Preparation and In Vitro Evaluation of Polystyrene-Coated Diltiazem-Resin Complex by Oil-in-Water Emulsion Solvent Evaporation Method

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ABSTRACT

The purpose of this study was to examine the suitability of polystyrene-coated (PS-coated) microcapsules of drug-resin complex for achieving prolonged release of diltiazem-HCl, a highly water-soluble drug, in simulated gastric and intestinal fluid. The drug was bound to Indion 254, a cation-exchange resin, and the resulting resinate was microencapsulated with PS using an oil-in-water emulsion-solvent evaporation method. The effect of various formulation parameters on the characteristics of the microcapsules was studied. Mean diameter and encapsulation efficiency of the microcapsules rose with an increase in the concentration of emulsion stabilizer and the coat/core ratio, while the same characteristics tended to decrease with an increase in the volume of the organic disperse phase. The desorption of drug from the uncoated resinate was quite rapid and independent of the pH of the dissolution media. On the other hand, the drug release from the microcapsules was prolonged for different periods of time depending on the formulation parameters and was also found to be independent of the pH of the dissolution media. Both the encapsulation efficiency and the retardation of drug release were found to be dependent on the uniformity of coating, which in turn was influenced by the formulation parameters. Kinetic studies revealed that the desorption of drug from the resinate obeyed the typical particle diffusion process, whereas the drug release from the microencapsulated resinate followed the diffusion-controlled model in accordance with the Higuchi equation. PS appeared to be a suitable polymer to provide prolonged release of diltiazem independent of the pH of the dissolution media.

KEYWORDS: Diltiazem, cation exchange resin, polystyrene microcapsules, drug release, release kinetics.

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INTRODUCTION

Multiunit controlled-release drug delivery systems such as microcapsules and microspheres are becoming popular because they (1) pass through the gut as if a solution, avoiding the vagaries of gastric emptying and different transit rates,[1] (2) spread over a large area of absorbing mucosa, preventing exposure to high drug concentrations,[2] and (3) release drug in a more predictable manner.[3] One of the widely investigated methods for microencapsulation of drugs is the oil-in-water emulsion-solvent evaporation (ESE) technique.[4] The characteristics of the microcapsules such as drug entrapment efficiency and release of drug, however, depend on the aqueous solubility of the drug, the type of organic solvent or solvent mixture used, the phase ratio of the emulsion system, the temperature, and the type and concentration of emulsion stabilizers.[5] The encapsulation efficiency of water-soluble drugs, in particular, by the oil-in-water ESE method has been low because of partitioning of drugs from the organic phase to the external aqueous phase.[6] Several strategies have been developed to improve the encapsulation of water-soluble drugs by the oil-in-water ESE method. Adjustment of pH and saturation of the external aqueous phase with the drug have been used to reduce the partitioning of the drug from the organic disperse phase to the external aqueous phase and, thereby, to improve the drug content of microcapsules.[7] A water-in-oil-in-water ESE technique has also been developed to encapsulate highly water-soluble drugs.[8,9] However, use of ion-exchange resinate, instead of free drug, appears to be more useful in achieving high loading of water-soluble drugs and prolonged release from the microcapsules prepared by the oil-in-water ESE method. Various sulfonic acid and carboxylic acid types of cation exchange resins such as Amberlite and Dowex have been extensively used to provide drug-resin complexes for subsequent microencapsulation.[10-16] Indion 254, another sulfonic acid type of cation exchange resin, has not been used for this purpose. Like other cation exchange resins, Indion 254 forms resinates with cationic drugs.

Although different polymers such as ethylcellulose, polymethylmethacrylate, Eudragit RS 100,[11] and cellulose acetate butyrate[12] have been used to coat resinates by the oil-in-water ESE method, to the best of our knowledge polystyrene (PS) has not been used to encapsulate the drug-resin

complex for achieving prolonged release. PS is the polymer most often used to study phagocytosis, owing to its ready availability, uniform size, stability, and nontoxic properties.[17] PS has also been used to encapsulate corrosion inhibitors[18] and unresinated ketoprofen in combination with cellulose acetate butyrate[19] and to prepare nanocapsules as a carrier for human epithelium growth factor.[20] There appears to be no report on the use of PS as a coating material for resinates.

