Preparation of Spherical Matrixes of Prolonged-Release Drugs from Liquid Suspension

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Abstract □ A simple and less expensive method for the preparation of spherical matrixes of prolonged-release drugs was developed from liquid suspension. The drugs dispersed in distilled water were agglomerated with a small amount of organic solution or melt of matrix material. The process, called a "solution" or "melting" method, depended on the state of matrix material. In the present study, sulfamethoxazole and sulfanilamide were agglomerated with white beeswax and ethylcellulose. Furthermore, the parameters affecting the average size and release behavior of the resultant matrixes were investigated. Increasing the amount of matrix material used yielded large matrixes and prolonged-release action. The drugs rendered hydrophobic by surface treatment produced larger matrixes that released drug more slowly than untreated drugs. The sizes of the matrixes decreased and became uniform with increasing agitation speed. The sulfamethoxazole matrixes with wax proved to be enteric coated since the release rate was fast in the alkaline test solution (pH 7.5) but slow in the acidic one (pH 1.2).

Keyphrases □ Spherical agglomeration—preparation of spherical matrixes of prolonged-release drugs from liquid suspension, sulfamethoxazole and sulfanilamide □ Prolonged-release drugs—preparation of spherical matrixes from liquid suspension, sulfamethoxazole and sulfanilamide □ Sulfamethoxazole—drug release behavior, preparation of spherical matrixes from liquid suspension □ Sulfanilamide—drug release behavior, preparation of spherical matrixes from liquid suspension

Previous investigators (1) found that the dispersed particles in liquid suspension were spherically agglomerated with a small amount of second immiscible liquid, which preferentially wetted the particles. By developing this research further, other investigators (2–4) established the "spherical agglomeration" technique as a favorable method for agglomeration of fine particles in liquid.

By using a modified spherical agglomeration technique, a simple and less expensive process was developed in the present study to prepare spherical matrixes of prolonged-release drugs as an alternative to spray-congealing methods (5–7). An organic solution (*e.g.*, benzene) or a melt of matrix material such as a wax-like material or ethylcellulose was used as a second immiscible liquid, *i.e.*, a collecting liquid. The parameters affecting micromeritic properties and drug release behavior of the resultant matrixes also were studied.

EXPERIMENTAL

Materials—Sulfamethoxaxole[1], having geometric mean diameters of 6 and 380 μm and geometric standard deviations of 1.4 and 1.2 μm, respectively, was used. Fine sulfamethoxazole particles were supplied by pulverizing the coarse particles. Sulfanilamide[2] particles of a 297-μm geometric mean diameter with a geometric standard deviation of 1.1 μm also were used for agglomeration. White beeswax[3] and ethylcellulose[4] were used as matrix materials.

Surface-treated drugs were rendered strongly hydrophobic to increase their affinity with matrix material to attain a well-coated matrix. Surface treatment was done by allowing adsorption of palmitic acid[4] onto the drug surface. Adsorption was achieved by dispersing 10 g of particles in 200 ml of 3% palmitic acid–alcohol solutions and leaving the system for 2 days. The drugs adsorbed with palmitic acid were filtered and dried at 40° for 1 day. No significant changes in particle size after the treatment were observed.

Preparation of Matrixes—*Melting Method*—Sulfamethoxazole particles (10 g) were dispersed in 300 ml of distilled water contained in an 8 × 18.5-cm glass cylindrical vessel. The system was agitated at 241, 382, 620, and 1100 rpm by a turbine-type agitator with four blades, 4 cm in diameter, to examine the effect of agitation speed on product size. The agitator was set 1 cm from the bottom of the vessel.

The system was heated gradually to 90° by a mantel heater. When the system reached 90°, powdered white beeswax, weighing 1.25 or 1.5 g, was added to change the coating thickness of resultant matrixes. Then the system was agitated for 10 min at 90°. The molten white beeswax collected the dispersed drug and yielded spherical agglomerates. By removing the mantel heater, the system was cooled gradually to room temperature while stirring to harden the agglomerates. The resultant agglomerates were filtered and dried for 24 hr at 40°. The average diameter of the dried agglomerates was determined by a sieving method using standard sieves specified in the JP, the opening of which was nearly the same as that of the Tyler sieve. The size range varied from 16 to 84%.

