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In vitro controlled release of theophylline from tablets containing a silicone elastomer latex

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Summary

Two batches of controlled-release theophylline tablets were prepared using a silicone elastomer latex, one batch by the wet granulation process, the other by direct compression. In the wet granulation process, a dispersion consisting of silicone elastomer latex and fumed silica was used as the granulation fluid, whereas in the direct compression process, a dry, silica-filled silicone elastomer powder prepared from the latex was employed. The release profile of theophylline from the tablets prepared by wet granulation suggests that a matrix-diffusion controlled drug-release mechanism was at work. On the other hand, the directly compressed tablets displayed a drug-release profile that is explained by a matrix-erosion mechanism. Tablets prepared by direct compression resulted in a faster drug-release rate when compared with the rate of those tablets prepared by wet granulation, even though both batches of tablets had the same formulation. In both the wet granulation and direct compression processes, tablets with a higher percent of silicone elastomer exhibited a slower drug-release rate. Directly compressed tablets formulated with a silicone elastomer powder containing a higher percentage of silica showed a faster drug-release rate. With all other factors unchanged, when a smaller particle size of silicone elastomer powder was used in the direct compression process, tablets with a slower drug-release rate were formed. The effect of the pH of the dissolution medium on the drug-release rate was found to be insignificant.

Introduction

In spite of the recent technological advances in the fabrication of oral controlled-release dosage forms, matrix tablets continue to be one of the most commonly used dosage forms for controlled oral drug delivery. This is due in part to the relatively low cost associated with tablet manufacturing. Furthermore, tampering incidences associated with hard gelatin capsules have also served to promote the use of tablets for oral controlled-release medication.

Latex and pseudolatex systems are aqueous colloidal dispersions of water-insoluble polymers (Chang et al., 1987). Pharmaceutically, a variety of commercial latex and pseudolatex products have been developed for controlled-release film coatings (Chang et al., 1987). Polymer dispersions have been used in the manufacture of controlled-release matrix tablets (Kawashima et al., 1989).

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Generally, polymer dispersions are used as a granulation fluid in a wet granulation process. However, in some cases, dry powder is commercially prepared from polymer dispersions and is available for use in direct tablet compression. In tablets formed with an aqueous polymer dispersion by either the wet granulation process or the direct compression process, the water-insoluble polymer functions as a retardant, controlling the penetration rate of dissolution fluid into the matrix and the subsequent diffusion of the dissolved drug out of the matrix.

Latex and pseudolatex systems currently available for matrix tablet manufacturing are the dispersions of acrylate copolymers and ethylcellulose. A silicone elastomer latex which is composed of a cross-linked hydroxy-end-blocked polydimethylsiloxane (PDMS) has been evaluated for controlled-release tablet film coating (Li and Peck, 1989a).

The main objective of this study was to investigate the use of the silicone elastomer latex system in the preparation of controlled-release matrix tablets containing theophylline as a model drug. Factors affecting drug release from the tablet were also evaluated.

Materials and Methods

Materials

The silicone elastomer latex was supplied by the Dow Corning Co. Midland, MI. The latex has a mean particle size of 0.2 μm and a pH of 8.2. The amorphous fumed silica (EH-5), which has a mean particle size of 0.007 μm, was obtained from the Cabot Corp., Tuscola, IL. Theophylline anhydrous, USP, was obtained from the Sigma Chemical Co., St. Louis, MO.

Methods

Preparation of tablets by the wet granulation process

A predetermined amount of silicone elastomer latex was diluted with an adequate amount of water and mixed with fumed silica using a mortar and pestle to form a dispersion with a silicone elastomer-to-silica weight ratio of 1:1. The dispersion was added and mixed with the active ingredient to form a wet mass. The wet mass was dried in an oven at 60°C, overnight. The dried mass was milled in a stainless-steel blender. Milled granules which passed through a no. 60 screen but were retained on a no. 100 screen (a sieve-cut of 60/100 mesh) were used for tablet compression. Theophylline granules containing 2.5, 5.0, and 10.0% of silicone elastomer solids were prepared. Prior to tablet compression, the dried granules were blended with 1% magnesium stearate using a V-blender. An amount of granules containing 400 mg of theophylline was weighed and compressed into a 1/2-inch flat tablet using a laboratory Carver press (Model C) at a 3000 lb compression load.

