient
VRP	0.55	4.2	0.999
DIP	0.29	25.2	0.992
NFD	0.76	0.49	0.994
NCD	0.85	0.48	0.971

DIP, dipyridamole; NCD, nicardapine hydrochloride; NFD, nifedipine; VRP, verapamil hydrochloride.
[a] Calculated from Eq. 4.

Fickian transport, while for the VRP-loaded microspheres, the n value is 0.55, hence the release may be non-Fickian and not case II. For drugs like NFD and NCD that are sparingly water soluble, the values of n are 0.76 and 0.85, respectively, suggesting that the release follows the non-Fickian or case II transport. We observed a wide variation in the values of k. For instance, $k = 0.252$ for DIP, while it was quite a bit smaller, about 0.0048, in the case of NFD- and NCD-loaded microspheres. Intermediate values of $k = 0.042$ were observed for the VRP-loaded microspheres.

CONCLUSIONS

The present study reports the development of drug-loaded hollow microspheres of cellulose acetate using less toxic solvents like ethyl acetate, acetone, or methanol. The microspheres produced exhibited better encapsulation efficiencies and micromeritic properties for formulation as single-unit dosage forms. The microspheres, having lower densities, exhibited buoyancy and may be retained in the gastric environment for more than 12 h. This helps improve the bioavailability of basic drugs like verapamil hydrochloride and dipyridamole. Even though the CR systems released the drugs for a longer time, once these passed through the upper portion of the small intestine, the released drug cannot be utilized because of a gastric retention time less than 8–12 h. Therefore, it is not possible to deliver the drug from the oral route for more than 12 h. The present study demonstrated that the hollow microspheres developed floated for more than 12 h, so we can deliver drugs like nifedipine and nicardapine hydrochloride for a longer time (>15 h) for effective management of hypertension.

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