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Research Article

Silicone Adhesive Matrix of Verapamil Hydrochloride to Provide pH-Independent Sustained Release

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Abstract. Providing pH-independent oral release of weakly basic drugs with conventional matrix tablets can be challenging because of the pH-dependent solubility characteristics of the drugs and the changing pH environment along the gastrointestinal tract. The aim of the present study was to use a hydrophobic polymer to overcome the issue of pH-dependent release of weakly basic model drug verapamil hydrochloride from matrix tablets without the use of organic buffers in the matrix formulations. Silicone pressure-sensitive adhesive (PSA) polymer was evaluated because of its unique properties of low surface energy, hydrophobicity, low glass transition temperature, high electrical resistance, and barrier to hydrogen ion diffusion. Drug release, hydrogen ion diffusion, tablet contact angle, and internal tablet microenvironment pH with matrix tablets prepared using PSA were compared with those using water-insoluble ethyl cellulose (EC). Silicone PSA films showed higher resistance to hydrogen ion diffusion compared with EC films. Verapamil hydrochloride tablets prepared using silicone PSA showed higher hydrophobicity and lower water uptake than EC tablets. Silicone PSA tablets also showed pH-independent release of verapamil and decreased in dimensions during drug dissolution. By contrast, verapamil hydrochloride tablets prepared using EC did not achieve pH-independent release.

KEY WORDS: ethyl cellulose; pH-independent release; silicone; sustained release oral; verapamil hydrochloride; weakly basic drug.

INTRODUCTION

The majority of therapeutically active drugs are either weak acids or weak bases. Their solubility varies depending on the pH of the surrounding solution, thereby showing pH-dependent solubility. As a result, the dissolution rates of ionizable drugs can vary depending on the pH of the external dissolution media (1). These drugs in oral dosage forms therefore show variable drug release when exposed to the wide pH range (pH 1.2–8) in the gastrointestinal (GI) tract *in vivo* (2), leading to variability in oral absorption *in vivo*.

Several strategies have been employed to overcome the challenges of pH-dependent release of weakly ionizable drugs in oral hydrophilic matrices. A method of maintaining constant microenvironment pH in the immediate vicinity of weakly basic drugs in tablet matrices is achieved by the addition of buffers or organic acids such as tartaric, fumaric, or succinic acids (3–5). Conversely, basic excipients such as dicalcium phosphate, magnesium oxide, or magnesium hydroxide can be used to maintain microenvironment pH for matrices containing weakly acidic drugs (6). It has been observed that because of the high solubility and low molecular weight of the organic buffers, they can readily diffuse out of the matrices leaving the drugs behind, which leads to the failure of achieving pH-independent drug release. To ensure pH-independent release, large quantities of pH-stabilizing excipients are required. This could result in an increase in the sizes of the tablets making swallowing of the tablets difficult for drugs that require high daily doses (7).

An alternative strategy to overcome the challenges of pH-dependent drug release is to coat the drug particles with pH-dependent copolymers such as methacrylic acid and phthalates (8,9). In this case, complicated processes such as spray drying and multiple drug coatings are usually required to achieve pH-independent release of weakly ionizable drugs, making the manufacturing process expensive and time consuming (10). Simple mixing and compression of pH-dependent polymers, such as hydroxypropyl methylcellulose acetate succinate with an ionizable drug, have failed to show pH-independent release (11).

Another strategy used to achieve pH-independent release of ionizable drugs is the utilization of silicone in oral dosage form design. In this approach, a drug is in its unionized form with pH-adjusting agents in silicone microspheres. As the unionized drug has higher partitioning and drug release through silicone compared with the pH-adjusting agents (12), this improves the retention of the pH-adjusting agents inside the microspheres and provides pH-independent release (13). However, if the drug is deposited outside the hydrophobic polymer fibers in a matrix above its percolation threshold or solubility limit, release of the ionized fraction of the drug can

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occur through the aqueous pore network formed within the monolithic matrix of silicone (14).

Silicone pressure-sensitive adhesive (PSA) polymers are flexible, water repellant viscoelastic polymers with high cohesive strengths (15). They are cross-linked polymers of polydimethylsiloxane (PDMS) and silicate resin. The polymers are in rubbery state at room temperature because of their low glass transition temperature. Silicone PSA polymers also have low surface tension (24 mN/m) and can spread easily on surfaces. In addition, these polymers have liquid-like properties and are able to flow under pressure making them suitable as adhesives in transdermal patches (16,17). Silicone elastomers have been evaluated as microelectromechanical system device coating material because of their excellent ion permeation barrier properties (18,19). Although silicone PSA is not used in commercial oral products, polysiloxane is listed on the FDA-inactive ingredient list for use in oral capsules and in antacid preparations (20). Oral dosage prepared using silicone elastomer was investigated in humans and was found to be eliminated in the feces with no GI absorption and without adverse events (21,22).

Hydrophobic resin polymers have previously been evaluated for oral delivery *in vivo* without showing any adverse events (23). Hydrophobic cellulose ether such as ethyl cellulose (EC) is widely used as coating polymers to provide sustained release and taste masking of drugs (24). Particularly, EC is used in peroral delivery systems of tablets, capsules, and suspensions. EC is a rigid polymer and can be plasticized to produce flexible films in tablet coating (25). Drug release from EC coated beads was shown to be pH dependent, related to drug ionization and pH of the dissolution medium (26). A previous comparison of the tensile strength and drug release from tablets prepared using flexible silicone PSA and rigid EC matrices using water-soluble model drug acetaminophen (APAP) has shown that silicone PSA can provide tablets with higher tensile strength and lower friability compared with tablets prepared using EC. However, the effect of pH upon drug release from silicone PSA was not evaluated because APAP is unionized at physiological pH, and the dissolution medium pH conditions are not expected to affect APAP drug release (27).

