However, this prominent action of pilocarpine on salivary and other exocrine glands constitutes an undesirable effect in most cases (19). Stimulation of lacrimal glands following instillation of pilocarpine into the conjunctival sac would conceivably enhance its removal by tears into the nasolacrimal duct, thereby reducing its ocular penetration and increasing systemic absorption. These effects should be less evident with *N*-demethylated carbachol.

The use of the LD_{50}/ED_{50} ratio to compare the margin of safety of two drugs is not valid in instances where the slopes of the dose–response curves for toxicity and/or effect of the drugs are not parallel. For this reason, the observation of equal LD_{50} values for pilocarpine and *N*-demethylated carbachol does not necessarily imply that they have equal margins of safety. In addition, determinations of lethality may give no indication of the tendency of a drug to produce side effects. In this regard, preliminary studies showed marked irritation of the canine eye following topical application of a 1% pilocarpine solution while no irritation was observed after similar applications of *N*-demethylated carbachol in concentrations as high as 4%[7].

In summary, the tertiary nitrogen-containing analog of carbachol was tested and found to be an effective cholinergic stimulant active at both muscarinic and nicotinic sites. Unlike pilocarpine, *N*-demethylated carbachol shows less tendency to produce exocrine gland and sympathetic effects, properties that should make it a useful alternative to pilocarpine. Both compounds are currently being evaluated in a canine model of glaucoma.

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Effects of Compression Force, Particle Size, and Lubricants on Dissolution Rate

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Abstract □ The effects of compression force, particle size, and lubricant concentration on the dissolution rates of compressed disks of salicylic acid, aspirin, and an equimolar mixture of aspirin and salicylic acid were investigated. Compression forces from 450 to 9100 kg had no effect on dissolution rates. With 5% starch incorporated into an equimolar mixture of aspirin and salicylic acid, the dissolution rates were independent of compression forces from 910 to 9100 kg. A 10-fold change of particle size of the materials being compressed did not affect the dissolution rates. An increase in the concentration from 0.1 to 5% of calcium stearate, glyceryl monostearate, magnesium stearate, and stearic acid progressively slowed the dissolution rate. An increase in the concentration from 0.1 to 5% talc and polyethylene glycol 4000 did not affect the dissolution rates. An increase in the concentration of starch from 0.1 to 5% progressively increased the dissolution rates.

Keyphrases □ Dissolution rate—compressed disks of salicylic acid, aspirin, and equimolar mixture, effects of compression force, particle size, and lubricants □ Compression force—effect on dissolution rate of compressed disks of salicylic acid, aspirin, and equimolar mixture □ Particle size—effect on dissolution rate of compressed disks of salicylic acid, aspirin, and equimolar mixture □ Lubricants, various—effect on dissolution rate of compressed disks of salicylic acid, aspirin, and equimolar mixture □ Salicylic acid—compressed disks alone and equimolar mixture with aspirin, dissolution rate, effects of compression force, particle size, and lubricants □ Aspirin—compressed disks alone and equimolar mixture with salicylic acid, dissolution rate, effects of compression force, particle size, and lubricants

The kinetics of dissolution for pure materials and for two-component solids have been published (1–5). Various relationships between dissolution rate and compression force have been reported (6–11). As Knoechel *et al.* (12) suggested, although compression force may influence the dissolution rate, the formulation and the particular medicinal compound have a greater effect.

Finholt and Solvang (13) studied the effect of particle size of granules used to prepare phenacetin tablets on the dissolution rate. The rate was increased in diluted gastric

Table I—Effect of Compression Force on Dissolution Rate of 80/100-Mesh Material Compressed into a 1.27-cm Disk

Compression Force, kg	Rate of Mass Loss[a], g/hr		Dissolution Rate, g/hr/cm²	
	Aspirin	Salicylic Acid	Aspirin	Salicylic Acid
		Salicylic Acid		
450		0.047		0.037
1135		0.047		0.037
2270		0.047		0.037
3400		0.047		0.037
4550		0.045		0.036
5680		0.048		0.038
6820		0.045		0.036
7950		0.045		0.036
9100		0.048		0.038
	Aspirin			
450	0.076		0.060	
1135	0.080		0.063	
2270	0.074		0.059	
3400	0.079		0.062	
4550	0.078		0.062	
5680	0.077		0.060	
6820	0.079		0.062	
7950	0.077		0.061	
9100	0.078		0.062	
	Equimolar Aspirin and Salicylic Acid			
450	0.037	0.038	0.029	0.030
1135	0.042	0.040	0.033	0.032
2270	0.039	0.039	0.031	0.031
3400	0.038	0.037	0.030	0.029
4550	0.041	0.039	0.032	0.031
5680	0.038	0.039	0.032	0.031
6820	0.038	0.037	0.030	0.029
7950	0.036	0.037	0.028	0.029
9100	0.037	0.038	0.029	0.030

[a] Average of two determinations.

juice as the particle size was decreased; however, the opposite effect occurred when 0.1 *N* HCl was used as the dissolution medium. In another study, no difference was detected in dissolution of phenobarbital and phenacetin tablets containing starch and gelatin if the tablets were prepared from different sizes of granulation (14).