Solution Method—A small amount of benzene solution of white beeswax or ethylcellulose was used instead of a white beeswax melt. Sulfamethoxazole particles (5 g) were agglomerated with 0.5, 1.3, or 3.0 ml of a 7% benzene solution of ethylcellulose. Then the system was agitated continuously at 620 rpm for 2 hr to evaporate the benzene and to harden the agglomerates. Sulfanilamide particles (10 g) were agglomerated with 4 or 8 ml of a 9.3% benzene solution of white beeswax. The resultant agglomerates were filtered and dried as described for the melting method.

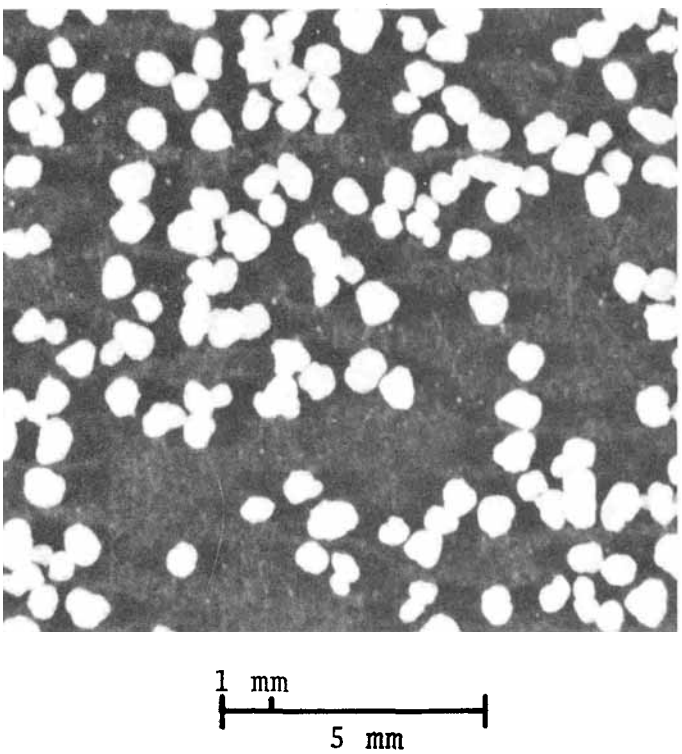

Figure 1—*Photomicrograph of sulfamethoxazole matrixes with white beeswax used for the release test.*

[1] Shionogi Pharmaceutical Co., Osaka, Japan.
[2] Nakarai Chemical Co., Tokyo, Japan.
[3] Miki Chemical Co., Tokyo, Japan.
[4] Kishida Chemical Co., Tokyo, Japan.

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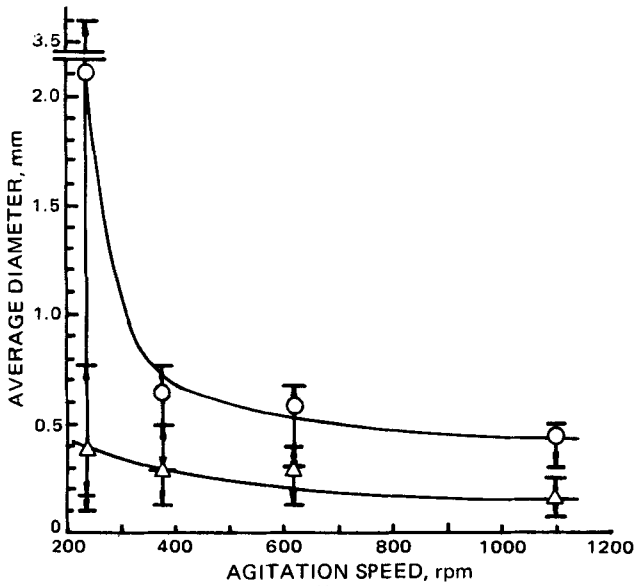

Figure 2—*Effect of agitation speed on the average diameter of matrixes. The material was pulverized sulfamethoxazole, and the collecting liquid was 1.5 g of a white beeswax melt. Key: ○, with surface treatment; and △, without surface treatment.*

Drug Release Test of Agglomerates—The dissolution tests were conducted by a beaker method. A USP rotating basket was modified by attaching a propeller to the top, which was used as an agitator. Thus, the adsorption of air bubbles to the basket was prevented and agitation was promoted. The agglomerates, fractionated to 500–1000 μm, were used to cancel the surface area effect on the dissolution rate.

