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RESEARCH PAPER

Microencapsulation of a Hydrophilic Drug into a Hydrophobic Matrix Using a Salting-Out Procedure. II. Effects of Adsorbents on Microsphere Properties

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ABSTRACT

Wax microspheres of the hydrophilic drug guaifenesin were prepared by the congealable disperse-phase method using a salting-out procedure. In order to improve the particle properties of the microspheres, adsorbents (colloidal silica, magnesium stearate, and talc) were used during preparation. The effects of adsorbents on microsphere properties such as the angle of repose (AR), compressibility index (CI), geometric mean diameter (GMD), loading efficiency (LE), and in vitro drug release (DR) were determined. The AR, CI, and GMD of the microspheres were significantly reduced in the presence of the adsorbents. Increase in the concentrations of colloidal silica and magnesium stearate led to lower LE and faster DR, while talc showed no effect, which could be due to the particle diameter and specific surface area of the adsorbents. The microspheres prepared with colloidal silica were chosen to be compressed into tablets since they were smaller, more uniform, and had better flow properties than those made with magnesium stearate and talc. The in vitro drug release profile of the microsphere tablets was compared with that of commercially available Mucinex®, sustained release guaifenesin matrix tablets. Similar release profiles were observed between the two tablets. Scanning electronic microscopy (SEM) studies of the broken tablets revealed that the deformation of the microspheres caused by compression was minimal.

Key Words: Guaifenesin; Wax microspheres; Salting-out; Adsorbents; Tableted microspheres.

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INTRODUCTION

Multiple-unit sustained release dosage forms have been extensively used for the delivery of therapeutic agents due to their inherent clinical advantages over single-unit dosage forms.[1] These dosage forms spread out uniformly in the gastrointestinal tract and potentially reduce the risk of local irritation and dose-dumping, which are often seen with single-unit dosage forms.[2,3] In the last two decades, encapsulated and tableted microspheres have gained widespread popularity as multiple-unit dosage forms for the delivery of many therapeutic compounds.[4]

The congealable disperse-phase method for preparing sustained release microspheres is an oil-in-water emulsification process, which employs molten wax as the disperse phase into which the drug is loaded.[5] The advantages of this procedure are its simplicity, the minimal use of organic solvents, and well-formed spherical particles. Ceresine wax has been commonly used as the hydrophobic wax matrix in this procedure due to its inertness, nontoxicity, low melting range, and viscosity. In addition, it is highly retentive and forms microspheres that exhibit sustained release dissolution profiles. However, attempts to entrap highly water-soluble drugs using this method have resulted in low entrapment efficiencies (<15%), as the drugs could not be intimately dispersed in the wax phase and partitioned into the external aqueous phase during emulsification. To reduce the partitioning of the drug into the external phase, a salting-out agent and a hydrophobic wetting agent were included in the process. The hydrophobic wetting agent used improved the wettability of the drug by the molten wax to obtain a fine dispersion of the drug in wax, and the salting-out agent reduced the partitioning of the drug into the external phase during emulsification. In our previous experiments, the effects of other formulation variables on the entrapment efficiency such as the type of dispersant, the amount of wetting agent, the volume of external phase, and stirring speed and time were determined, based on which a drug-to-wax ratio of 1:4, monobasic sodium phosphate as salting-out agent, and span 60 as wetting agent were chosen for the present study.

While the ability of the wax matrix to undergo plastic deformation makes them suitable for compaction into tablets, the microspheres prepared show a tendency to be tacky, which leads to agglomeration, nonuniform particle size distribution, and poor flow behavior, due to which further processing into compressed tablets has been difficult.[6] Adsorbents have been commonly used to prevent particle agglomeration and improve the flowability of microspheres prepared using emulsification processes.[7–9] These studies have shown that the adsorbents used stabilized the emulsion by forming a physical barrier between the disperse-phase droplets and preventing their agglomeration. This led to the formation of microspheres with smaller, more uniform particle size distribution and enhanced flowability.

In the present study, colloidal silica, magnesium stearate, and talc were used as adsorbents to obtain microspheres with uniform particle size distribution and improved flow behavior and hence make their properties suitable for compression into tablets. The adsorbents were chosen on the basis of their low bulk density and high surface area. The effects of adsorbents on the geometric mean diameter, loading efficiency, angle of repose, compressibility index, and in vitro drug release rate of the microspheres were determined. The microspheres with optimum properties were compressed into tablets and the in vitro drug release rate of the tablets was compared to those of commercial Mucinex® tablets.