In the present study, a pH-independent controlled-release matrix utilizing silicone PSA for the sustained release of a weakly basic drug was evaluated and compared with EC. It was hypothesized that drug-loaded silicone PSA matrices could provide a hindrance to the permeation of ions from the external dissolution media into the drug matrices, thereby reducing microenvironment pH fluctuation in the matrices and providing pH-independent drug release without the use of organic buffers. Verapamil hydrochloride, a weakly basic drug with pH-dependent solubility, was used as the model drug in this study. Experiments were conducted to characterize the silicone PSA delivery system by tablet contact angle, tablet water uptake, tablet physical dimensions, and tablet internal environment pH on exposure of the tablets to varying dissolution medium pH. In addition, transport and electrical resistance measurements across polymer films and the matrix tablets were performed.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride, USP, was purchased from Letco Medicals (Decatur, AL, USA). EC (degree of substitution of 2.5, ethoxy content of 48%) was obtained from Scientific Polymer Products Inc (Ontario, NY, USA). Silicone PSA BIO-PSA® 7-4202 in ethyl acetate was obtained from Dow Corning Corporation (Midland, MI, USA). Silicone PSA was dried overnight in fume hood followed by 10 min at 70°C before use. APAP was obtained from Mallinckrodt (St Louis, MO, USA). Methyl red (sodium salt) was obtained from Fisher Scientific (Pittsburgh, PA, USA). Scotchpak™ 1022 fluoropolymer coated release liner was obtained from 3 M (St Paul, MN, USA). All other chemicals used were of reagent grade.

Preparation of Polymer Matrix Tablets

Dried silicone PSA or EC powder (2.0 g) was weighed and dissolved in 7 mL ethyl acetate in a glass vial to obtain a mixture capable of uniform mixing. The vial was allowed to rotate on a rotating mixer until the polymers were completely dissolved in ethyl acetate. The required amount of verapamil hydrochloride powder (~8.0 g) was added to the polymer solution. The suspension obtained was allowed to rotate for 4 h on a rotating mixer. The suspension was deposited on the fluoropolymer coated side of the Scotchpak™ release liner and allowed to dry overnight. Residual ethyl acetate after the drying procedure was found to be lower than the acceptable daily limit for a class 3 solvent (28). Considering the cohesive nature of silicone PSA, the dried matrix was cohesive and nonflowing. Then, 500 mg of the dried matrix was weighed and compressed using a manual single-punch tableting machine (Fred S Carver Inc., Summit, NJ, USA) with compression force of 8.7 kN to produce a flat-faced tablet (13 mm in diameter). The final tablet weight was 500±5 mg. Table I shows the compositions of the investigated tablets.

Differential Scanning Calorimetry Characterization

Verapamil hydrochloride powder and dried final matrix tablets of PSA and EC (formulations 1 and 2 in Table I) were characterized using differential scanning calorimetry (DSC) (Netzsch STA 409, Germany). The samples were heated in a closed aluminum pan at a rate of 10°C/min from 25°C to 250°C. DSC curves were obtained under argon flow rate of 30 mL/min.

Table I. Composition (%, *w*/*w*) of Investigated Verapamil Hydrochloride Matrix Tablets

Formulation	1	2	3	4	5[a]	6[a]	7[b]	8[b]
Verapamil hydrochloride	80	80	85	90	79.8	79.8		
Silicone PSA	20		15	10	20		20	
EC		20				20		20
Methyl red					0.2	0.2		
APAP							80	80

[a] For tablet morphology and imaging study
[b] For electrical resistance study

Preparation of Polymer Films

Polymer films of 100% silicone PSA and 100% EC were prepared by dispersing a 40% (*w*/*v*) solution of the polymer in ethyl acetate using a film casting knife (MTI Corporation, Richmond, USA) at 40 mil gap on the Scotchpak™ fluoropolymer coated release liner. The thickness of the dried films was measured using digital calipers (Mitutoyo, Japan) at five different locations and the average thickness was used.

Contact Angle Measurements

Contact angle measurements were performed on the PSA and EC polymer film and tablet surfaces using a Rame–Hart goniometer (Mountain Lakes, NJ, USA). The goniometer was attached to a video camera for digital image capturing in contact angle measurements. Advancing angles were measured using the sessile drop technique, similar to the method described by Zografi *et al.* (29). Briefly, a 5-μL drop of the dissolution media was placed on the polymer film or the tablet surface using a calibrated micropipette. Contact angle was measured at 35° angle. The average of five measurements was reported.

In Vitro Drug Release Studies

In vitro drug release from the tablets, tablet water uptake, and changes in tablet dimensions were studied using USP apparatus 1 rotating basket with a stirring speed of 100 rpm (Vankel, Cary, NC, USA). USP apparatus 1 was used to prevent tablet sticking to the dissolution vessel wall. Dissolution studies were carried out using 900 mL of either simulated gastric fluid (SGF; pH 1.2) without enzyme or simulated intestinal fluid (SIF; pH 6.8; USP 30) maintained at 37°C ($n \geq 3$). At predetermined time intervals, 1 mL of dissolution medium was sampled and replaced with fresh medium. When necessary, samples were diluted with appropriate volume of distilled deionized water before analyses. Verapamil hydrochloride concentration in the dissolution samples was analyzed using a UV spectrophotometer (Beckman, Indianapolis, IN, USA) at 278 nm wavelength. The percent cumulative drug release was calculated and plotted against time. Standards for the calibration curve were prepared using powder verapamil hydrochloride in the dissolution medium in the range of 15–250 μg/mL.

Water Uptake and Tablet Dimension Changes During Drug Dissolution

Tablets containing 0.2% methyl red pH indicator were used for water uptake and internal morphology change studies (formulations 5 and 6 in Table I). In these studies, separate experiments were carried out to collect tablets at each time point in the dissolution media SGF and SIF under the same dissolution conditions described in the above section in triplicates. The rate of water uptake was determined gravimetrically. Initial tablet weight and dimensions (V_0) were measured before the immersion of the tablets in the dissolution media. At predetermined time points (t_t), tablets were removed from the dissolution bath. The wet weight and dimensions of the tablets were recorded. Wet tablets were immediately transferred into individual glass vials and frozen using dry ice. Frozen tablets were freeze-dried to remove the dissolution medium by sublimation. It was assumed that immediate freezing and freeze-drying stopped the movement of liquid within the tablet. The dimensions (V_t) of freeze-dried tablets at time t_t were measured using calipers. The percent water content in the tablets (or water uptake) at time t_t was calculated using the following equation:

$$\%\,\text{water content} = \left(\frac{\text{wet weight}\,(t_t) - \text{dry weight}(t_t)}{\text{dry weight}(t_t)}\right) \times 100 \quad (1)$$