The 90-mg test samples were added to 900 ml of distilled water or acidic (pH 1.2) or alkaline (pH 7.5) disintegration test solutions specified in the JP. Adhesion of agglomerates to the basket was slight. The system was controlled thermally at 37° and agitated at 150 rpm. At various adequate intervals, 2-ml aliquots were withdrawn from the system and filtered through a 0.2-μm filter[5]. The dissolved amounts of drug were determined spectrophotometrically at the UV wavelengths of 250 and 257 nm using a double-beam spectrophotometer[6].

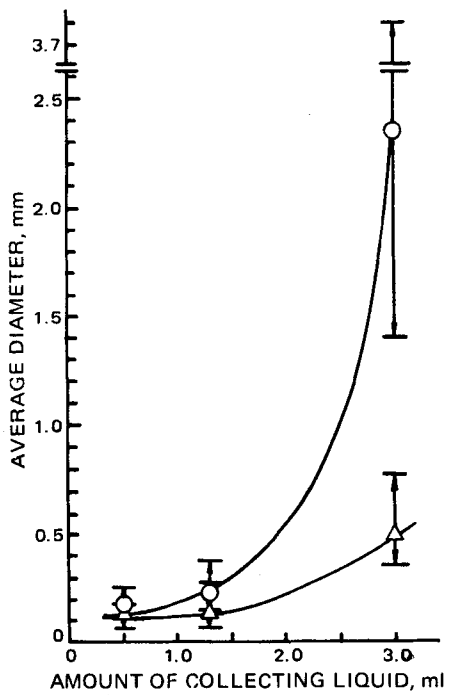

Figure 3—*Effect of collecting liquid on the average diameter of matrixes. The material was pulverized sulfamethoxazole, the collecting liquid was ethylcellulose solution, and the agitation speed was 1100 rpm. Key: ○, with surface treatment; and △, without surface treatment.*

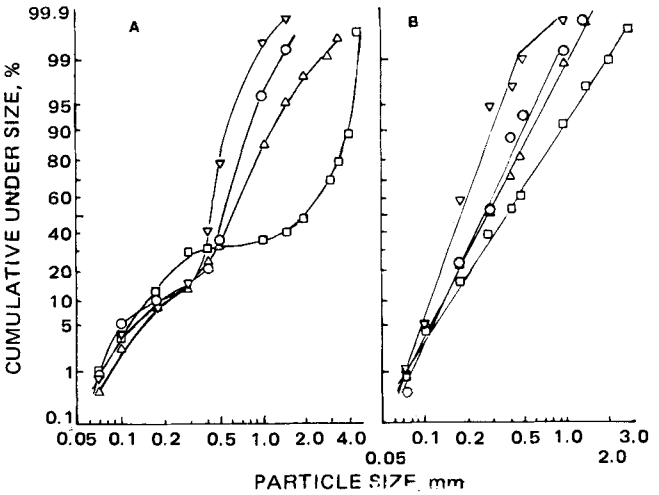

Figure 4—*Effect of surface treatment (A, with; and B, without) of raw materials and agitation speed on the size distribution of matrixes. The material was pulverized sulfamethoxazole, and the collecting liquid was 1.5 g of a white beeswax melt. Key: ▽, 1100 rpm; ○, 620 rpm; △, 382 rpm; and □, 241 rpm.*

RESULTS AND DISCUSSION

Parameters Affecting Agglomerate Particle Size—The products prepared by this technique were fairly rounded spheres, varying from 50 μm to 4 mm in size. Products prepared by the melting method appeared to be coated with white beeswax (Fig. 1).