MATERIALS AND METHODS

Materials

Guaifenesin [melting point (MP) 78° C] was obtained from Napp Technologies Co. (Newark, NJ). Ceresine wax (MP 62 °C) was purchased from Strahl & Pitsch, Co. (West Babylon, NY). Monobasic sodium phosphate and tribasic sodium posphate were obtained from Fisher Scientific Co. (Pittsburgh, PA). Span 60 (sorbitan monostearate) was obtained from Ruger Chemical Co. (Irvington, NJ). Pluronic F-127 (PF-127) was obtained from BASF (Mount Olive, NJ). Also obtained were Avicel PH 101 (FMC Corp., Newark, DE), Talc (Gallipot Inc., St. Paul, MN), Magnesium Stearate (Van Waters and Rogers, Inc., Charleston, SC), Cabosil (Cabot Corp., Tuscola, IL), and Explotab (Penwest Corp., Paterson, NY). The compounds were used as received.

Wax Microspheres

Preparation

One hundred and sixty (160) g of ceresine wax was transferred to a 3-L-tall glass beaker and heated to 85° C. After the wax melted completely, a preweighed amount of adsorbent was added to the molten wax and stirred for 5 min using a mechanical stirrer (Lab Stirrer

LR 4000, Yamato Scientific Co., Ltd., Tokyo, Japan). Forty (40) g of guaifenesin, 10 g Span 60, and 10 g of Pluronic F-127 were then added to the melt and stirring was continued for 20 min. Subsequently the mixture was emulsified in 400 mL of 6 M monobasic sodium phosphate solution (maintained at 85° C) for 1 min at 900 rpm. One liter of 6 M monobasic sodium phosphate solution, previously cooled in an ice bath, was then added to the emulsion while stirring was continued. The suspension of hardened wax microspheres containing drug was filtered, washed with purified water, and dried at 40° C in vacuum for 48 h. Microsphere batches were prepared with 5, 10, and 15 g of the adsorbents and had batch sizes of 225, 230, and 235 g, respectively. The amount of adsorbents used corresponded to about 2%, 4%, and 6% of the total weight, respectively.

Assay

Aqueous solutions of guaifenesin were prepared at concentrations of 25, 50, 75, and 100 μg/mL. The solutions were assayed using a double beam UV spectrophotometer (Spectronic 2000, Bausch & Lomb, Rochester, NY) at 274 nm to generate a calibration plot. To calculate the drug content, 0.25 g of the microspheres were weighed into 500 mL volumetric flasks. Two hundred milliliters of purified water were added to the individual volumetric flasks and the solutions were stirred at 85° C for 45 min. At the end of stirring, the flasks were allowed to cool down and were made up to volume with purified water. Each microsphere batch was prepared for assay in triplicate. A 5-mL sample of the test solution was filtered using a 0.45-μm Millipore filter and assayed by UV spectrophotometry at 274 nm. The wax and the other ingredients present in the microspheres did not interfere with the assay of guaifenesin.

Geometric Mean Diameter

The separation of microspheres into various size fractions was carried out using a mechanical sieve shaker (Model RX-86, W.S. Tyler Inc., Gastonia, NC). A series of five standard stainless steel sieves (ASC Scientific, Jamestown, RI) were arranged in the order of decreasing aperture size (105–550 μm). Ten grams of drug-loaded microspheres were placed on the uppermost sieve and mechanically shaken for a period of 10 min. The individual sieves were weighed to determine the amount of microspheres retained. From the weight distribution, the geometric mean diameter, d_g, was calculated for each microsphere batch.

Angle of Repose and Compressibility Index

The static angle of repose was measured according to the fixed funnel and free standing cone method.[10] A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured at its tip 2 cm high (H) above a graph paper placed on a flat horizontal surface. The microspheres were poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. The mean diameter (2R) of the base of the powder cone was measured and the tangent of the angle of repose was calculated by:

$$\tan\alpha = H/R$$

where α and R are the angle of repose and radius of the base of the powder cone, respectively.

The compressibility index (CI) of the microspheres was determined by measuring the initial volume of the microspheres (V_o) in a graduated cylinder and the final volume (V) after subjecting the filled cylinder to 100 tappings using the following equation:

$$CI = [1 - (V/V_o)] \times 100$$

Both determinations were made in duplicate for each microsphere batch.

Measurement of In Vitro Release Rate

The in vitro drug release studies of the microspheres were performed in triplicate using the USP Type I apparatus (Model Premier 5100, Distek Inc., North Brunswick, NJ). The microspheres, which had a tendency to float in water, were placed in baskets and immersed in the dissolution medium of 500 mL of pure water. The agitation speed was 50 rpm and temperature was maintained at 37° C ± 0.5° C. Suitable amounts of the microspheres equivalent to 100 mg of guaifenesin were transferred to each basket. Dissolution samples of 5.0 mL were removed at 1, 2, 6, 12, and 24 h and were filtered using a 0.45 μm Millipore filter, diluted appropriately and analyzed by UV spectrophotometry at 274 nm. The microspheres were used as is for the release rate study.