The objective of this study was to examine the suitability of PS-coated microcapsules of diltiazem-Indion 254 complex as a prolonged-released device and the effect of some formulation variables on the various characteristics of the resinate-loaded microcapsules. Diltiazem HCl has been selected as a model water-soluble cationic drug. Moreover, this calcium channel blocker, which is used to treat angina pectoris, arrhythmias, and hypertension, appears to be a suitable drug candidate for microencapsulation because of its short biological half-life and frequent administration.

Materials and Methods

Materials

Diltiazem HCl (Stadmed Pvt Ltd, Kolkata, India), sulfonic acid cation exchange resin in Na^+ form (Indion 254; Ion Exchange (India) Pvt Ltd, Mumbai, India), and PS (Grade McG-100, general purpose; M/S Hindusthan Polymers, Kolkata, India) were obtained as gift samples. Methylcellulose (3000-4000 mps, Loba Chemi, Mumbai, India) and all other reagents were obtained commercially and used as received.

Methods

Preparation of Resinate

Resins (300-350 mesh) were washed with deionized water (200 mL) and methanol (2 × 50 mL) to remove impurities. The resins were activated by recycling alternately 3 times with 1M NaOH (60 mL) and 1M HCl (60 mL) and washing after each treatment with deionized water. The resins in hydrogen/acid form were washed with deionized water until the elute was neutral and were then vacuum-dried at 50°C to constant weight.

Resins of about 100 mg, accurately weighed, were stirred at 30°C in 75 mL of diltiazem HCl solution (0.8 mg/mL) for 3 hours. The resulting resinates were separated by vacuum filtration and washed with deionized water until the filtrate showed no absorbance at 236 nm for diltiazem. The resinate was vacuum-dried at 50°C to constant weight.

Drug Content of Resinate

About 20 mg of accurately weighed resinate was shaken for 48 hours in 250 mL of USP phosphate buffer solution (pH 7.2) and then filtered. The filtrate, following suitable dilution, was assayed spectrophotometrically (Hitachi, 200-20, Tokyo, Japan) at 236 nm for diltiazem HCl.

Preparation of Microcapsules

Resinate-loaded PS microcapsules were prepared by the oil-in-water ESE method. A known amount of resinate was dispersed in the dichloromethane solution of PS at 15°C and was emulsified at 500 rpm in 150 mL of methylcellulose mucilage maintained at 15°C. Stirring was continued at ambient temperature for 2 hours. The suspension of the microcapsules was poured into 600 mL of cold deionized water and was stirred for 2 more hours. The resulting microcapsules were vacuum-filtered, washed with 3 × 50 mL deionized water, and dried at 50°C under the vacuum for 24 hours. The microcapsules were fractionated by sieving.

The following experimental parameters were varied: (1) keeping the coat/core ratio and the volume of the organic disperse phase constant, the concentration of methylcellulose was varied from 0.025% to 0.2% wt/vol; (2) keeping the methylcellulose concentration and the coat/core ratio constant, the volume of the organic disperse phase was varied from 5 to 12 mL; and (3) keeping all the parameters constant, the coat/core ratios were varied from 5:2 to 10:1.

Mean Diameter of Microcapsules

The microcapsules were placed on the top of a nest of British Standard sieves stacked from bottom to top in ascending order of aperture sizes ranging from 44 to 350 μm. The sieves were shaken using a mechanical shaker for 15 minutes. The particles that passed through a 300-mesh screen were studied under a microscope, found to be uncoated resinate, and discarded. The microcapsules retained on each sieve were weighed, and the arithmetic mean diameter was calculated.

Drug Entrapment Efficiency of Microcapsules

About 20 mg of accurately weighed resinate-containing microcapsules having a mean diameter of 163 μm were dissolved in 25 mL of chloroform. Exactly 250 mL of USP phosphate buffer solution (pH 7.2) was added, heated with continuous stirring to remove chloroform, and cooled down to 30°C. The stirring was continued for ~48 hours. Then the resinates were removed by filtering through Whatman filter paper. The filtrate following suitable dilution was assayed spectrophotometrically (Hitachi, 200-20) for diltiazem HCl

at 236 nm. Drug entrapment efficiency was determined as follows:

$$\text{Drug entrapment efficiency} = \frac{\text{Experimental diltiazem content}}{\text{Theoretical diltiazem content}} \times 100 \quad (1)$$

$$\text{Theoretical drug content (mg/100mg of microcapsules)} = \frac{\text{Amount of resinate taken} \times \text{Drug content of resinate}}{\text{Total weight of microcapsules}} \times 100 \quad (2)$$