The effects of the agitation speed of the system on agglomerate size are shown in Fig. 2. The median diameters of the products of the fine sulfamethoxazole particles prepared by the melting method were plotted against the agitation speeds. With increasing agitation speed, the average size of the particle agglomerates without surface treatment decreased gradually from 380 to 150 μm. The surface-treated particles yielded larger agglomerates than particles without surface treatment. The surface-treated particles could be wetted easily by molten wax due to their strong hydrophobic properties, resulting in large agglomerates.

Agitation speed strongly affected the product size of the surface-treated particles. The average particle size decreased sharply from 2.1 to 0.62 mm when the agitation speed was increased from 241 to 382 rpm (Fig. 2). With the coarse sulfamethoxazole particle, the agitation speed similarly affected agglomerate size. However, there was little difference in product size between the particles with and without surface treatment. This result indicates that it is difficult to make the coarse particles hydrophobic by surface treatment because of their poor adsorption of palmitic acid.

The effects of the amount of collecting liquid on agglomerate size are seen in Fig. 3. The median diameter of the products of the fine sulfamethoxazole particles prepared by the solution method increased with the increasing amounts of benzene solutions of white beeswax used. This trend was evident for products of the surface-treated particles and may have been due to increased affinity with the collecting liquid caused by the hydrophobic nature of the particles. The increase in the agglomerate size caused by surface treatment was also confirmed with the sulfanilamide products.

The effects of surface treatment on the size distribution of the agglomerates of the fine sulfamethoxazole particles are seen in Fig. 4. The size distribution of the products without surface treatment was described by a log-normal form (Fig. 4B). The slope of the line, representing a geometric standard deviation, decreased with increasing agitation speed. This result suggests that the agglomerates of a fairly uniform size can be produced by increasing the agitation speed. The size distributions of the products of the surface-treated particles were not represented by a log-normal form (Fig. 4A), because they were heterogeneous mixtures containing some extraordinarily large particles, which increased in number at the lower agitation speed. At the lower stirring speed, the collecting liquid was not dispersed uniformly, resulting in a heterogeneous mixture. Furthermore, the adhesive force between the surface-treated particles

[5] Millipore.

[6] Hitachi model 556.

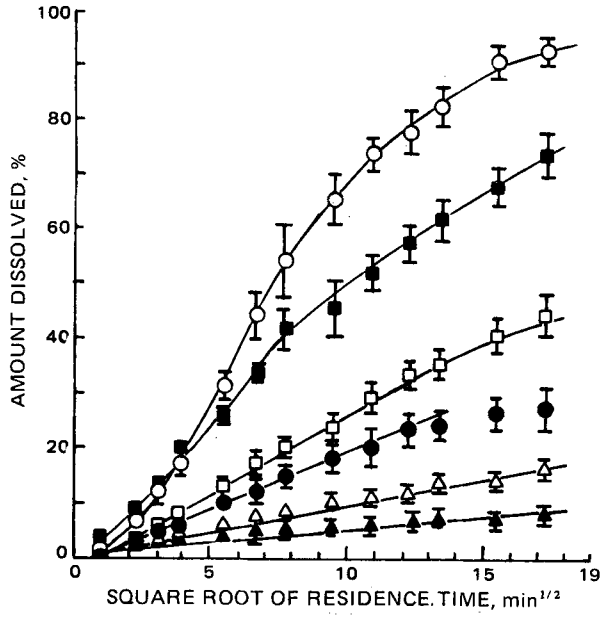

Figure 5—*Drug release patterns of sulfamethoxazole matrixes in distilled water. Key: ●, fine particle size, without surface treatment, 1.5 g of wax; △, coarse particle size, without surface treatment, 1.25 g of wax; ▲, coarse particle size, with surface treatment, 1.25 g of wax; □, fine particle size, with surface treatment, 1.3 ml of ethylcellulose solution; ■, fine particle size, without surface treatment, 1.3 ml of ethylcellulose solution; and ○, original sulfamethoxazole. Standard deviation bars for only representative batches are exhibited to avoid superimposing.*

might be stronger than the destructive force brought about by agitation. Therefore, once a large agglomerate was produced, it was rarely destroyed. Similar phenomena were observed for other products of sulfanilamide and sulfamethoxazole.