Preparation of tablets by the direct compression process

A predetermined weight of fumed silica was mixed with the silicone elastomer latex and an adequate amount of water in a mortar to form a thick slurry. The slurry was dried in an oven at 60°C overnight. The dried silica-filled silicone elastomer was subsequently milled using a stainless-steel blender. Granules of two sieve-cuts, 60/100 and 120/200 mesh, were obtained and used for direct compression tablet formulation. Silicone elastomer granules with silicone elastomer-to-silica weight ratios of 1:1 and 1:4 were also prepared. Prior to tablet compression, a predetermined amount of theophylline was mixed with the silicone elastomer granules using a specific sieve-cut in a V-blender. Magnesium stearate (1%) was added to the powder mixture as a lubricant. An amount of granules containing 400 mg of theophylline was weighed and subsequently compressed into a 1/2-inch flat tablet using a laboratory Carver press (Model C) at a 3000 lb compression load.

Dissolution test

Three theophylline tablets representing a specific formulation were used in the dissolution test. The in vitro release profiles of theophylline from the tablets were determined using the stan-

dard USP Dissolution Method II, the paddle method. The apparatus used was a six-unit dissolution tester (Vanderkamp 600). The dissolution medium was 900 ml of degassed USP simulated gastric fluid or intestinal fluid (without enzyme) which was maintained at 37°C. The paddle stirring rate was set at 100 rpm. A 10.0 ml sample was taken from the dissolution apparatus at 1-h intervals over 12 h. Each withdrawn sample was replaced by an equal volume of fresh dissolution medium. The absorbance of each sample solution, after appropriate dilution, was determined at a wavelength of 276 nm using a UV spectrophotometer (Perkin-Elmer Lambda 3B). The concentration of theophylline in each sample was determined by means of a calibration curve. The cumulative percent of the total dose released was plotted against the time elapsed to give a drug-release profile.

Results and Discussion

Figs 1 and 2 depict the release profiles of theophylline from tablets containing three different levels of silicone elastomer. The tablets used to generate the data in Figs 1 and 2 were prepared by the wet granulation process and the direct compression process, respectively. Table 1 gives the cumulative percent of the total dose released at different time intervals. It is apparent that tablets containing a low level of silicone elastomer exhibited a faster drug-release rate regardless of the method of tablet preparation. Tablets with the same level of silicone elastomer prepared by direct compression released the active ingredient at a faster rate.

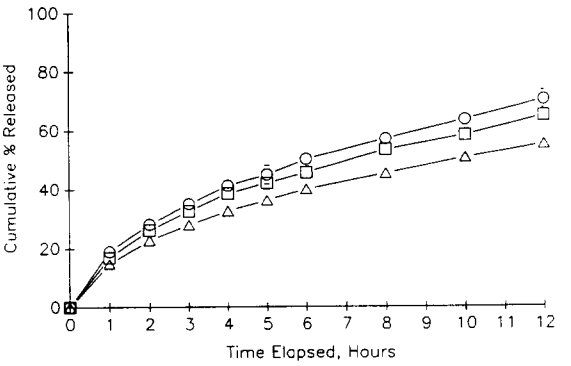

Fig. 1. Release of theophylline from tablets prepared by wet granulation and containing three different levels of silicone elastomer with a silicone polymer-to-silica weight ratio of 1:1. Granules with a sieve-cut of 60/100 mesh were used. The pH of the dissolution medium was 1.2. Silicone elastomer levels: (○) 2.5%, (□) 5.0% and (△) 10.0%.