Resinate encapsulation efficiency

After weighing, microcapsules were placed on the top of a nest of British Standard sieves stacked from bottom to top in ascending order of aperture sizes ranging from 44 to 350 μm. The sieves were shaken using a mechanical shaker for 15 minutes. The microcapsules retained in each sieve were weighed. The microcapsules retained on the sieve of aperture size 44 μm were studied under a microscope and were found to be uncoated resinate and discarded. The resinate encapsulation efficiency was determined as follows:

$$\text{Resinate encapsulation efficiency (\%)} = \frac{\text{Amount of resinate taken} - \text{Amount of uncoated resinate}}{\text{Amount of resinate taken}} \times 100 \quad (3)$$

Drug Release Study

In vitro release of diltiazem from the resinate (48.5 μm) and the microcapsules (mean diameter 163 μm) was monitored in 900 mL of simulated gastric fluid (SGF; 0.1N HCl, pH 1.2) and simulated intestinal fluid (SIF; USP phosphate buffer solution, pH 7.2) at 37 ± 1°C using a programmable dissolution tester (paddle type, Electrolab, model TDT-06P (USP), Mumbai, India) at 100 and 50 rpm, respectively. Aliquots were removed at predetermined times and were replenished immediately with the same volume of fresh media. The aliquots, following suitable dilution, were assayed spectrophotometrically at 236 nm.

Scanning Electron Microscopy

The dried microcapsules were mounted onto stubs using double-sided adhesive tape and vacuum-coated with gold film using a sputter coater (Edward S 150, Watford, UK). The coated surface was observed under a scanning electron microscope (Jeol, JSM-5200, Tokyo, Japan).

Statistical Analysis

Each formulation was prepared in duplicate, and each analysis was duplicated. Statistical analysis of the data was performed using analysis of variance (single factor) with the aid of Microsoft Excel 2002. Differences were considered significant when $P < .05$.

Results and Discussion

In the absence of emulsifier, emulsification at 500 rpm in deionized water of a disperse phase containing 18.57% wt/wt resinate in 5% wt/vol PS solution led to rapid coalescence of the dispersed droplets, resulting in the formation of an agglomerated mass. Although 0.4% sodium lauryl sulfate was reported to stabilize ethylcellulose microcapsules containing unresinated sulphathiazole,[21] neither sodium lauryl sulfate (0.01%-0.1%) nor Tween 80 (0.01%-0.1%) was capable of stabilizing the resinate-loaded PS microcapsules. However, methylcellulose (0.025%-0.2%) was found to stabilize the emulsion and to form nonagglomerated microcapsules. The formulation parameters that were varied to prepare the PS microcapsules have been presented in Table 1. Sieve analysis revealed that out of the average yield of ~92%, more than 66% (by weight) of the microcapsules were within the size range of 111.5 to 323.5 μm. However, the size distribution pattern was influenced by the various formulation parameters.

Size Distribution of Microcapsules

Effect of Concentration of Emulsion Stabilizer

An increase in the concentration of emulsion stabilizer increased the diameter of the microcapsules (Table 2). As the concentration of emulsion stabilizer was increased, the viscosity of the aqueous dispersion medium increased, which hindered the initial breakdown of the disperse phase into the smaller droplets and led to the formation of bigger microcapsules.

Table 1. Formulation Parameters of Polystyrene Microcapsules

Formulation Code	Methylcellulose Concentration in Aqueous Dispersion Medium (% wt/vol)*	Formulation Code	Coat/Core Ratio†	Formulation Code	Mean Diameter (μm)‡
A	0.025	E	5:1	G	6
B	0.05	F	10:1	H	9
C	0.1			I	12
D	0.2				

*Coat/core ratio 5:2; volume of dichloromethane 10 mL.

†Methylcellulose in aqueous dispersion medium 0.1% wt/vol; volume of dichloromethane 10 mL.

‡Methylcellulose in aqueous dispersion medium 0.1% wt/vol; coat/core ratio 5:2.