Drug Release Behavior from Agglomerates—Dissolution tests were undertaken to examine the prolonged-release behavior of the products. Dissolution behavior was represented by plotting the percentage of the drug released from the agglomerates on a semi-square root graph. The

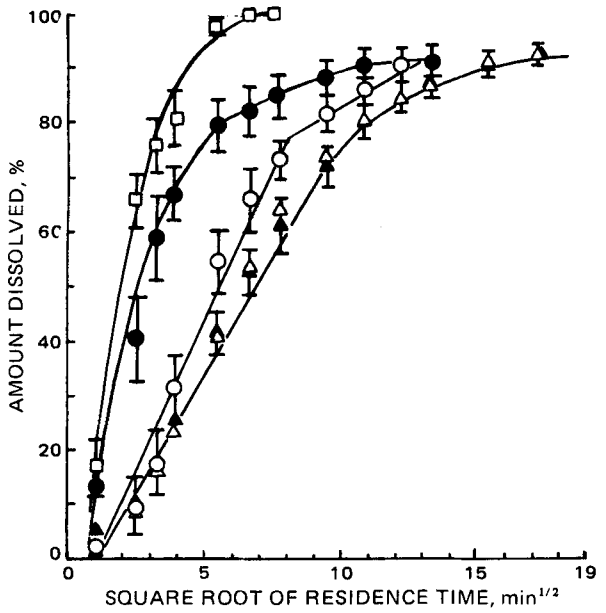

Figure 6—*Drug release patterns of sulfanilamide matrixes in distilled water. Key: ○, with surface treatment, 4 ml of collecting liquid; ●, without surface treatment, 4 ml of collecting liquid; △, with surface treatment, 8 ml of collecting liquid; ▲, without surface treatment, 8 ml of collecting liquid; and □, original sulfanilamide. Standard deviation bars for only representative batches are exhibited to avoid superimposing.*

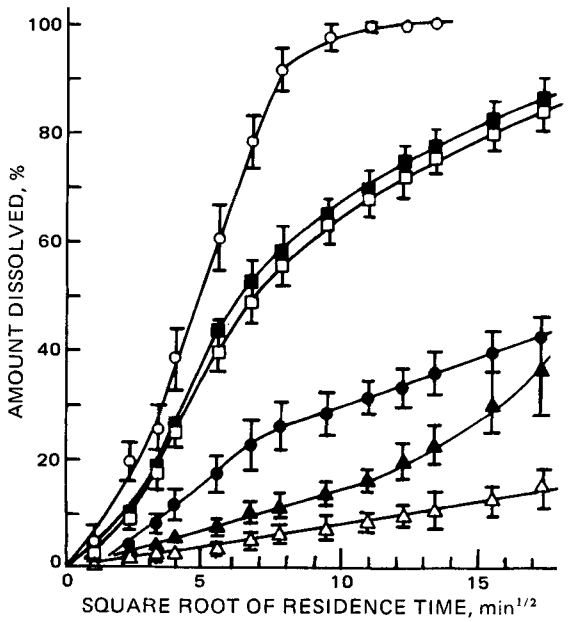

Figure 7—*Drug release patterns of sulfamethoxazole matrixes in acidic solution. Key: ●, fine particle size, without surface treatment, 1.5 g of wax; ▲, coarse particle size, without surface treatment, 1.25 g of wax; △, coarse particle size, with surface treatment, 1.25 g of wax; □, fine particle size, with surface treatment, 1.3 ml of ethylcellulose solution; ■, fine particle size, without surface treatment, 1.3 ml of ethylcellulose solution; and ○, original sulfamethoxazole. Standard deviation bars for only representative batches are exhibited to avoid superimposing.*

release behavior of the sulfamethoxazole and sulfanilamide products in distilled water is seen in Figs. 5 and 6, respectively. Compared with the original particles, all sulfamethoxazole products prepared by both the melting and solution methods released the drug slowly, although the release rates varied extensively, depending on the preparation condition (Fig. 5). The release patterns of the agglomerates with wax became fairly straight lines. This finding indicates that the release process obeys the