Microsphere Tablets

Preparation

Appropriate amounts of the microspheres, Avicel PH 101® and Explotab®, were transferred and blended in a planetary mixer for 10 min. Magnesium stearate

was added to the powder blend and mixing was continued for 2 min. The mixture was subsequently compressed using a rotary tablet press (Stokes, Model RD-3, Key Industries, Englishtown, NJ) to a weight of 1200 mg per tablet and hardness in the range of 10–12 kp. The compression force used was 3.8 MPa. The formulation contained 78% of drug-loaded microspheres, 18.9% of Avicel PH101, 2.5% Explotab, and 0.6% magnesium stearate. Each scored, capsule-shaped tablet contained 150 mg of guaifenesin. The disintegration time was determined using the USP disintegration apparatus (Model 35-1000, Van Kel Technology Group, Cary, NC).

Content Uniformity

The content uniformity of the tablets was determined using the USP procedure ⟨905⟩. Ten tablets were ground individually and transferred to 500 mL volumetric flasks. Two hundred milliliters of deionized (DI) water was added to each volumetric flask and stirred at 85° C for 45 min. At the end of stirring, the flasks were allowed to cool down and were made up to volume with DI water. An aliquot of the solutions was diluted 10 times using DI water, filtered using a 0.45 μm Millipore filter, and assayed by UV spectrophotometry at 274 nm.

In Vitro Drug Release

The in vitro drug release studies of the tablets were performed using the USP Type II apparatus (Model Premier 5100, Distek Inc., North Brunswick, NJ) using a modified method.[11] Six replicates of the microsphere and Mucinex® tablets were placed in the dissolution medium, which was 675 mL of 0.1 N HCl. Samples of 5.0 mL were removed at 1 and 2 h from each vessel. Immediately after the two-hour dissolution samples were withdrawn, 225 mL of 0.2 M tribasic sodium phosphate was added to each vessel to increase the solution to pH 6.8 in order to simulate gastrointestinal pH conditions. The dissolution medium was maintained at 37° C ± 0.5° C throughout the study. Samples of 5.0 mL were subsequently removed at 4, 6, 10, and 12 h. The dissolution samples were filtered using a 0.45-μm Millipore filter, diluted appropriately and analyzed by UV spectrophotometry at 274 nm.

Scanning Electron Microscopy

The morphology of the microspheres was evaluated using a scanning electron microscope (FE-SEM, LEO Electron Microsopy, Inc., Thornwood, NY). The surface characteristics of the microspheres were observed by coating the particles with chromium to a thickness of 50 nm using a vacuum evaporator. The tablets were broken along the score and the surface was sputter-coated with gold to a thickness of 50 nm to observe the surface morphology of the compressed microspheres.

RESULTS AND DISCUSSION

The formulation of microspheres into compressed tablets has been preferred due to its significant advantages over other dosage forms.[12] In order to successfully compress wax microspheres into tablets, their particle properties have to be improved. Particularly, the reduction in agglomeration and improved flowability of the microspheres are critical for preparing compressed microsphere tablets. In order to reduce the tackiness and agglomeration of the wax microspheres, compounds such as stearyl alcohol and glyceryl monostearate have been used.[5] In this study, colloidal silica, magnesium stearate, and talc were used as adsorbents to prevent clumping and agglomeration of the microspheres and thereby improve their particle properties and flowability.

Geometric Mean Diameter and Loading Efficiency of the Microspheres

Table 1 shows the geometric mean diameter and loading efficiency obtained for the microspheres. It was observed that the particle size of the microspheres was generally smaller in the presence of adsorbents. The highest decrease in particle size was caused by colloidal silica, followed by magnesium stearate, while there was no significant change in the presence of talc. The adsorbents apparently reduced the agglomeration of the disperse-phase wax droplets and led to a finer distribution of the wax droplets during emulsification, which caused a reduction in the particle size of the microspheres. In addition, the clumping of the microspheres due to the tackiness of the wax was also reduced by the formation of a physical barrier between the individual particles by the adsorbents. Colloidal silica possessed the lowest bulk density and the highest surface area followed by magnesium stearate and talc. Due to the small particle size and high specific surface area, colloidal silica was dispersed better in the molten wax.[13] Hence, it reduced the physical contact between the disperse-phase droplets to a greater extent and reduced the agglomeration of the microspheres.

Table 1. Effects of adsorbents on loading efficiency and geometric mean diameter of microspheres.

Adsorbent	Amount[a]	% Drug loading	Loading efficiency[a] ± SD	Geometric mean diameter[b] (d_g)
No adsorbent	N/A	18.2	93.1 ± 0.8	325 ± 5
Colloidal silica	2.0	17.8	89.7 ± 1.2	189 ± 5
	4.0	17.4	86.9 ± 0.8	164 ± 10
	6.0	17.0	82.1 ± 0.9	148 ± 9
Magnesium stearate	2.0	17.8	90.8 ± 0.8	259 ± 5
	4.0	17.4	89.1 ± 1.0	231 ± 8
	6.0	17.0	88.3 ± 1.2	207 ± 10
Talc	2.0	17.8	92.2 ± 0.8	316 ± 11
	4.0	17.4	90.9 ± 0.8	311 ± 8
	6.0	17.0	90.1 ± 0.8	310 ± 6

[a]%.
[b]μm.