Table 2. Effect of Formulation Variables on Mean Diameter, Resinate Encapsulation Efficiency, and Drug Entrapment Efficiency of Resinate-Loaded Polystyrene Microcapsules

Formulation Code	Mean Diameter (μm)	Resinate Encapsulation Efficiency (%) of Unsieved Microcapsules	Drug Entrapment Efficiency(%) of Microcapsules Having 163 μm
A	127	40.14 ± 1.03	39.02
B	139	63.38 ± 0.98	61.26
C	161	79.11 ± 0.56	77.76
D	165	80.89 ± 0.94	80.13
E	195	92.88 ± 1.40	92.19
F	207	94.46 ± 0.91	93.98
G	246	98.55 ± 1.22	98.00
H	175	88.33 ± 1.14	87.60
I	135	50.95 ± 0.85	45.80

Effect of Volume of Organic Disperse Phase

To investigate the effect of the volume of the organic disperse phase on the size distribution of the microcapsules, the volume of dichloromethane was varied from 5 to 12 mL; the results are shown in Table 2. Increasing the volume of the organic disperse phase decreased the diameter of the microcapsules. At the lowest volume, the disperse phase was highly viscous, adhered to the propeller shaft and vessel wall, and was agglomerated. When the volume was increased above this level, the disperse phase became more and more fluid and was converted into particles of gradually decreasing sizes.

Effect of Coat/Core Ratio

With the concentration of emulsion stabilizer and the volume of the organic disperse phase constant, increasing the coat/core ratio increased the diameter of the microcapsules (Table 2). The gradual augmentation of the microcapsules' diameter with increases in the coat/core ratio was attributed to the higher viscosity of the disperse phase, which in turn increased the interfacial viscosity, making the breakdown of the disperse phase into smaller droplets difficult.

Resinate Encapsulation Efficiency of Microcapsules

The resinate encapsulation efficiency of the microcapsules was found to be influenced by the concentration of emulsion stabilizer, the coat/core ratio, and the volume of the organic disperse phase (Table 2). Increases in the concentration of emulsion stabilizer and the coat/core ratio and decreases in the volume of the organic disperse phase increased the resinate encapsulation efficiency of the microcapsules. It has been reported that the resinate encapsulation efficiency of microcapsules prepared by the oil-in-water ESE method is related to the partitioning of the resinate from the organic disperse phase to the aqueous dispersion medium and that increases in the drug loading make the resinate more hydrophobic and decrease the partitioning of the resinate in the aqueous phase, increasing the resinate encapsulation efficiency.[11] Since, in the present study, the maximum drug-loaded resinate was used for encapsulation, the encapsulation efficiency appeared to depend on the viscosity of both the disperse phase and the aqueous dispersion medium. Low viscosity of the dispersion medium and disperse phase, resulting from decreases in the concentration of the emulsion stabilizer and coat/core ratio and increases in the volume of the organic disperse phase, enabled the resinate situated at the periphery of the microcapsules to hydrate and swell easily, leading to rupture of the microcapsules and liberation of resinate in the aqueous dispersion medium. Scanning electron microscope studies of the gross morphology of the microcapsules (Figure 1) also demonstrated that

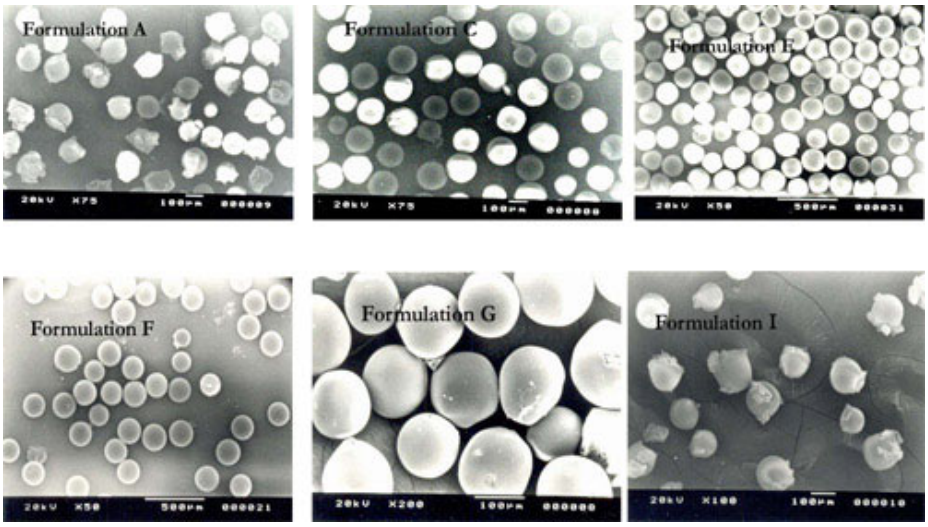

Figure 1. Scanning electron micrographs of 6 formulations of resinate-loaded polystyrene microcapsules.

as the concentration of emulsion stabilizer and the coat/core ratio were increased and the volume of the organic disperse phase was decreased, the amount of fractured microcapsules decreased and more uniformly coated microcapsules were formed.