The volume of the tablets was estimated using Eq. (2) assuming a cylindrical shape:

$$V = \pi h\left(\frac{D}{2}\right)^2 \quad (2)$$

The changes in volume of the tablets after drug release were determined using Eq. (3):

$$\%V = \frac{(V_0 - V_t)}{V_0} \times 100 \quad (3)$$

Changes in Internal Tablet Morphology

Dynamic changes in the external and internal morphology of the tablets containing pH indicator methyl red (formulations 5 and 6 in Table I) were monitored on exposure of the tablets to SGF and SIF dissolution media using the dissolution experimental conditions described in the section above (10,31). Tablets were removed upon exposure to the dissolution medium at pre-determined time intervals, frozen immediately in dry ice, and freeze-dried for complete dryness as described above. The tablets were placed under a stereomicroscope attached to a digital camera (VHX-1000 Keyence, Osaka, Japan) equipped with high-resolution lens (VHZ-20R, Keyence, Osaka, Japan) and examined under ×20 magnification to acquire the surface images. Digital images were obtained in jpeg format under constant magnification and light settings. Cross-section images of freeze-dried tablets were obtained by cutting the tablets in the radial direction using a surgical scalpel (blade no. 11) and with the optical imaging system described above. After acquisition of the images with the digital camera, the image files were analyzed by Adobe Photoshop (Adobe, San Jose, CA, USA).

Hydrogen Ion Diffusion Across Silicone PSA and EC Films

In the diffusion experiments, dried polymer films supported by filter paper on both sides were placed in a vertical diffusion cell (1 cm diameter opening; 0.785 cm^2 diffusion area). The donor solution was 0.1 M HCl, and the receptor solution was 0.154 M NaCl. The temperature was maintained at 37°C. The pH of the receptor solution was measured over time using a pH microprobe (Beckman Instruments, Irvine, USA). The measured pH was converted to hydrogen ion concentration using: $pH = -(\log [H^+])$. The pH of the

receptor solution at the start of the experiment was 5.62. The EC and PSA films used in this experiment had approximate thicknesses of 10.5 and 12.4 mil, respectively.

Measurement of Resistance of Polymer Films and Tablets

The electrical resistances of the polymer films and of the tablets before and during drug dissolution were measured in a diffusion cell setup at 37°C. Polymer films of 100% EC and PSA polymers and drug matrix tablets containing 80% APAP and 20% (*w*/*w*) polymer were prepared by the same procedure as described for the verapamil hydrochloride matrix tablets. Nonionizable drug APAP was used as the model drug in the tablets instead of verapamil hydrochloride for the electrical resistance measurements to avoid interference of drug ion (verapamil hydrochloride) to the background electrolyte ions in the resistance measurements. In these experiments, the tablets were removed during drug release from the USP apparatus at 1, 5, and 9 h, and the tablet (or film) was sandwiched between a 50-mil-thick silicone sheet and a 25-mil-thick plastic sheet as gaskets on both sides and mounted on a vertical diffusion cell. The silicone and plastic sheets each had a 6-mm diameter hole and were aligned to provide an effective diffusion area of 28.3 mm^2. Both sides of the diffusion cell were filled with 0.154 M NaCl. A sinusoidal alternating current of 10 V peak to peak and 20 Hz with no direct current offset was applied across the polymer tablet (or film) using a Agilent 33220A waveform generator (Agilent Technologies, Santa Clara, CA, USA) and Ag/AgCl electrodes. A 100 kΩ fixed resistor was placed in series to the polymer tablet (or film) in the electric circuit. The electrical potentials across the tablet (or film) and the fixed resistor were measured using a Keithley 175A auto ranging multimeter (Keithley Instruments, Cleveland, OH). The electrical resistance across the polymer tablet (or film) was calculated using Ohm's law (Voltage = Current × Resistance). Resistance measurements were performed in triplicate and the electrical resistance results obtained were normalized by the thickness of the polymer tablet (or film) at each time point.

Statistical Analysis

Comparisons between groups were performed using paired *t*-test with a statistically significant difference defined as p value <0.05.

RESULTS

DSC Characterization

DSC was performed to evaluate the melting temperature of verapamil hydrochloride. The compatibility of verapamil hydrochloride with PSA and EC polymers in 20% polymer and 80% verapamil hydrochloride (*w*/*w*) matrix tablets was also studied. DSC thermograms of verapamil hydrochloride powder and tablets matrices are shown in Fig. 1. The melting point of verapamil hydrochloride was found to be 146°C, which was similar to previous findings (30). The melting temperature of verapamil hydrochloride remained unchanged in the PSA and EC matrix tablets demonstrating the compatibility of the process used to prepare the tablets and with the polymers.

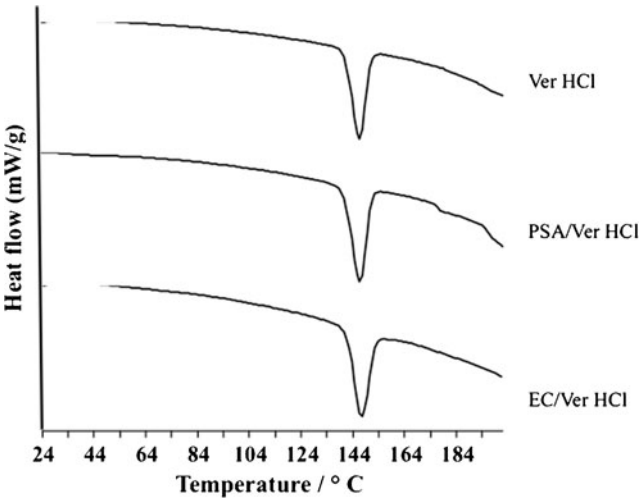

Fig. 1. DSC thermograms of verapamil hydrochloride (Ver HCl) powder and matrix tablets of 20% silicone PSA and 80% verapamil hydrochloride (*w*/*w*) and 20% EC and 80% verapamil hydrochloride (*w*/*w*)

Contact Angle

Contact angle measurements were performed to evaluate the hydrophobicity of the surfaces of silicone PSA and EC films and tablets, and the results are presented in Table II. The contact angles on silicone PSA films were higher than those of EC films. On the addition of water-soluble drug verapamil hydrochloride in the water-insoluble polymer matrices, the contact angles decreased. The change in contact angle due to the addition of verapamil hydrochloride to the EC matrices was larger compared with silicone PSA. The contact angle of 83.9° for silicone PSA tablets indicates a hydrophobic surface.