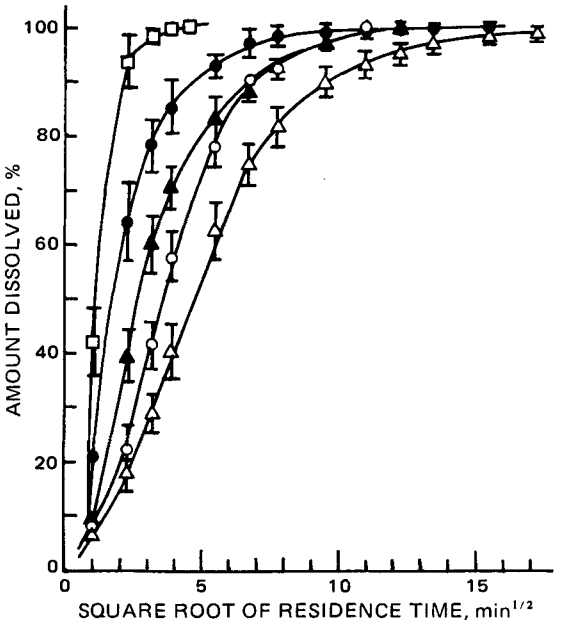

Figure 8—*Drug release patterns of sulfanilamide matrixes in acidic solution. Key: ○, with surface treatment, 4 ml of collecting liquid; ●, without surface treatment, 4 ml of collecting liquid; △, with surface treatment, 8 ml of collecting liquid; ▲, without surface treatment, 8 ml of collecting liquid; and □, original sulfanilamide. Standard deviation bars for only representative batches are exhibited to avoid superimposing.*

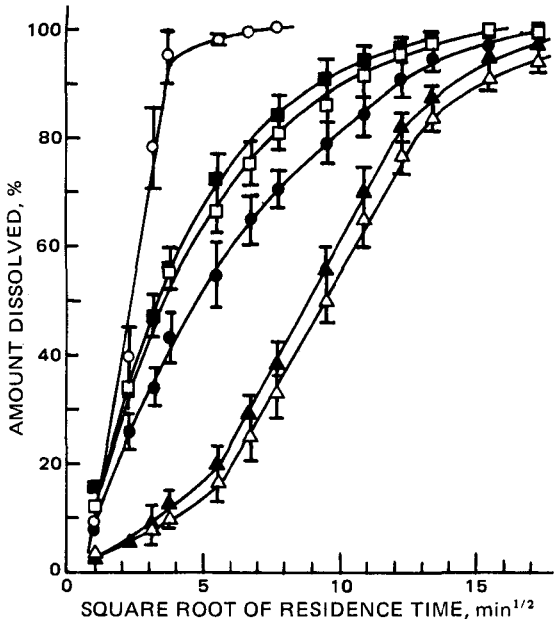

Figure 9—*Drug release patterns of sulfamethoxazole matrixes in alkaline solution. Key: ●, fine particle size, without surface treatment, 1.5 g of wax; ▲, coarse particle size, without surface treatment, 1.25 g of wax; △, coarse particle size, with surface treatment, 1.25 g of wax; □, fine particle size, with surface treatment, 1.3 ml of ethylcellulose solution; ■, fine particle size, without surface treatment, 1.3 ml of ethylcellulose solution; and ○, original sulfamethoxazole. Standard deviation bars for only representative batches are exhibited to avoid superimposing.*