In order to further characterize the release kinetics of the drug from the tablets, the cumulative percents of the total dose released (P) up to

TABLE 1

Effect of tablet preparation method on the cumulative percent of the total dose released from theophylline tablets containing three different levels of silicone elastomer with a 1:1 silicone polymer and silica weight ratio

Time	Percent of silicone elastomer					
	Wet granulation			Direct compression		
	2.5	5.0	10.0	2.5	5.0	10.0
1.0	19.0	16.9	14.8	20.6	17.8	15.8
2.0	28.2	26.2	22.8	33.9	30.5	24.4
3.0	35.1	32.7	28.0	44.9	41.4	31.0
4.0	41.3	38.6	32.7	56.8	53.1	39.0
5.0	45.0	42.2	36.3	67.0	61.8	47.1
6.0	50.2	45.7	40.0	75.3	71.6	53.2
8.0	56.9	53.2	45.3	89.1	84.3	65.2
10.0	63.4	58.2	50.6	94.1	90.1	73.5
12.0	70.1	64.6	55.0	99.1	95.3	82.3
n	0.519	0.527	0.520	0.716	0.728	0.680
r	0.999	0.997	0.998	0.999	0.996	0.999

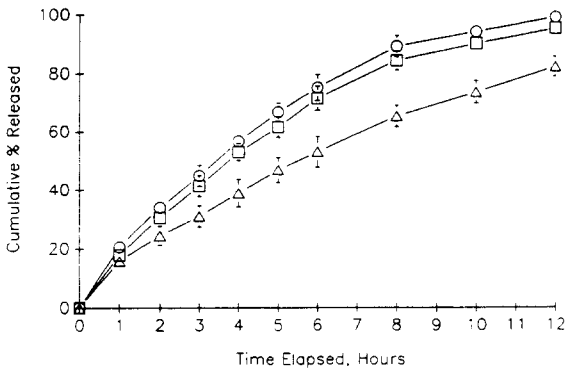

Fig. 2. Release of theophylline from tablets prepared by direct compression and containing three different levels of silicone elastomer with a silicone polymer-to-silica weight ratio of 1:1. A powder with a sieve-cut of 60/100 mesh was used. The pH of the dissolution medium was 1.2. Silicone elastomer levels: (○) 2.5%, (□) 5.0% and (△) 10.0%.

90% were expressed as a power function of time (t) according to the following equation:

$$P = bt^n \quad (1)$$

When n approximates 0.5, a Fickian/diffusion-controlled release is indicated, whereas the value of n approaching 1 suggests a zero-order release kinetics (Korsmeyer et al., 1983; Lee, 1985; Ford et al., 1987). The cumulative percent of the total dose released, the value of n, and the correlation coefficient r are tabulated in Table 1. It is seen that the n values approximate 0.5, indicating a Fickian/diffusion-controlled release for tablets prepared by the wet granulation method. The values of n approximating 0.7 are noted for tablets prepared by the direct compression process, sug-