Effect of Dissolution Medium pH on Verapamil Hydrochloride Release

The release profiles of verapamil hydrochloride from EC matrix tablets in acidic SGF pH 1.2 and neutral SIF pH 6.8 dissolution media are shown in Fig. 2a. The release rate of verapamil hydrochloride of EC matrix was slower in pH 6.8 dissolution medium than that in pH 1.2. For example, approximately 70% of verapamil hydrochloride was released from the EC matrix in SGF (pH 1.2) compared with approximately 50% in SIF (pH 6.8) at 4 h in the dissolution study. At 12 h, 100% of verapamil hydrochloride was released in SGF *versus* approximately 80% in SIF. Figure 2b shows the effect of

Table II. Contact Angle Measurements on 100% Polymer Films and 20% Polymer and 80% (*w*/*w*) Verapamil Hydrochloride Tablets with SGF

Polymer	Films (deg)	Tablets (deg)
EC	77.5 (±2.6)	27.9 (±2.8)
Silicone PSA	94.0 (±2.5)	83.9 (±4.6)

Mean±SD ($n=3$)

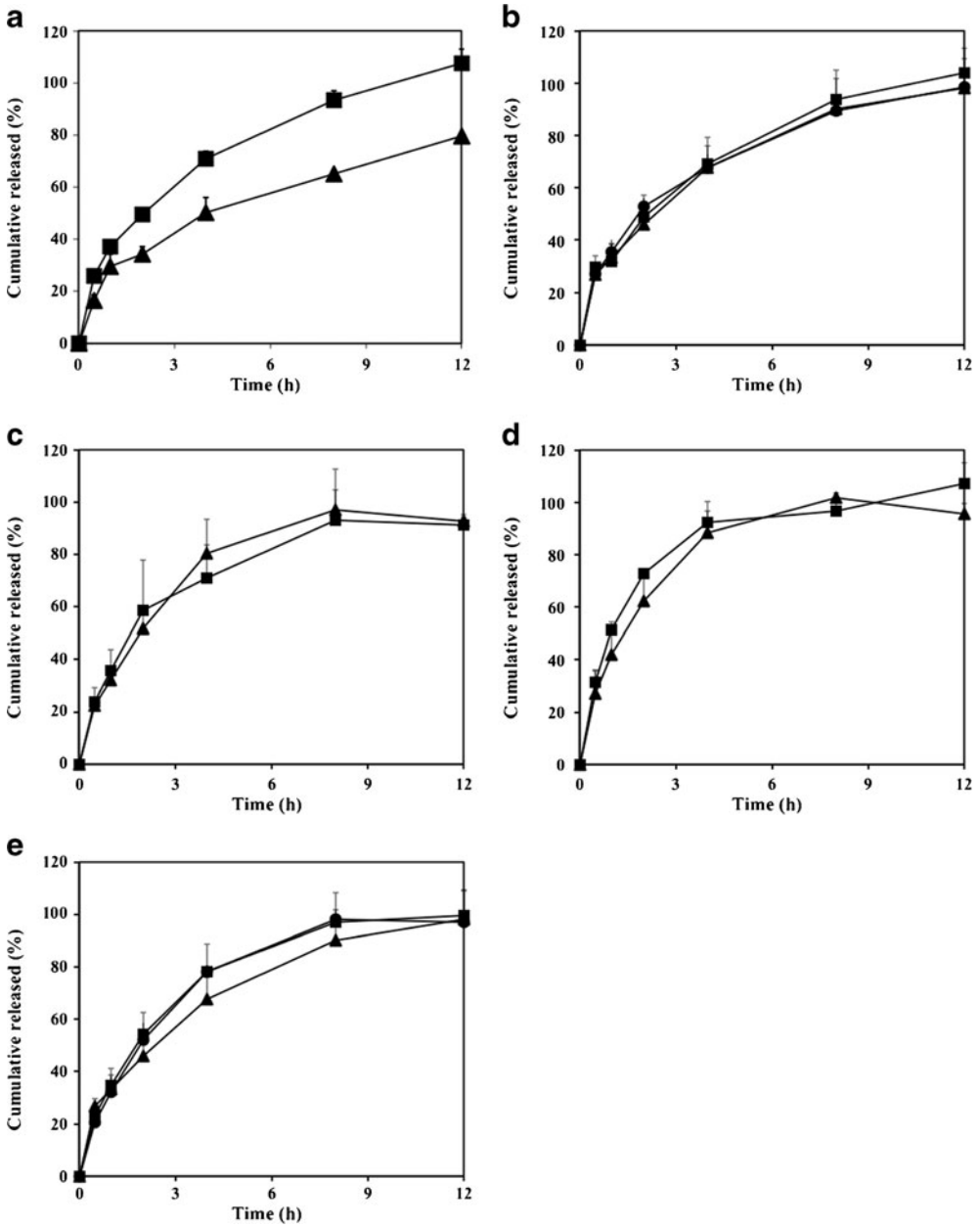

Fig. 2. Cumulative percent of verapamil released from matrices containing **a** 20% EC and 80% verapamil hydrochloride (*w*/*w*), **b** 20% silicone PSA and 80% verapamil hydrochloride (*w*/*w*), **c** 15% silicone PSA and 85% verapamil hydrochloride (*w*/*w*), and **d** 10% silicone PSA and 90% verapamil hydrochloride (*w*/*w*) tablets in dissolution medium SGF (*squares*), SIF (*triangles*), and SGF 2 h followed by SIG (*circles*) at 100 rpm stirring speed to study the effect of pH; and **e** 20% silicone PSA and 80% verapamil hydrochloride (*w*/*w*) tablet in SIF dissolution medium at stirring speed 100 rpm (*triangles*), 150 rpm (*circles*), and 200 rpm (*squares*) to study the effect of stirring speed. Mean±SD (n=3)