The loading efficiency of the microspheres was also reduced in the presence of adsorbents, with the greatest reduction found with colloidal silica, followed by magnesium stearate and talc. This could be attributed to the greater particle size reduction of the microspheres in the presence of colloidal silica as compared to magnesium stearate and talc. The smaller particles produced in the presence of colloidal silica represented greater surface area, which caused the microspheres to come into increased contact with the aqueous phase during filtration and washing of the microspheres. This led to greater partitioning of the drug into the aqueous phase and reduced loading efficiency. In addition, small particles (<130 μm) produced were prone to be lost during filtration and recovery of the microspheres and lowered the loading efficiency.[5]

Angle of Repose and Compressibility Index

The flow behavior of powders is extremely complex and is usually a function of interparticulate interactions, which are greatly influenced by the area of contact between the individual particles.[13] Powder materials that undergo agglomeration and plastic deformation, which increase the area of contact, exhibit poor flow characteristics.[14] This type of behavior is commonly exhibited by waxy materials and explains the high angle of repose obtained for the microspheres in the absence of adsorbents as shown in Table 2.

Nash showed that adsorbents like colloidal silica function as flow conditioners and significantly improve the flow behavior of Carbowax powder.[14] In their study, colloidal silica particles were found to preferentially adsorb to the surface of the wax particles due to the plasticity of the wax and reduce contact between the wax particles. A similar mechanism of action led to better flowability of the microspheres and decreased the angle of repose. The reduction in the angle of repose was accentuated with increase in the concentration of colloidal silica and magnesium stearate.

The compressibility index (CI) of a material indicates the ease with which it can be induced to flow.[6] An increase in CI is indicative of better packing and consolidation of the powder material and represents an increase in interparticulate interactions causing resistance to flowability. Values of CI up to 25% usually indicate good flowability.[15] The CI obtained for the microspheres without adsorbents were higher than 25%, as shown in Table 2, which suggests very poor flow characteristics. The tapping procedure led to a significant packing rearrangement of the

Table 2. Effect of adsorbents on angle of repose of microspheres.

Adsorbent	Amount[a]	Angle of repose	CI[a]
No adsorbent	N/A	39.7 ± 1.5	27.3 ± 2.3
Colloidal silica	2.0	22.7 ± 1.8	16.3 ± 1.9
	4.0	21.6 ± 0.9	15.8 ± 1.4
	6.0	20.4 ± 0.1	12.8 ± 2.7
Magnesium stearate	2.0	31.7 ± 1.5	22.7 ± 2.0
	4.0	28.5 ± 0.4	21.8 ± 0.3
	6.0	26.4 ± 1.6	18.5 ± 1.6
Talc	2.0	35.8 ± 1.9	25.3 ± 1.7
	4.0	34.1 ± 0.8	24.2 ± 1.1
	6.0	33.7 ± 1.1	23.6 ± 0.8

[a]%.