Drug Entrapment Efficiency of Microcapsules

The drug content in the resinate was experimentally found to be 38.41%. Therefore, at a coat/core ratio of 5:2, 5:1, and 10:1, the drug entrapment efficiency of the resinate-loaded microcapsules theoretically should be 10.97%, 6.40%, and 3.49%, respectively. However, the drug entrapment efficiency was found to be influenced by the formulation parameters and was related to resinate encapsulation efficiency (Table 2). Increasing the concentration of the emulsion stabilizer increased the drug entrapment efficiency of the microcapsules. On the other hand, decreasing the volume of the organic disperse phase and increasing the coat/core ratio tended to increase the drug entrapment efficiency. It has been reported that the drug entrapment efficiency is closely related to the initial coat/core ratio and polymer concentration.[12]

Drug Release From Microcapsules

The release profiles of the drug from uncoated resinate and coated resinate prepared using different concentrations of the emulsion stabilizer appear in Figure 2. The drug release from the uncoated resinate was rapid and complete in 2.5 hours. Although drug release from Dowex 2 × 10 resin has been reported to be slower in SGF than in SIF because of the larger size of the exchanging phosphate anion and the lower affinity of the functional groups of the resin for phosphate,[22] in the present study the drug release from the

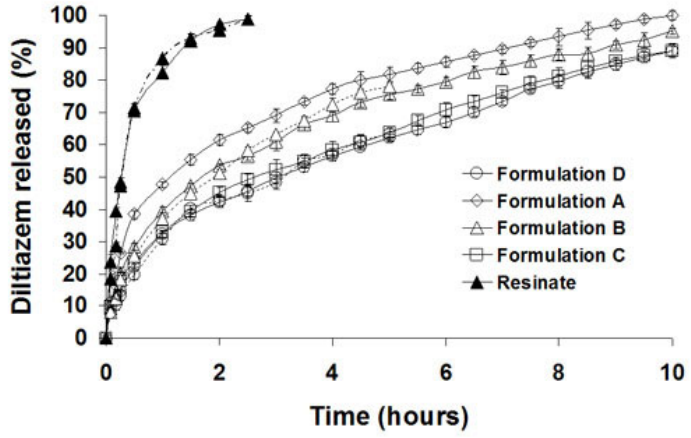

Figure 2. Release of diltiazem from resinate (▲) and resinate-loaded polystyrene microcapsules in simulated gastric fluid (dotted line) and simulated intestinal fluid (firm line).

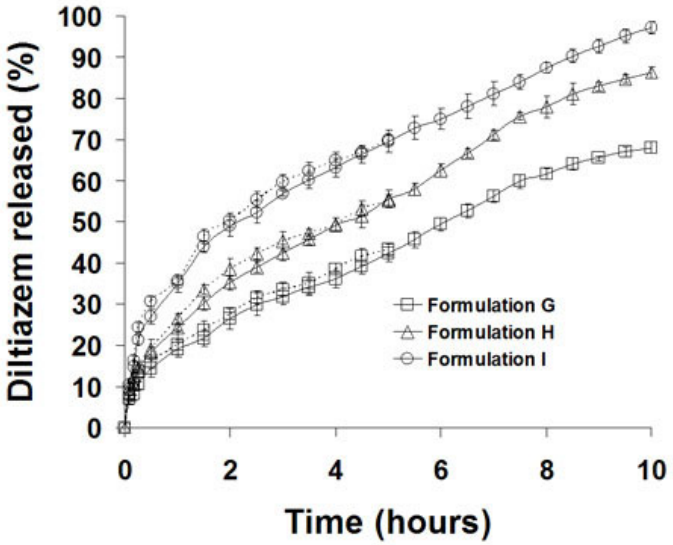

Figure 3. Release of diltiazem from resinate-loaded polystyrene microcapsules in simulated gastric fluid (dotted line) and simulated intestinal fluid (firm line).