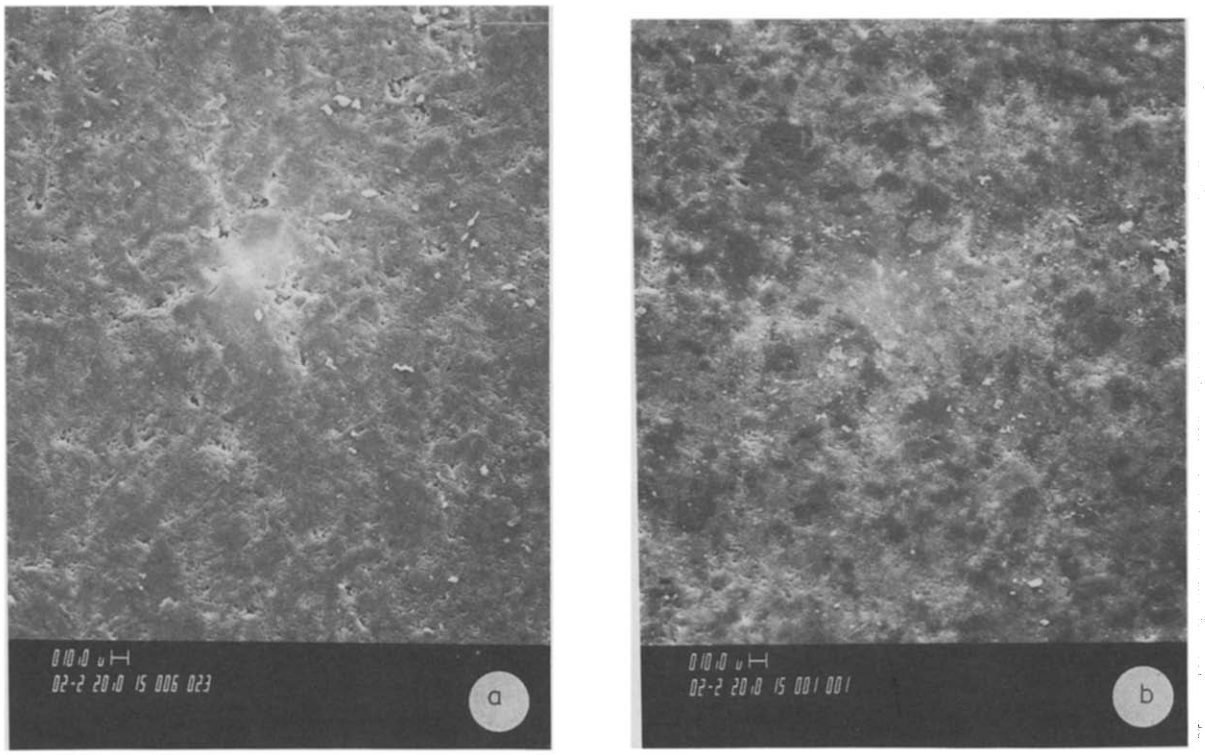

Fig. 3. (a) SEM photomicrograph of the surface of a theophylline tablet prepared by wet granulation and containing 10.0% silicone elastomer. (b) SEM photomicrograph of the surface of a theophylline tablet prepared by direct compression and containing 10.0% silicone elastomer.

gesting a deviation from the Fickian/diffusion-controlled release. It was observed that the approximate dimensions of the wet granulated tablets remained unchanged throughout the entire dissolution test, whereas the size of the directly compressed tablets diminished gradually. This indicates that matrix erosion took place in the directly compressed tablets during dissolution.

The SEM photomicrographs presented in Fig. 3a and b show the surface of a wet granulated tablet and that of a directly compressed tablet prior to dissolution. A comparison of these two panels shows the difference in the distribution of silicone elastomer in the tablet matrices. The relatively uniform tablet surface shown in Fig. 3a indicates a homogeneous distribution of the silicone elastomer in the wet granulated tablet, while the scattered dark spots seen in Fig. 3b delineate a heterogeneous distribution of the silicone elastomer powder in the directly compressed tablet. Fig. 4a and b shows the surface of the freeze-dried samples of these tablets after 3 h of dissolution. A sponge-like network is evident in the tablet prepared by the wet granulation process (Fig. 4a). This network, mainly consisting of undissolved silicone elastomer, was formed by the silicone elastomer dispersion which was added to the active ingredient during granulation. It is conceivable that, after drying, a network of silicone elastomer was formed in the granules containing theophylline solid particles. Upon compression, tablets containing theophylline particles entrapped in the silicone elastomer matrix were formed. The photomicrograph in Fig. 4a actually shows the distribution of the silicone elastomer in the wet granulated tablet. In a previous study, it was found that silicone elastomer free films de-