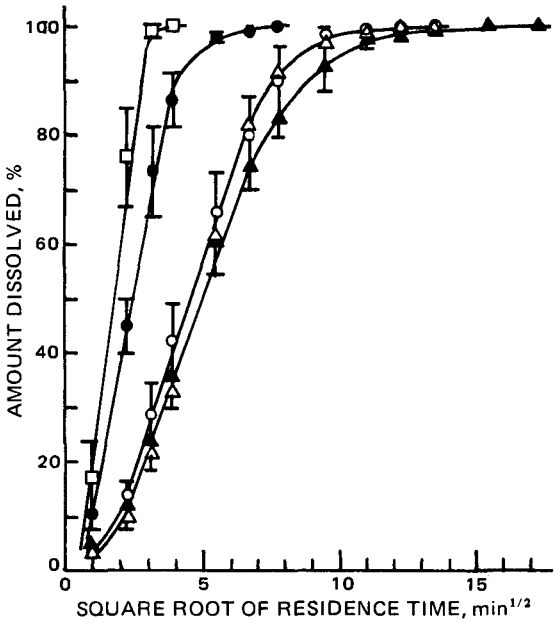

Figure 10—*Drug release patterns of sulfanilamide matrixes in alkaline solution. Key: ○, with surface treatment, 4 ml of collecting liquid; ●, without surface treatment, 4 ml of collecting liquid; △, with surface treatment, 8 ml of collecting liquid; ▲, without surface treatment, 8 ml of collecting liquid; and □, original sulfanilamide. Standard deviation bars for only representative batches are exhibited to avoid superimposing.*

Higuchi model (8), which explains the drug release process from a matrix as:

$$Q = [D(2A - C_s)C_s t]^{1/2} \quad \text{(Eq. 1)}$$

where Q is the amount dissolved per unit area of exposure at time t, A is the total volume of drug present in the matrix per unit volume, C_s is the solubility of the drug in the external phase of the matrix, and D is the diffusion constant. When $C_s \ll A$, Eq. 1 can be transformed to a more convenient form to exhibit the release patterns described in Figs. 5–10 (9):

$$C_r = 100[S_v(2DC_s t/A)^{1/2}] \quad \text{(Eq. 2)}$$

where C_r is the percentage of the drug dissolved and S_v is the specific surface area.

The surface treatment significantly delayed the drug release rate from the products. The product with surface treatment still retained 90% of the drug after a 5-hr exposure to the solvent. The size reduction of the raw materials adversely affected the prolonged-release action of the products (Fig. 5). This result may have been due to the fact that the fine particles can improve diffusivity in a matrix by their increased dissolution rate. The drug release rate of the agglomerate with ethylcellulose was faster than that of the agglomerates with wax, suggesting that the coating action of the ethylcellulose solution was weak compared with molten wax. The release pattern of the ethylcellulose product without surface treatment coincided with that of original sulfamethoxazole at the initial stage, although it deviated later. Figure 5 indicates that some uncoated drug on the product surface dissolved immediately on contact with the solvent, and the imbedded particles dissolved slowly at the later stage.

The release rates of the sulfanilamide products were faster than those of sulfamethoxazole (Fig. 6). The literature value of sulfanilamide solubility (10) is 7.5 g/liter (25°), whereas sulfamethoxazole is characterized as insoluble in the JP. The higher solubility of sulfanilamide, leading to the higher intrinsic dissolution rate, might be responsible for the increased release rate of sulfanilamide products. However, when a large amount of collecting liquid was used, the release pattern became a straight line with a decreased slope (Fig. 6). The surface treatment also delayed the release rate. Thus, it was confirmed that surface treatment of the raw materials and the amount of collecting liquid played an important role in controlling product release behavior.

The release patterns of the agglomerates in the acidic solution are displayed in Figs. 7 and 8. The release rates of the original and the agglomerates of sulfamethoxazole with ethylcellulose became faster than in distilled water (Fig. 7). While the release rates of the agglomerates with wax were almost the same as in distilled water, the release rates of both original sulfanilamide and its products (Fig. 8) were faster than in distilled water. The effects of the size and surface treatment of the raw materials on the release pattern of the products in Figs. 7 and 8 were similar to those in distilled water.

In the alkaline solution, the product release rates of both sulfamethoxazole and sulfanilamide were faster than in the other two media (Figs. 9 and 10). Enhancement of the release rate of sulfamethoxazole agglomerates with wax was particularly distinguished compared to the other products. The enteric-like action of the agglomerates with wax was proved by this finding. The fatty acid contained in the wax might be more soluble in the alkaline medium than in the acidic medium. In addition, the ester involved in the wax might be hydrolyzed more readily in the alkaline medium. These factors may promote the disintegration of the matrix and increase the release rate in the alkaline medium.

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