dissolution medium pH on the release of verapamil hydrochloride from the silicone PSA matrix. In contrast to the EC matrix, drug release from the silicone PSA matrix was not influenced by the pH of the dissolution medium in the range from pH 1.2 to 6.8. The release of verapamil hydrochloride from silicone PSA matrix was further studied under the dissolution condition of SGF for 2 h (from 0 to 2 h) and then SIF for 10 h (from 2 to 12 h), and the results are shown in Fig. 2b. The release profile under this dissolution condition was found to be similar to those of dissolution in 0–12 h of SGF and 0–12 h of SIF. Decreasing the polymer ratio from 20% to 15% and 10% (*w*/*w*) increased the release rate of verapamil hydrochloride, but the release profiles of verapamil hydrochloride were not affected by the pH of the dissolution medium (Fig. 2c, d). Changing the rotating basket stirring speed from 100–200 rpm did not significantly affect the release rate of verapamil from the silicone PSA tablets (Fig. 2e).

Water Uptake and Tablet Dimension Changes

Water uptake into the rigid EC and viscoelastic silicone PSA matrices was determined when the matrix tablets were exposed to the different dissolution media (Fig. 3). The results show that whereas the rate and extent of water uptake into the EC matrix tablet were affected by the dissolution medium pH, the rate and extent of water uptake into the silicone PSA tablet remained unchanged irrespective of the dissolution media. These findings are in agreement with the drug release data in Fig. 2a, b. In addition, the amount of water uptake in the EC matrix was higher than that in the silicone PSA matrix, suggesting higher resistance of the hydrophobic PSA matrix to water penetration.

The changes in tablet morphology during drug release for EC and silicone PSA matrices were studied by measuring the physical dimensions of the tablets during the course of drug release. The initial tablet diameter and thickness of both EC and silicone PSA tablets were 13.0 and 3.5 mm, respectively. On exposure to the dissolution media, the EC and silicone PSA matrices reacted differently during drug dissolution. Figure 4 presents the decrease in tablet diameter and thickness of EC and silicone PSA matrices upon exposure to SGF and SIF. EC is a water-insoluble polymer and does not swell in water. During drug dissolution, the EC matrix remained intact and the tablet dimensions did not change significantly over time. The average increase in EC tablet diameter was approximately 1% and the average increase in tablet thickness was approximately 4% after 12-h dissolution. These findings indicate an increase in EC tablet porosity during drug release. From mass balance and the mass of the dried EC matrix, a linear correlation was found between drug release and water uptake under the studied dissolution conditions (Fig. 5), suggesting that the drug released from the EC matrix was replaced by water during drug dissolution. Under this condition, the EC tablet was easy to break on slight pressure application. Different from the EC matrix tablet, the silicone PSA matrix tablet decreased in diameter and thickness over time as the drug was released in the dissolution study, indicating a decrease in tablet porosity. At the end of the dissolution study, an empty silicone PSA tablet without the drug and with minimal water content was left behind after the drug was released from the matrix.

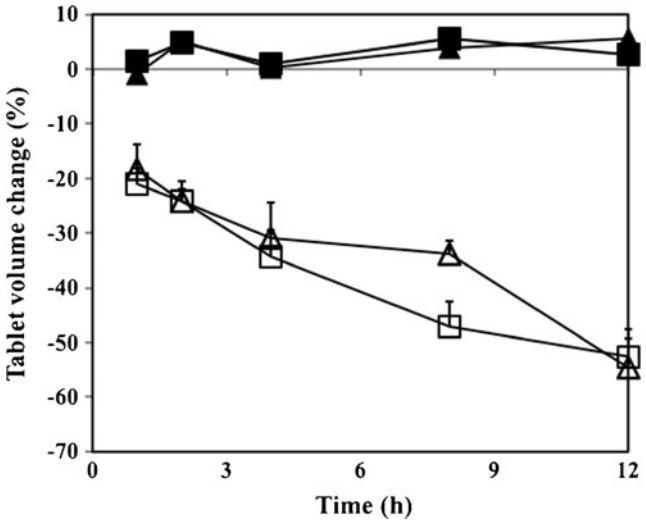

Fig. 4. Percent of volume changes in the matrices containing 20% polymer, 79.8% verapamil hydrochloride, and 0.2% methyl red (*w*/*w*) during dissolution in USP apparatus 1. Symbols: EC (*solid*) and silicone PSA tablets (*open*); dissolution medium SGF (*squares*) and SIF (*triangles*). Mean±SD (n=3). Some *error bars* are smaller than the symbols and are not shown in the figure

Morphological Changes and Matrix Microenvironment

To evaluate the internal morphological changes during drug release on exposure to SGF pH 1.2 or SIF pH 6.8, methyl red crystalline powder was added to the verapamil hydrochloride tablets. A solution of methyl red shows red color below

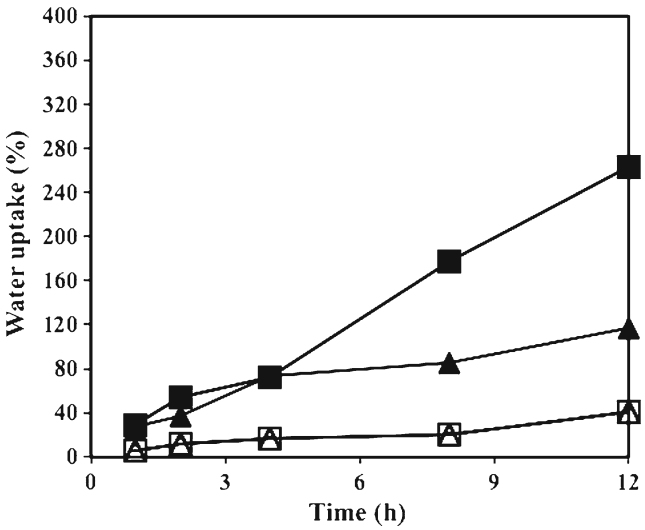

Fig. 3. Water content in the matrices containing 20% polymer, 79.8% verapamil hydrochloride, and 0.2% methyl red (*w*/*w*) during dissolution in USP apparatus 1. Symbols: EC (*solid*) and silicone PSA tablets (*open*); dissolution medium SGF (*squares*) and SIF (*triangles*). Mean± SD (n=3). *Error bars* are smaller than the symbols