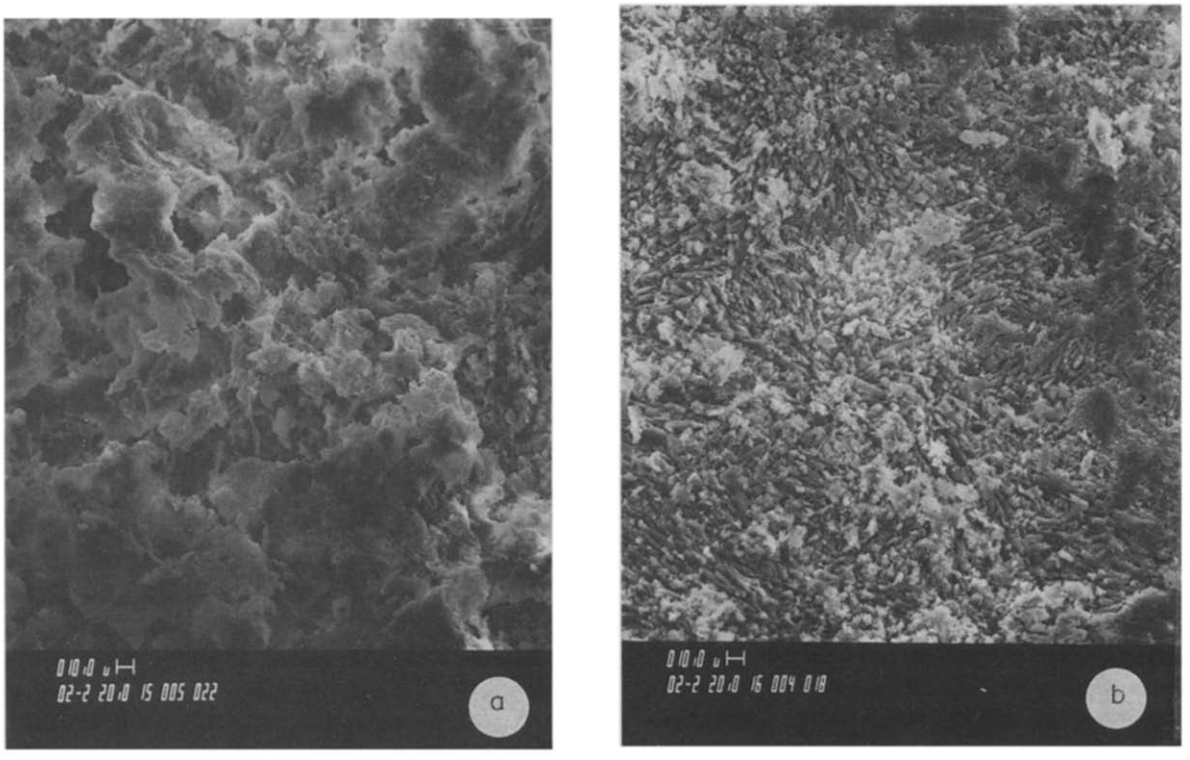

Fig. 4. (a) SEM photomicrograph of the surface of a theophylline tablet prepared by wet granulation and containing 10.0% silicone elastomer. The photomicrograph was taken using the freeze-dried sample of a tablet which was 3 h after dissolution. (b) SEM photomicrograph of the surface of a theophylline tablet prepared by direct compression and containing 10.0% silicone elastomer. The photomicrograph was taken using the freeze-dried sample of a tablet which was 3 h after dissolution.

rived from aqueous dispersion hydrated and swelled extensively in water (Li and Peck, 1989b). Therefore, during tablet dissolution the penetration of the dissolution fluid into the tablet matrix not only caused dissolution of the drug but also the hydration of the silicone elastomer network. The release of theophylline was primarily achieved by the diffusion of the dissolved drug through the compressed granules containing the drug particles and the hydrated silicone elastomer network.