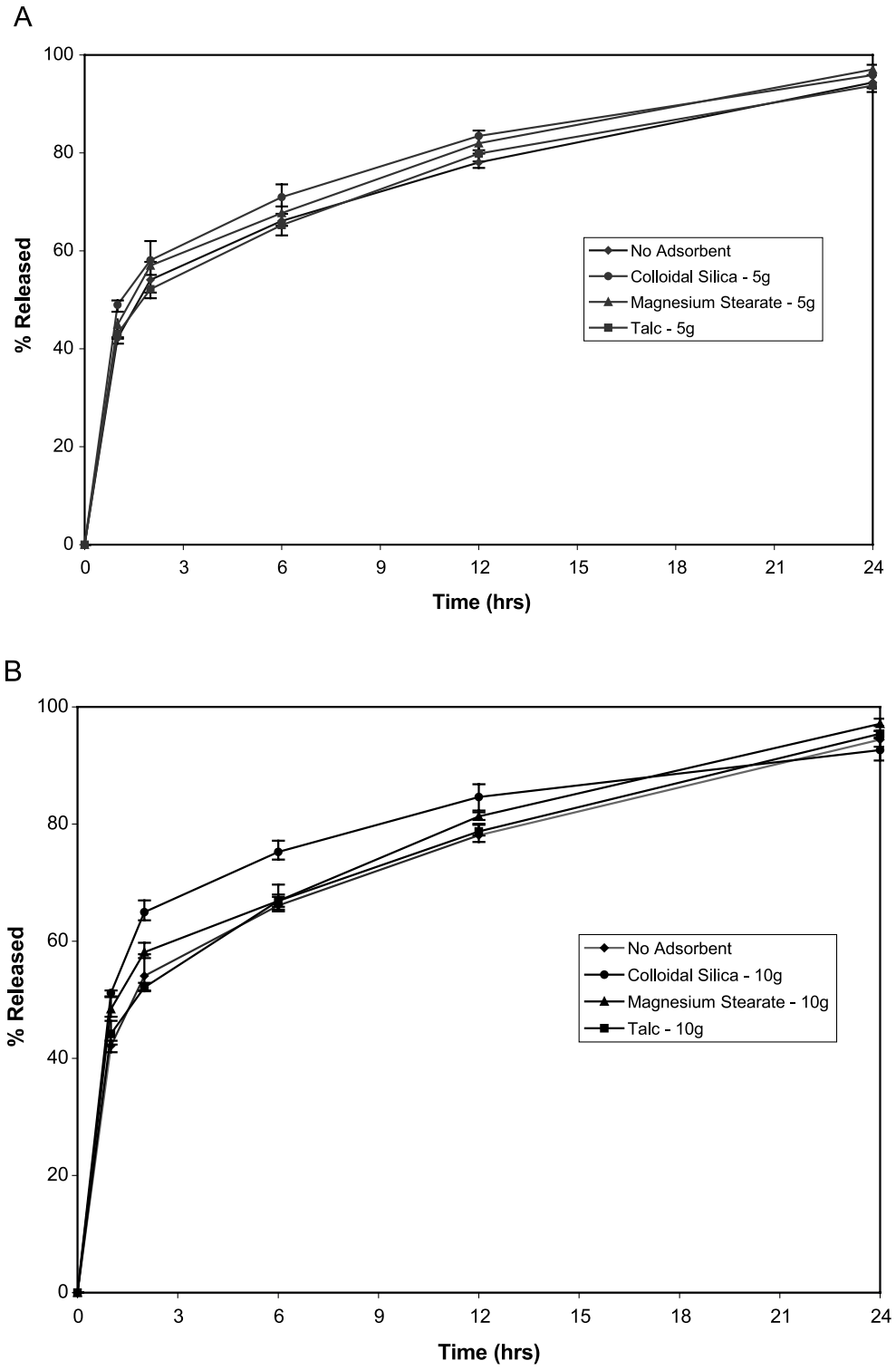

Figure 1. (A) Dissolution profiles of the microspheres with 2% adsorbents. (B) Dissolution profiles of the microspheres with 4% adsorbents. (C) Dissolution profiles of the microspheres with 6% adsorbents. (*View this art in color at www.dekker.com.*)

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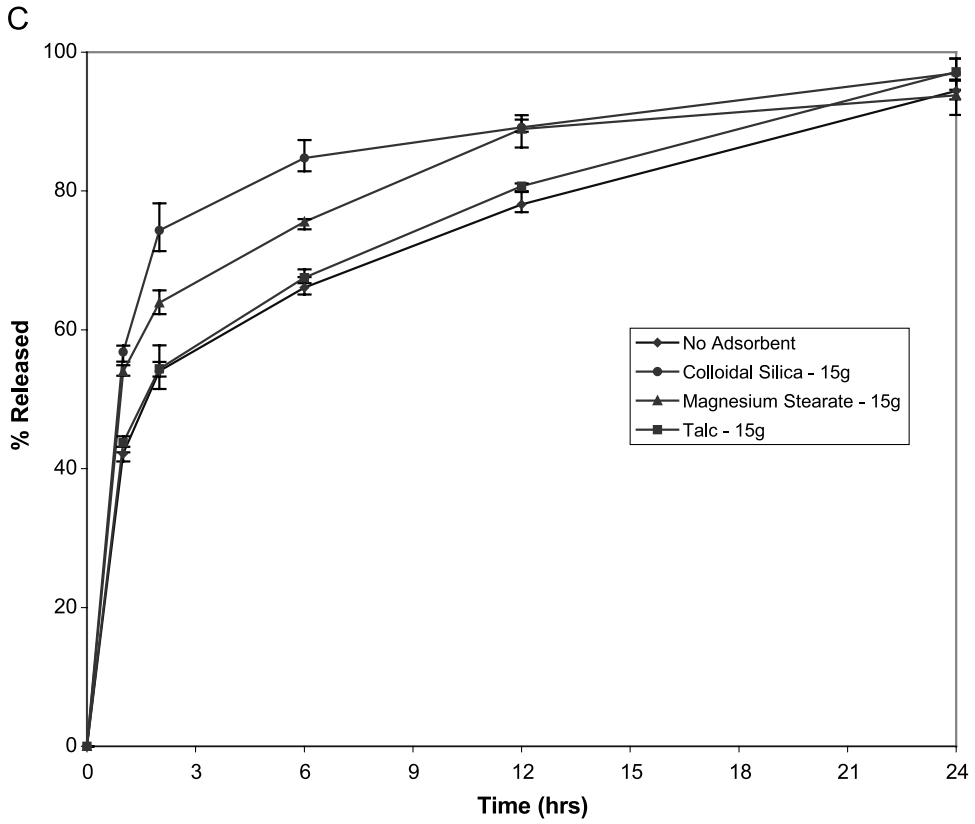

Figure 1. Continued.

microspheres without adsorbents, which could be due to the agglomeration and nonuniform particle size distribution of the microspheres, and also led to higher CI values.