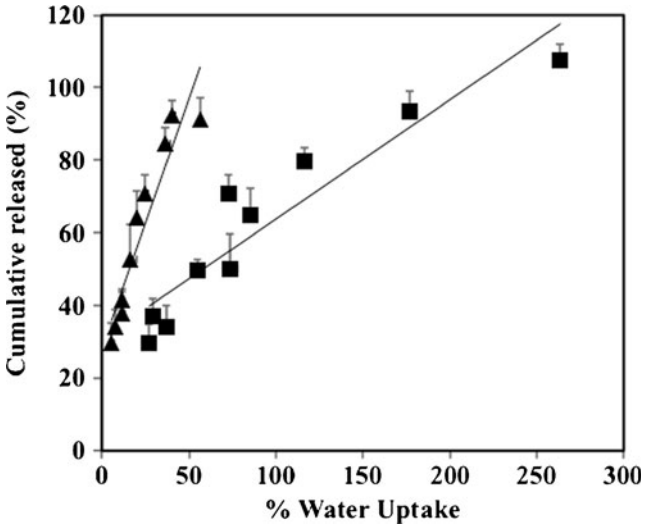

Fig. 5. Relationship between percent of cumulative verapamil released and water content of matrix tablets containing 20% polymer, 79.8% verapamil hydrochloride, and 0.2% methyl red (*w*/*w*) during dissolution in USP apparatus 1. Symbols: EC (*squares*) and silicone PSA tablets (*triangles*). Mean±SD (n=3). Some *error bars* are smaller than the symbols and are not shown in the figure

pH 4.4, orange above pH 6.2, and yellow in pH between 4.4 and 6.2. Methyl red was previously used as an indicator dye in the study of the microenvironment and morphological changes in tablet matrices (11). In the present study, matrix tablets containing 20% polymer (EC or silicone PSA), 0.2% methyl red, and 79.8% (*w*/*w*) verapamil hydrochloride were used to study the penetration of dissolution media into the matrix tablets during drug dissolution.

Figures 6 and 7 present the microscopic digital images of the surfaces of EC and silicone PSA tablets after 1–12 h exposure in SGF or SIF, respectively. The surface images of the tablets show a change in color to either red in SGF or orange in SIF for both EC and silicone PSA tablets (Figs. 6a and 7a). Figures 6b and 7b show the radial cross-sections of the tablets at different time points during drug dissolution. In Fig. 6, the cross-section image of EC matrix at 1 h in SGF does not show any dry verapamil hydrochloride powder (unaffected by the dissolution medium) in the matrix; the crystalline verapamil hydrochloride powder dispersed in the matrix would appear as white color inside the matrix. The image indicates that the acidic dissolution medium penetrated to the inner core of the EC matrix within 1 h after exposure to SGF. The surface of the EC tablets initially showed red color due to the acidic condition on the tablet surface, but the intensity of the red color on the surface of EC tablets diminished over time, possibly due to the release of methyl red from the tablets. Similar to the results of SGF, EC cross-section images at 1 h after exposure to SIF show orange color due to the penetration of the neutral dissolution medium. For silicone PSA matrices, Fig. 7 shows that the dissolution media interacted with the tablet surfaces producing red and orange color on the surfaces. The color on the surfaces of the tablets did not diminish over time, different from the case with EC tablets. Cross-section images of silicone PSA tablets show white crystalline verapamil hydrochloride powder inside the tablet cores. Even at 8 to 12 h, the drug in the innermost cores of the tablets remained unchanged. In these silicone PSA tablets, the outside region of the tablets with an increase in the intensity of red color is presumably the collapsed silicone PSA region. The results of the morphological studies suggest that silicone PSA is able to control the rate of water ingress into the tablet core. The collapsing nature of silicone PSA is evidenced by the decrease in the dimensions of the tablets during the drug release process. In contrast, EC matrices were porous allowing larger extent of dissolution media to penetrate the matrices. The dimensions of EC tablets remained essentially the same during drug dissolution. In addition, this collapsing nature of the silicone PSA tablets is further evidenced by the scanning electron microscopy results of EC and silicone PSA tablets, which showed an increase in the pore size on the EC tablets during dissolution but not on the silicone PSA tablets (unpublished data).

Polymer Film Properties for Ion Diffusion

To investigate the mechanism of pH-independent drug release observed for silicone PSA tablets, the permeability of silicone PSA and EC films to hydrogen ion was studied using a vertical diffusion cell. Figure 8 presents the change in pH of the receptor solution in this diffusion study. There was no significant change in pH of the receptor with the silicone PSA film. The lower pH in the receptor with EC film indicated higher permeability of the EC film to hydrogen ion than the silicone PSA film.

In addition to the hydrogen ion permeability study, electrical resistance measurements were performed for EC and silicone PSA film (without the drug) and the EC and silicone PSA tablet matrices containing 20% polymer and 80% APAP (*w*/*w*) obtained during drug dissolution. Table III presents the electrical resistivity (electrical resistance normalized by matrix thickness) of the EC and silicone PSA polymer films for comparison. The silicone PSA film has higher resistivity