The erosion drug-release mechanism proposed for the directly compressed tablets is further substantiated by the photomicrograph shown in Fig. 4b. Silicone elastomer particles are seen randomly distributed between theophylline crystals within the tablet. There is no evidence of a silicone elastomer network formed in the directly compressed tablet as there is in the wet granulation tablet. The silicone elastomer powder in the tablet formulation retarded the dissolution of theophylline by forming a discontinuous, poorly wetted barrier around the theophylline crystals. As soon as the theophylline particles were dissolved, the silicone elastomer particles were eroded slowly from the tablet and a new surface was exposed for further dissolution. This erosion mechanism provides an explanation for the non-Fickian/diffusion drug-release characteristics for tablets formed by direct compression. It is also obvious that silicone elastomer, when used in a dry powder form, is not as effective a diffusion barrier to the drug as when it is used in a dispersion form in wet granulation. However, in view of the more linear nature of the drug-release profile achieved by the directly compressed tablets, the use of silicone elastomer dry powder for direct compression may have some distinct advantages over the use of the latex in a wet granulation process.

Figs 1 and 2 also reveal the fact that an increase in the percentage of silicone elastomer in the tablet formulation results in a slower drug-release rate regardless of the method of tablet preparation. Fig. 5 depicts the release profiles of theophylline from tablets containing 2.5, 5.0, and 10.0% of silicone elastomer with a silicone polymer-to-silica weight ratio of 1:4. As compared to

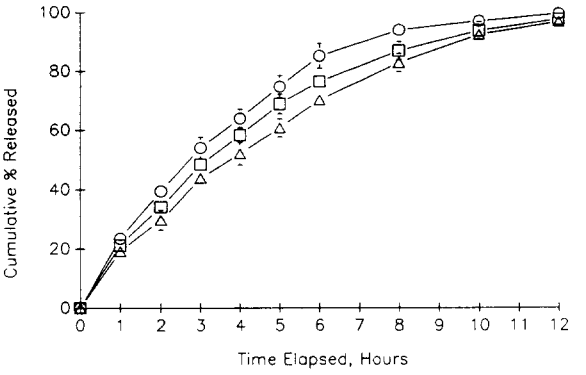

Fig. 5. Release of theophylline from tablets prepared by direct compression and containing three different levels of silicone elastomer with a silicone polymer-to-silica weight ratio of 1:4. A powder with a sieve-cut of 60/100 was used. The pH of the dissolution medium was 1.2. Silicone elastomer levels: (○) 2.5%, (□) 5.0% and (△) 10.0%.

the profiles displayed in Fig. 2, the drug-release rate of tablets formed with silicone elastomer consisting of a higher silica content is noticeably faster. The elucidation of the influence of silica content on the drug-release rate may require an understanding of the interaction between silica and silicone elastomer during the formation of silicone elastomer dry powder. When the fumed silica was mixed with the silicone elastomer latex, an intimate contact took place between the particles of these two components. Upon the removal of water, a strong filler-polymer bonding may have developed between the free silicone polymer chains on the surface of the latex particles and the surface hydroxyl groups of the silica. Due to the vast difference in their particle sizes, it is possible that the silicone elastomer particles were coated by the much smaller silica particles. As the percent of silica increased, the coalescence of silica particles probably gave rise to regions rich in hydrophilic silica within the elastomer networks (Saam et al., 1981). Therefore, an increase in the silica content would render the silicone elastomer less hydrophobic, leading to a faster penetration of the aqueous dissolution medium into the tablet and a more rapid drug-release rate.

The effect of particle size of the silicone elastomer powder on the release rate of theophylline

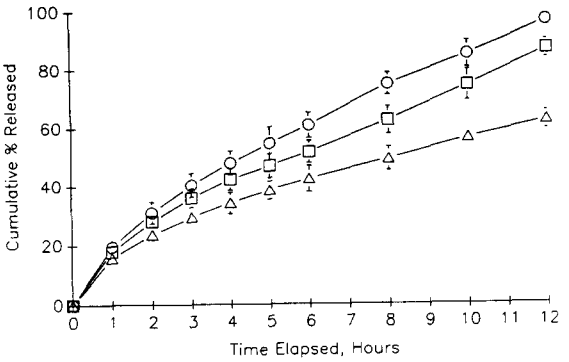

Fig. 6. Release of theophylline from tablets prepared by direct compression and containing three different levels of silicone elastomer with a silicone polymer-to-silica weight ratio of 1:1. A powder with a sieve-cut of 120/200 mesh was used. The pH of the dissolution medium was 1.2. Silicone elastomer levels: (○), 2.5%, (□) 5.0% and (△) 10.0%.