The CI obtained was below 25% with increasing concentrations of colloidal silica and magnesium stearate and to a lesser degree in the presence of talc, which indicated good flow characteristics. The differences in the bulk and tapped densities were lower in the case of the microspheres containing adsorbents due to their smaller particle size and more uniform particle size distribution as compared to the microspheres prepared without adsorbents.

In Vitro Release Rate of the Microspheres

Figures 1A–1C show the release profiles of guaifenesin from the microspheres prepared in the presence and absence of adsorbents. All of the release profiles exhibited an initial rapid release, followed by a slower rate, which was consistent with the Higuchi square root of time release model.[16] The initial rapid release was higher in the presence of colloidal silica and magnesium stearate than for the microspheres prepared without adsorbent, while talc did not show a significant effect on the drug release. In the microspheres, guaifenesin was primarily dispersed in the wax, which functions as a polymer matrix. The release of drug from the microspheres into the dissolution medium was by diffusion of drug from the matrix into the surrounding dissolution medium. An increase in the surface area of the microspheres in contact with the dissolution medium led to greater wetting of the microspheres and higher rate of diffusion. Hence, the in vitro release rate was higher for the microspheres with colloidal silica due to their greater surface area as compared to the microspheres with magnesium stearate and talc.

Content Uniformity and Disintegration of the Microsphere Tablets

The microspheres prepared with 2% colloidal silica were chosen to be compressed into tablets since they possessed good loading efficiency and uniformity

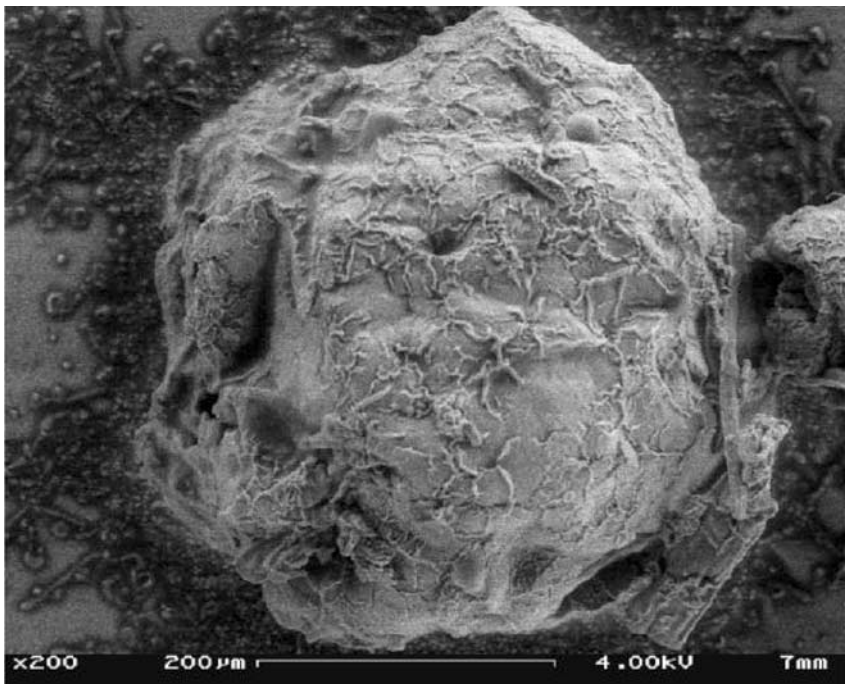

Figure 2. Scanning electron micrograph of microspheres without adsorbents.

and had better flow properties than the other batches of microspheres. The content uniformity values were between 89.5% and 99.8% and had a percent RSD of 3.7%.

Since the wax matrix is hydrophobic and nonporous, the entry of aqueous solution media into the microsphere tablets is very minimal. The disintegration time of the tablets into its constituent microspheres,