Indion 254 resin-drug complex was found to be independent of pH. The release of drug from the microcapsules was slower than that from the uncoated resinate, and the retardation of drug release was influenced by the formulation parameters. Figure 2 shows that increasing the concentration of emulsion stabilizer from 0.025% to 0.2% decreased the release of the drug: as significant difference ($P < .05$) was observed among the dissolution efficiency parameters (DEP).[23] However, beyond 0.1% no significant effect of the emulsion stabilizer in retarding the drug release was observed. Similarly, the microcapsules that were prepared using a decreased amount of the organic disperse phase and a higher coat/core ratio discharged the drug more slowly (Figures 3 and 4). The observation could be corroborated

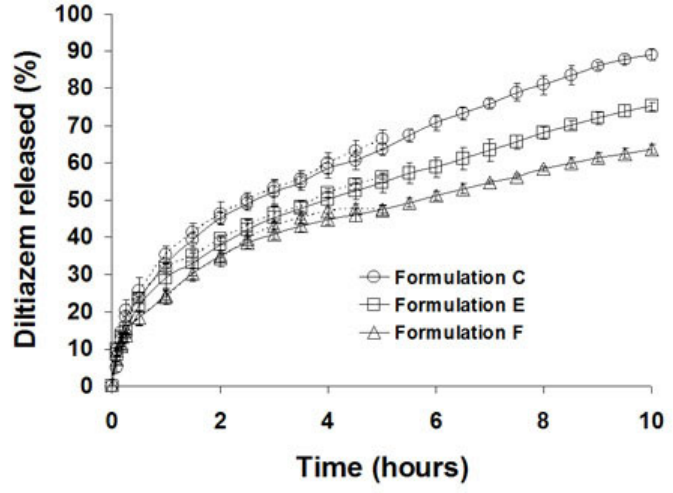

Figure 4. Release of diltiazem from resinate-loaded polystyrene microcapsules in simulated gastric fluid (dotted line) and simulated intestinal fluid (firm line).

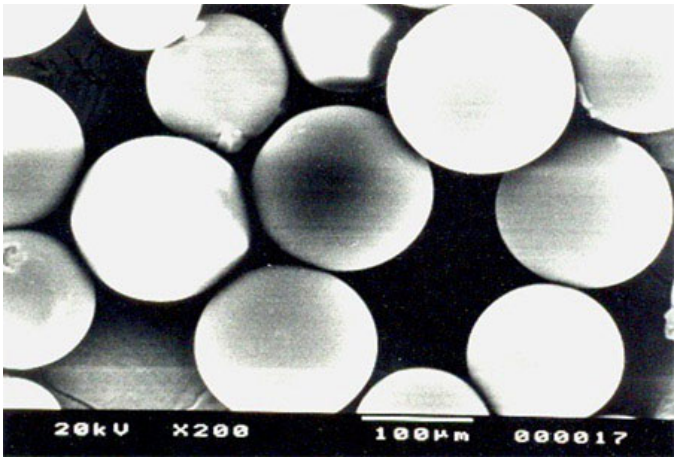

Figure 5. Scanning electron micrographs of resinate-loaded polystyrene microcapsules after in vitro release study of Formulation C.

by the morphology of the microcapsules and the complex drug release mechanism involving penetration of counter ions into the microcapsules, ion exchange, and subsequent diffusion of the free drug from the microcapsules. Although PS is nonporous and not easily permeated by aqueous media, porosity develops during the preparation of microcapsules/microspheres by the solvent evaporation technique; water-insoluble drugs such as ibuprofen and indomethacin have been reported to be released for a prolonged period from PS microspheres.[24,25] Use of a low concentration of emulsion stabilizer resulted in the formation of fractured, porous, and unevenly coated microcapsules that provided easy access to the counter ions. This resulted in comparatively rapid release of the drug. At higher concentrations of emulsion stabilizer, the microcapsules were well formed, less porous, and uniformly coated. Consequently, the typical drug release mechanism of the microencapsulated resinate became operative, resulting in a slower release. Similarly, increases in the coat/core ratio and decreases in the volume of the organic disperse phase increased the amount of polymer, which not only caused uniform coating but also increased the coating thickness of the microcapsules. This increased the path length through which the drug molecule had to diffuse and the time required to transverse the membrane and, hence, made the drug release slower from the microcapsules. The release profiles further indicated that the drug release from the microencapsulated resinates was independent of pH. Since the gastric residence time of microparticles is short, the DEP in SGF and SIF were compared up to 5 hours. No significant difference ($P > .05$) in DEP in SGF and SIF was noted in each of the formulations. Interestingly, the shape of the microcapsules after the dissolution studies was found to be unaltered (Figure 5). This indicates that the PS coating provided sufficient resistance to prevent the rupture of the coating film that would normally result from the rehydration and swelling of the dried resinate, and hence, that the process does not require any impregnating agent. There was a similar observation for the microcapsules prepared with nylon polymer.[26]