from the directly compressed tablets can be demonstrated by the comparison of the drug-release profiles presented in Figs 2 and 6. When a smaller particle size of silicone elastomer powder (< 120 mesh size) was used, a slower drug release rate was achieved. This is likely due to the larger surface area associated with the smaller particles, which result in a more efficient barrier to the dissolution of theophylline from the tablets. Fig. 7 depicts the drug-release profile of the tablets at

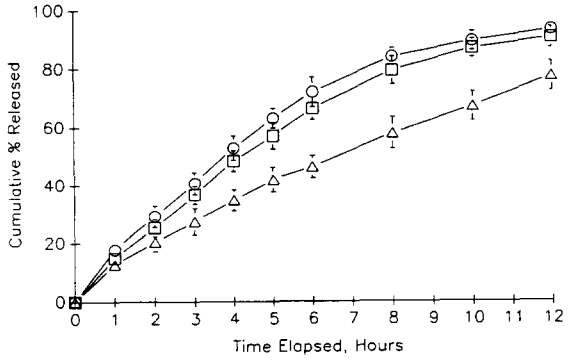

Fig. 7. Release of theophylline from tablets prepared by direct compression and containing three different levels of silicone elastomer with a silicone polymer-to-silica weight ratio of 1:1. A powder with a sieve-cut of 60/100 mesh was used. The pH of the dissolution medium was 7.5. Silicone elastomer levels: (○) 2.5%, (□) 5.0% and (△) 10.0%.

pH 7.5. A comparison of this profile with those shown in Fig. 2 indicates that the release of theophylline from the tablets was not significantly affected by the pH of the dissolution medium.

The silicone elastomer latex evaluated in this study offers some advantages over other commercial latex and pseudolatex products when it is used to prepare matrix tablets by wet granulation. The total solids content for the commercial latex and pseudolatex products is relatively low (about 30% by weight). Therefore, the amount of polymer that can be incorporated in a tablet formulation is always limited because the addition of a large quantity of the dispersion will render the granulation too damp for processing. It has been reported that a double- or even triple-granulation process was necessary to prepare granules with a high content of polymer from dispersions (Klinger et al., 1990). This process is very time-consuming and inefficient. Conversely, the silicone elastomer latex used in this study contains up to 50% polymer solids and the fumed silica which is added to the latex as a filler is capable of retaining large quantities of water without becoming excessively wet. Therefore, a relatively large amount of silicone elastomer latex can be added to the tablet formulation to achieve a high polymer content. Furthermore, when a direct compression process is considered, a dry silica-filled silicone elastomer powder can be readily prepared by a granulation process.

From the results of this study, it is evident that silicone elastomer at the levels used is adequate to control the release of a moderately water-soluble drug such as theophylline from a matrix tablet. For drugs with a relatively high water solubility, a higher concentration of silicone elastomer or a low silicone polymer-to-silica ratio may be needed to achieve controlled drug release from a tablet. However, because of the very elastic nature of silicone elastomer, a high percentage of silicone elastomer in the formulation may produce tablets with poor mechanical properties. In these cases, the addition of water-insoluble direct compression diluent such as microcrystalline cellulose (Avicel™) and compressible calcium phosphate (DiTab™) may be needed to improve the compressibility of the formulation.

In conclusion, it has been shown that silicone elastomer latex can be used to form controlled-release tablets by either a wet granulation process or a direct compression process. The wet granulated tablets displayed diffusion-controlled drug-release characteristics while tablets prepared by direct compression exhibited a drug-release profile approaching a zero-order kinetics which is achieved by surface erosion.

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