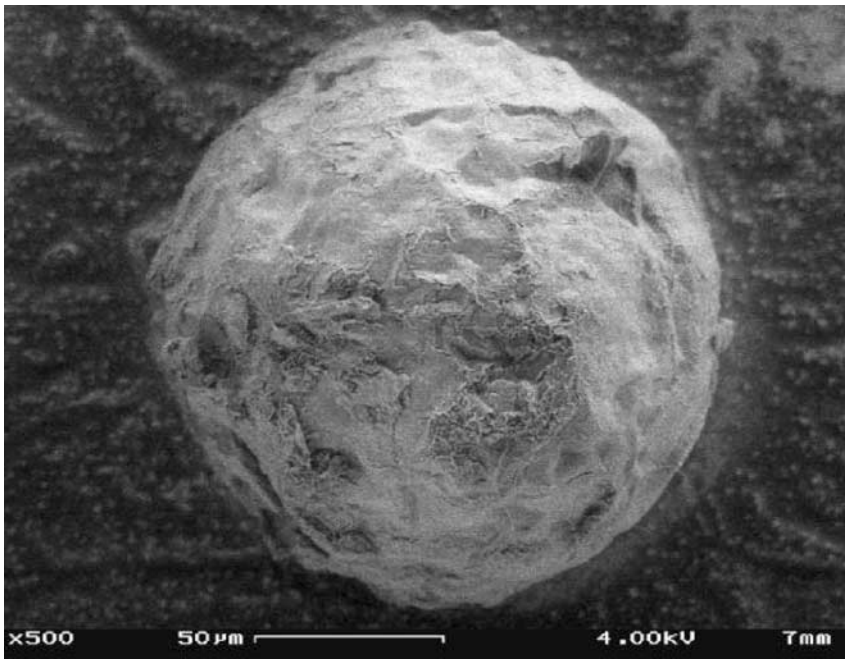

Figure 3. Scanning electron micrograph of microspheres with colloidal silica.

which was a critical factor affecting drug release was nearly 2 h in the absence of suitable excipients, but was greatly reduced in the presence of the disintegrating agent Explotab and was less than 30 min in 0.1 N HCl.

Scanning Electron Microscopy

Figures 2–4 show the scanning electron micrographs of the microspheres and the broken microsphere tablets. The microspheres had a rough exterior in which the drug particles were embedded. The microspheres without adsorbent were agglomerated and had irregular and textured external surfaces, while those containing adsorbents were more spherical with smoother external surfaces and did not show any significant agglomeration. The micrographs obtained on the broken tablets showed the presence of intact microspheres on the surfaces of the broken tablets. This indicated that the compression pressure applied on the microspheres did not greatly deform the microspheres.

In Vitro Drug Release from the Microsphere Tablets

Figure 5 shows the dissolution profiles obtained on the microsphere tablets and the Mucinex matrix tablets. The T_{50} (time for 50% release) was 1.8 and 2.9 h for the microsphere and Mucinex matrix tablets, respectively. The release profiles for both the tablets consisted of an initial rapid release of the drug at 1 h, followed by a slower rate of release. Mucinex is a commercially available, bilayered tablet comprising of immediate and sustained release portions containing guaifenesin and has been shown to possess in vitro and in vivo sustained release dissolution profiles.[11] The drug present in the immediate release portion completely dissolved within 1 h and contributed to the initial release of drug. The release of guaifenesin from the microsphere tablets on the other hand, was dependent on the disintegration of the tablets into their constituent microspheres and subsequent diffusion of the drug from the microspheres into the dissolution medium. In the present study, the microsphere tablets disintegrated completely within 30 min. The drug particles in the microspheres were either completely or partially entrapped in the wax matrix, the proportion of which depended on the drug/wax ratio. The particles that were partially entrapped in the wax matrix diffused very quickly into the dissolution medium and caused the initial rapid release of drug. At the drug/wax ratio of 1:4 used in this study, the amount of drug partially entrapped in the wax was apparently higher than the drug contained in the immediate release portion of Mucinex tablets and hence the percent drug released at 1 h was higher for the microsphere tablets

The drug release rate after 1 h was controlled by the sustained release portion of Mucinex tablets, which

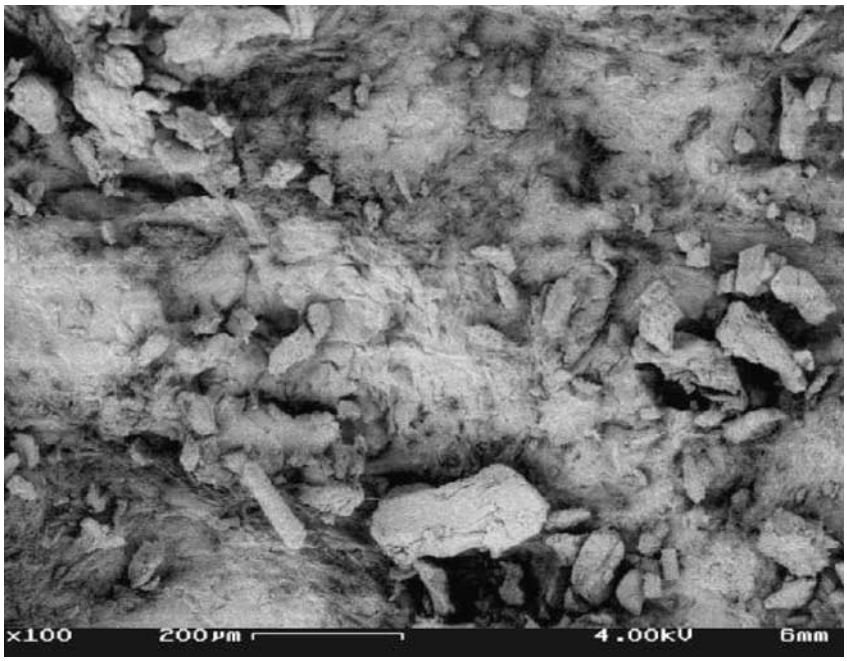

Figure 4. Scanning electron micrograph of the broken microsphere tablets.