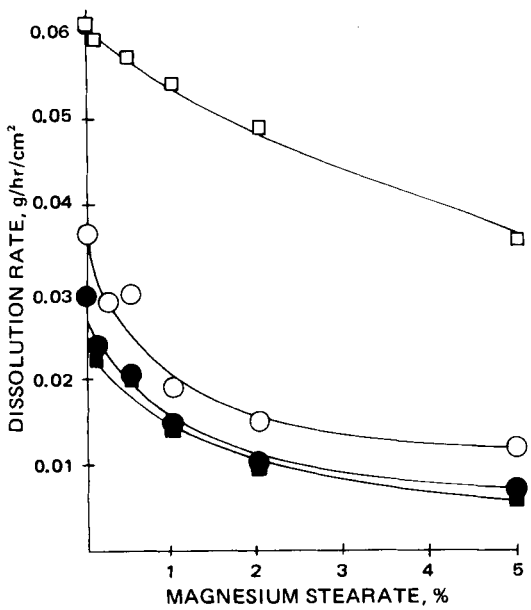

Figure 1—*Effect of concentration of magnesium stearate on dissolution rate of 80/100-mesh materials compressed at 1135 kg. Key: ○, salicylic acid; □, aspirin; ●, salicylic acid from equimolar mixture of aspirin and salicylic acid; and ■, aspirin from equimolar mixture of aspirin and salicylic acid.*

Table II—Effect of Particle Size of Materials Compressed at 1135 kg on Dissolution Rate of 1.27-cm Disks

Mesh Size Fraction	Rate of Mass Loss[a], g/hr		Dissolution Rate, g/hr/cm²	
	Aspirin	Salicylic Acid	Aspirin	Salicylic Acid
		Salicylic Acid		
40/60		0.050		0.039
60/80		0.050		0.039
80/100		0.051		0.040
100/140		0.050		0.039
140/200		0.051		0.040
	Aspirin			
40/60	0.076		0.060	
60/80	0.074		0.059	
80/100	0.080		0.063	
100/140	0.077		0.061	
140/200	0.080		0.063	
	Equimolar Aspirin and Salicylic Acid			
40/60	0.035	0.035	0.028	0.026
60/80	0.034	0.035	0.027	0.027
80/100	0.033	0.035	0.026	0.027
100/140	0.033	0.034	0.026	0.027
140/200	0.035	0.033	0.028	0.026

[a] Average of two determinations.

With triamterene tablets prepared from granules of different sizes, when terra alba or glycine was used as the excipient, the dissolution rate was increased as the particle size was decreased; however, when starch was the excipient, size had no effect on the dissolution rate (15). With salicylic acid tablets, the dissolution rate was increased as the granule size was decreased (16).

Although satisfactory in performing their function as lubricants, lubricants may possess the disadvantage of slowing dissolution. Increasing magnesium stearate to 1.5% caused a slowing of dissolution of phenobarbital tablets (17, 18), and 3% magnesium stearate slowed the dissolution of salicylic acid tablets (19). With triamterene tablets, an increase of lubricant greater than 2.5% caused a decrease in the dissolution rate (15). However, Finholt *et al.* (20) concluded that lubricants have very little effect on the dissolution rate of phenobarbital tablets.

The purpose of this investigation was to determine for the materials used the influence on the dissolution rate of compression force, particle size of the material being compressed, and concentration of lubricants with various particle sizes of materials being compressed.

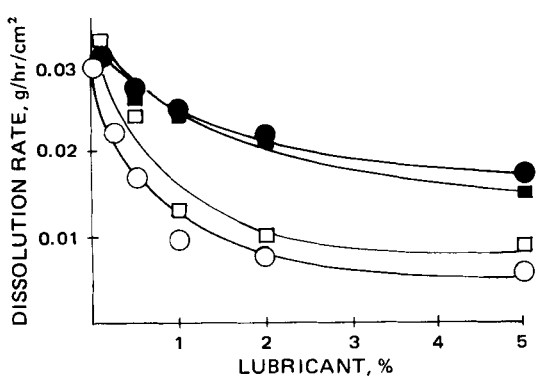

Figure 2—*Effect of concentration of calcium stearate and glyceryl monostearate on dissolution rate of 80/100-mesh equimolar mixture of aspirin and salicylic acid compressed at 1135 kg. Key: ○, salicylic acid with calcium stearate; □, aspirin with calcium stearate; ●, salicylic acid with glyceryl monostearate; and ■, aspirin with glyceryl monostearate.*

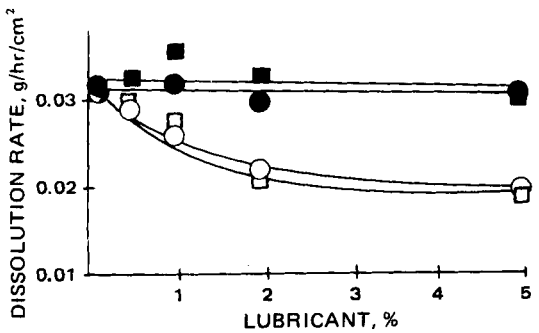

Figure 3—*Effect of concentration of stearic acid and polyethylene glycol 4000 on dissolution rate of 80/100-mesh materials compressed at 1135 kg. Key: ○, salicylic acid with stearic acid; □, aspirin with stearic acid; ●, salicylic acid with polyethylene glycol 4000; and ■, aspirin with polyethylene glycol 4000.*