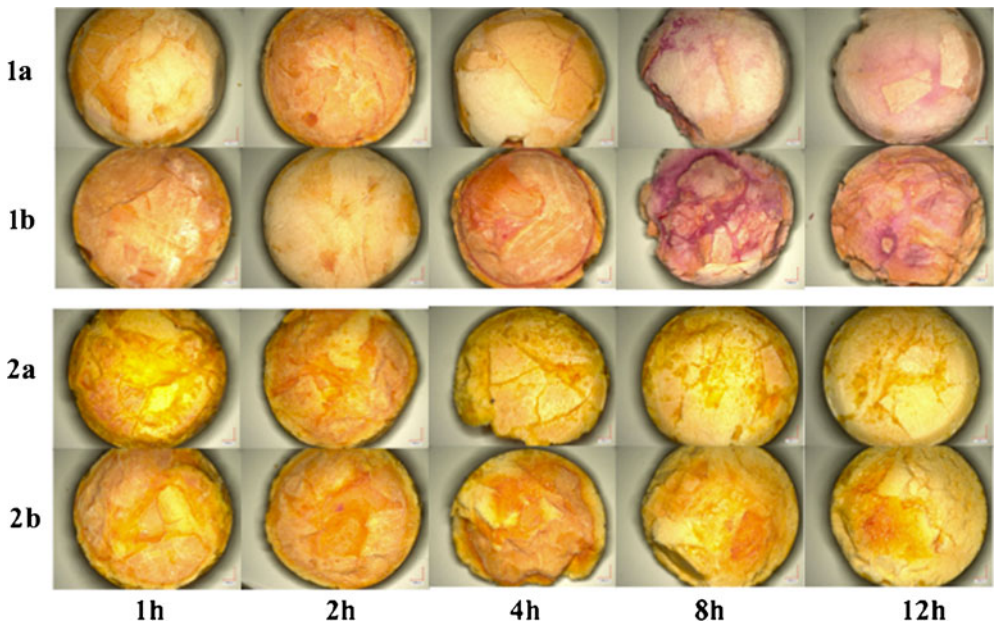

Fig. 6. *a* Surface and *b* radial cross-sectioned images of 20% EC (*w*/*w*) tablets containing 0.2% (*w*/*w*) methyl red on exposure to acidic SGF (*1a*, *1b*) and neutral SIF (*2a*, *2b*) dissolution media at different time points during drug dissolution

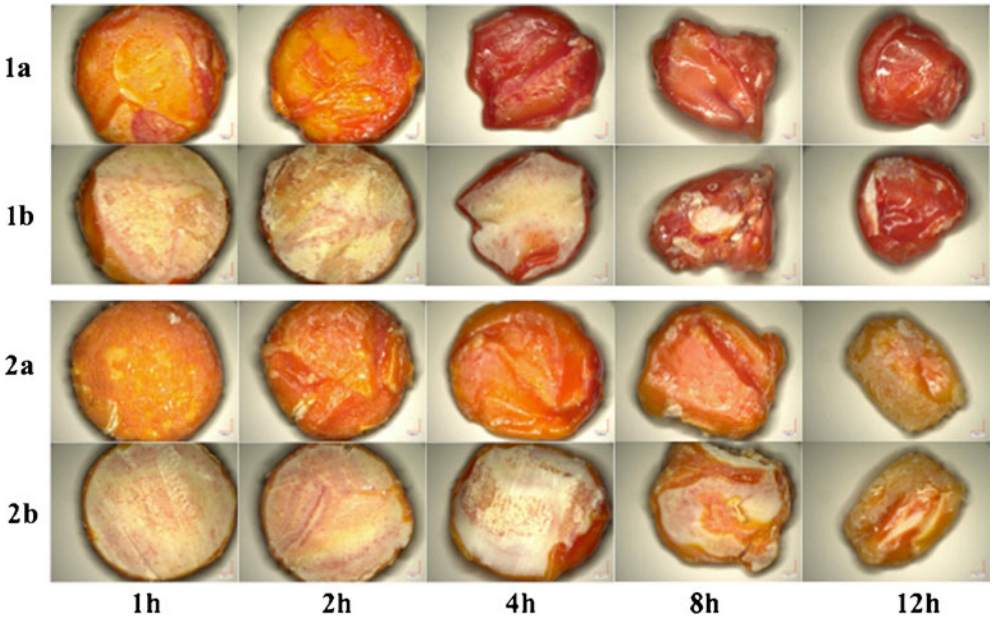

Fig. 7. *a* Surface and *b* radial cross-sectioned images of 20% silicone PSA (*w*/*w*) tablets containing 0.2% (*w*/*w*) methyl red on exposure to acidic SGF (*1a*, *1b*) and neutral SIF (*2a*, *2b*) dissolution media at different time points during drug dissolution

compared with EC film. Figure 9 shows the electrical resistivity of tablets containing 20% polymer and 80% APAP (*w*/*w*) during drug dissolution. The resistivity of EC tablets decreased in the aqueous medium during drug dissolution and remained low at the end of the dissolution experiment. In contrast, the resistivity of the silicone PSA tablets decreased slightly upon drug release initially and was relatively constant during drug dissolution. The electrical resistivity of the silicone PSA tablets was higher than that of EC tablets at all time.

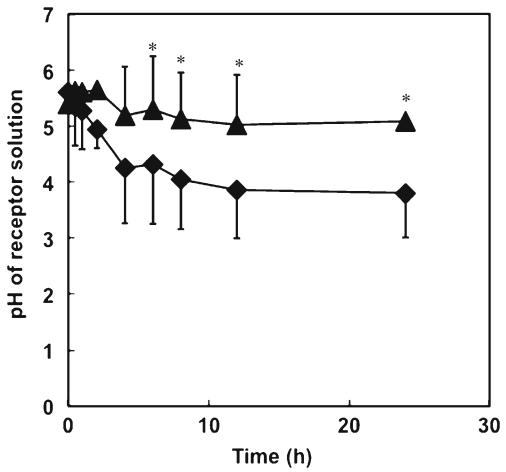

Fig. 8. Receptor solution pH in hydrogen ion transport experiments with pure polymer films of silicone PSA (*triangles*) and EC (*diamonds*). A 0.1 M HCl solution was the donor solution in the vertical diffusion cell, and 0.154 M NaCl was the receptor solution. Mean±SD (n=3)

DISCUSSION

Verapamil hydrochloride, a weakly basic drug (pK_a, 8.7), was used as the model drug in the present study because it demonstrated pH-dependent solubility over the physiological pH range in the GI tract. The solubilities of verapamil hydrochloride reported in the literature were 2.71 mg/mL at pH 6.8 and over 100 mg/mL at pH 1.2 (11,32); it is present mainly in its ionized form at pH 1.2 and to a lesser extent at pH 6.8. pH-independent release of verapamil hydrochloride is difficult to achieve without the incorporation of high amounts of organic buffers in the oral dosage form (10). The aim of the present study was to demonstrate the feasibility of water-insoluble polymer capable of hindering ion penetration for achieving pH-independent release of verapamil hydrochloride without the use of organic buffers. Silicone PSA was chosen as the polymer in the present study because of the intrinsic properties of silicone polymer membranes such as low surface tension, low permeability to hydrogen ion, and high electrical resistance (33). EC was chosen as a control for comparison.