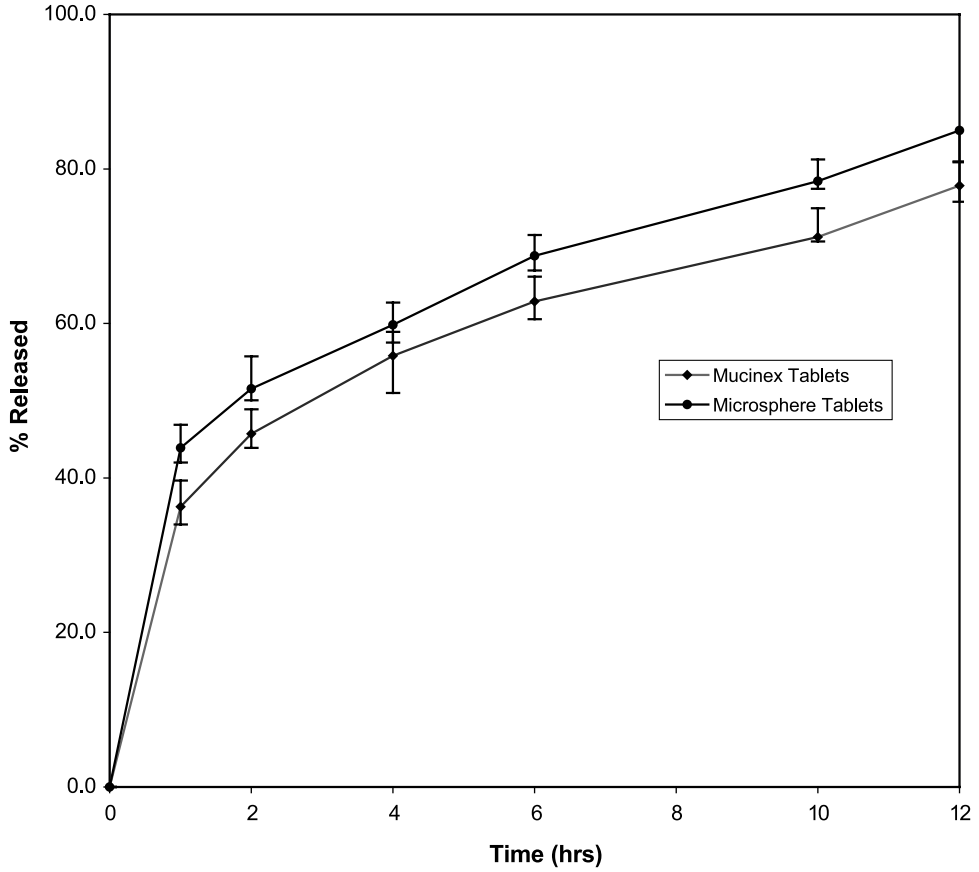

Figure 5. In vitro drug release profiles of Mucinex and microsphere tablets. (*View this art in color at www.dekker.com.*)

contained the hydrophilic polymer hydroxypropylmethylcellulose as the matrix former. The penetration of the dissolution medium into the tablet matrix led to the swelling of the tablets, which led to the slow release of the drug over 12 h. The sustained release portion remained as a solid core throughout the dissolution experiment. In the microsphere tablets, the diffusion of the drug entrapped in the wax matrix over a 12-h time period led to the slow release of drug. It was also observed that the dissolution profiles obtained for the microsphere tablets were very similar to those of the microspheres before compression ($T_{50} = 1.7$ h), which indicated that the drug release from the microspheres was not significantly affected by the compression pressure applied to form tablets, which was also indicated by the SEM results.

A regression analysis was performed on the release profiles of the tablets subsequent to the 1-h time point, which represented the sustained release portion. The cumulative percentages of drug released against time were plotted, and best-fit regression lines were obtained. The slopes and intercepts of the best-fit lines were 3.0548 and 3.0271 and 48.184 and 42.016 and the correlation coefficients were 0.9856 and 0.9743 for the microsphere and Mucinex tablets, respectively, which indicated good linearity of the plots and showed that a constant drug release was obtained after the 1-h time point.

Due to the rapid disintegration of the microsphere tablets into their constituent microspheres, they behaved as multiple-unit dosage forms and hence could be clinically advantageous as compared to single-unit matrix tablets. Multiple-unit dosage forms are known to provide a more predictable gastric emptying and enhance bioavailablity.[17] Since multiple-unit dosage forms are quickly dispersed in the gastrointestinal tract, the risk of high local concentration, which could damage the mucosa, could be minimized.[18]

CONCLUSIONS

This study illustrated the role of adsorbents in the formulation of guaifenesin wax microspheres prepared by the hydrophobic congealable disperse-phase method.

The improved particle properties of the microspheres due to the presence of adsorbents rendered them more suitable for processing into compressed tablets. The microsphere tablet formulation showed sustained release dissolution profiles that were similar to those obtained for the commercially available single-unit matrix tablet of this drug.

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