Kinetics of Drug Release

The exchange of drug from the uncoated resinate was found to follow the particle diffusion process in accordance with the equation proposed by Reichenberg in 1953.[27] The drug exchange data also fit well into the equation developed by Bhaskar et al (1986),[28] confirming that the release rate from the resin was controlled by particle diffusion (Table 3). Drug release from the coated resinates has also been reported to follow the particle diffusion process.[26,29,30] However, diltiazem release from the PS-coated resinates was found to deviate from the particle diffusion mechanism. Hence, the data were fitted into the Korsmeyer-Peppas[31] equation $Mt/M_\alpha = at^n$, where a is a constant incorporating structural and geometric characteristics of the dosage form; n is the release exponent, indicative of the drug release mechanism; and the function of t is Mt/M_α (fractional release of drug). Acceptable linearity was observed, and the values of n varied from 0.43 to 0.53 (Table 3). This indicates that the Fickian type of transport mechanism might be operative in the release of diltiazem from the microencapsulated

Table 3. Effect of Formulation Factors on Diltiazem Release Kinetics Data from Polystyrene Microcapsules at pH 7.2

	Bhaskar's Equation	Korsmeyer-Peppas's Equation		Higuchi Equation	
Formulation Code	Correlation Coefficient (r^2)	Correlation Coefficient (r^2)	n	Correlation Coefficient (r^2)	Diffusion Rate (K_H) ($h^{-1/2}$)
A	0.888	0.962	0.52	0.964	29.97
B	0.962	0.986	0.53	0.982	29.45
C	0.955	0.996	0.45	0.997	27.41
D	0.940	0.994	0.50	0.997	27.52
E	0.990	0.991	0.43	0.989	22.87
F	0.990	0.996	0.44	0.996	19.29
G	0.956	0.987	0.47	0.983	21.65
H	0.913	0.998	0.47	0.990	27.36
I	0.857	0.983	0.47	0.996	29.48

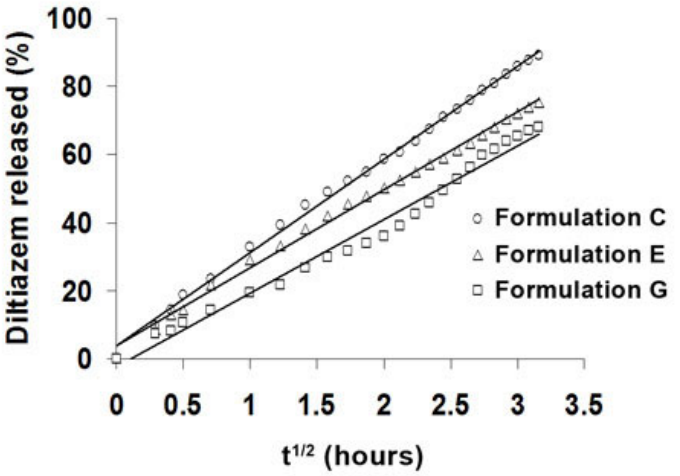

Figure 6. Higuchi plot of resinate-loaded polystyrene microcapsules.

resinate. Fitting the release data into the Higuchi equation[32] yielded comparable linearity (Figure 6) for all the microcapsules. Although inconclusive without further investigation, the present study indicated that release of diltiazem from the PS-coated resinates obeyed a diffusion-controlled process.

CONCLUSION

The study revealed that uniformly coated resinate-loaded PS microcapsules can be prepared by an oil-in-water ESE method through proper adjustment of the formulation parameters. The microcapsules having a reasonably high resinate loading efficiency maintained their integrity throughout the dissolution process and discharged the drug independent of the pH of the dissolution media. The microcapsules appeared suitable as a prolonged-release device for water-soluble drugs such as diltiazem.

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