Although both silicone PSA and EC are water-insoluble hydrophobic polymers, EC is a rigid polymer with high glass transition (Tg) temperature above 70°C compared with the low Tg of silicone PSA (−123°C) (34). Silicone PSA, which consists of PDMS, has a low surface tension around 24 mN/m.

Table III. Electrical Resistivity (Electrical Resistance Normalized by Thickness) Across 100% EC and 100% Silicone PSA Films

Membrane	Thickness (mm; ±SD)	Resistivity (kΩ cm)
EC film	0.26 (±0.04)	8.5 (±1.2)
Silicone PSA film	0.89 (±0.02)	28.4 (±14.4)

Mean±SD (n=3)

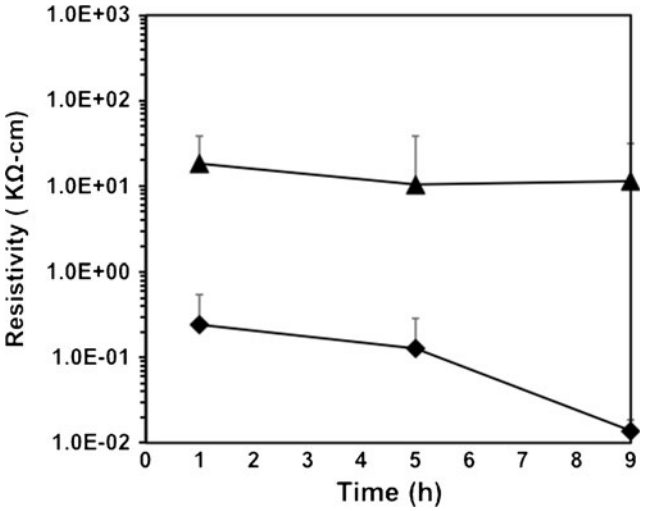

Fig. 9. Electrical resistivity (electrical resistance normalized by thickness) of 20% polymer and 80% APAP (*w*/*w*) tablets obtained at different time points during drug dissolution. Symbols: EC (*diamonds*) and silicone PSA (*triangles*). Mean±SD (n=3)

Considering these properties, silicone PSA is able to spread easily over substrates to form thin films. These films are highly hydrophobic and thereby tablets prepared using silicone PSA show high contact angles to water. In contrast, although EC is a polymer widely used for oral controlled release with good film forming capability, EC films have lower surface tension and better wettability compared with silicone PSA (29,35). The extent of dissolution medium penetration into the matrix is believed to be controlled by the wetting property of the tablet surface and its porosity during drug dissolution, and porous matrices generally result in higher penetration of the dissolution media compared with nonporous matrices (35).

Nonplasticized EC membranes are generally impermeable to hydrogen ion, but the addition of water-soluble material into the membranes to form matrices can increase their wettability and hydrogen ion permeability (19,34). Different from EC, as shown in the present study, drug loaded silicone PSA matrices could maintain their hydrophobicity and restrict water and ion penetration. Silicone PSA film also provided higher resistance to the permeation of hydrogen ion than EC film. This might explain the differences in the internal morphologies of silicone PSA and EC matrices on exposure to different dissolution media; for example, while the pH indicator dye in silicone PSA matrix tablets did not change color inside the tablet core, the color of the dye in the EC tablets changed readily on exposure to the dissolution media, which can be attributed to the hydrophobicity and low surface tension properties of silicone PSA.

Drug release from a hydrophobic polymer matrix tablet containing a water-soluble drug generally involves the following sequence: (a) the tablet comes in contact with the dissolution medium, (b) the dissolution medium enters the tablet matrix, (c) the drug is dissolved in the dissolution medium inside the matrix, and (d) the diffusion of the drug out of the tablet matrix into the external dissolution medium due to the drug concentration gradient (36). The rate of drug release is controlled by drug dissolution in the tablet matrix, drug diffusion in the matrix, or both. For EC matrix tablets, the matrix pores are filled with the dissolution medium after drug release. The present *in vitro* release studies of verapamil hydrochloride at pH 1.2 and 6.8 with EC showed pH-dependent drug release. Silicone PSA matrix tablets collapsed during drug dissolution. This minimized the amount of dissolution medium uptake into the matrix tablets. Given this collapsing nature of silicone PSA, the sizes of the matrix pores decreased, providing higher resistance to the permeation of ions (higher electrical resistance) and lower water uptake, and resulting in pH-independent release of verapamil hydrochloride.

CONCLUSIONS

Sustained release matrices containing 20% polymer (silicone PSA or EC) and 80% verapamil hydrochloride (*w*/*w*) were studied. Silicone PSA matrices showed pH-independent verapamil release. EC matrices prepared using a similar method and composition failed to achieve pH-independent release. Silicone PSA matrices showed higher contact angle to the dissolution media, higher electrical resistance, and lower water uptake compared with EC matrices. Given the low glass transition temperature and viscoelastic nature of silicone PSA, its matrix tablets decreased in size during drug release in the dissolution media. This decrease in tablet dimensions during drug release corresponded to the maintenance of resistivity of the polymer matrix to ion diffusion inside the matrix tablets. Although EC is water insoluble, EC tablets were found to have lower hydrophobicity, higher water uptake, and lower electrical resistance compared with silicone PSA tablets. These findings suggest that the unique properties offered by silicone PSA may be useful in the construction of controlled release matrices of ionizable drugs to reduce the variability of drug release related to the changing pH conditions encountered in oral absorption *in vivo*.

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