EXPERIMENTAL

Preparation of Compressed Disks—Crystals of salicylic acid[1] and aspirin[2] were triturated with a mortar and pestle. The powdered drugs were separated by sieves into 40/60-, 60/80-, 80/100-, and 140/200-mesh size fractions. The materials were compressed by a hydraulic press[3] into flat-faced disks having diameters of 1.270 ± 0.005 cm. Compression forces ranged from 450 to 9100 kg.

Dissolution Rate—Disks were embedded in paraffin and mounted in a holder so that only a flat surface of the disk would be exposed to the dissolution medium. The dissolution rate was determined in 2 liters of distilled water at 25 ± 0.1° under conditions where the concentration did not exceed 5% of the solubility. The dissolution apparatus consisted of a 2-liter beaker in which a 3.0 × 1.5-cm stainless steel paddle, operating at 324 rpm, was positioned 1 cm above the exposed surface of a disk centered in the beaker bottom.

Samples were withdrawn by a pipet fitted with a filter and were analyzed spectrophotometrically according to a previously described method (5). The dissolution rate was defined as the grams of a compound dissolved from 1 cm^2 of surface of a disk/hr.

RESULTS AND DISCUSSION

Influence of Compression Force and Particle Size on Dissolution Rate—The data in Table I for compressed disks of salicylic acid, aspirin, and an equimolar mixture of aspirin and salicylic acid show that, under essentially sink conditions, the dissolution rate of nondisintegrating solids was independent of compression force from 450 to 9100 kg.

As shown in Table II for a size range of approximately 90 to 335 μm, the particle size of salicylic acid, aspirin, and an equimolar mixture of aspirin and salicylic acid compressed into a disk by a force of 1135 kg did not affect the dissolution rate of the nondisintegrating solid.

Kanke and Sekiguchi (6) found that, for benzoic acid, the compression force exerted no influence on the dissolution rate and that the size of sulfathiazole particles being compressed had no effect on the dissolution rate. The observed independence of dissolution rate from compression force and size of the material being compressed is in agreement with previous reports (4, 5, 20–23).

Influence of Concentration of Lubricants on Dissolution Rate—The general impression is that an increase in concentration of an insoluble lubricant in a compressed mass will slow the dissolution of the mass by decreasing the effective solid–solvent interface (19), by making the mass hydrophobic (23), and/or by physically coating the particles prior to compression (24). Hydrophobic lubricants investigated were calcium stearate[4], glyceryl monostearate[5], magnesium stearate[6], stearic acid[7], and talc[8]. The dissolution rates were determined using disks, containing from 0.1 to 5% lubricants of a 140/200-mesh size fraction, compressed at 1135 kg from an 80/100-mesh size of the materials.

As shown in Fig. 1, an increase in concentration of magnesium stearate

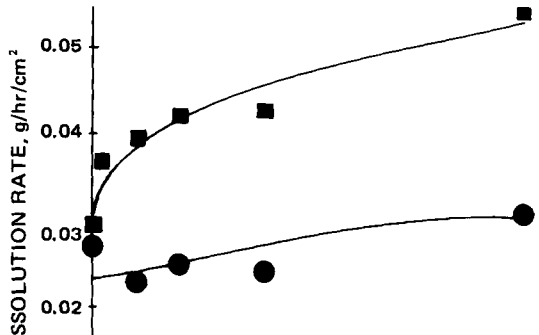

Figure 5—*Effect of concentration of starch on dissolution rate of 80/100-mesh equimolar mixture of aspirin and salicylic acid compressed at 1135 kg. Key: ●, salicylic acid; and ■, aspirin.*

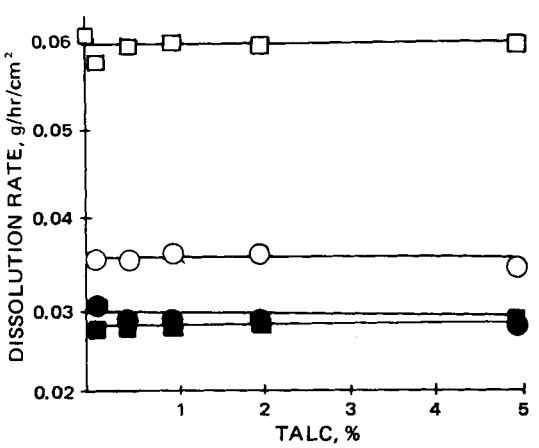

Figure 4—*Effect of concentration of talc on dissolution rate of 80/100-mesh materials compressed at 1135 kg. Key: ○, salicylic acid; □, aspirin; ●, salicylic acid from equimolar mixture of aspirin and salicylic acid; and ■, aspirin from equimolar mixture of aspirin and salicylic acid.*

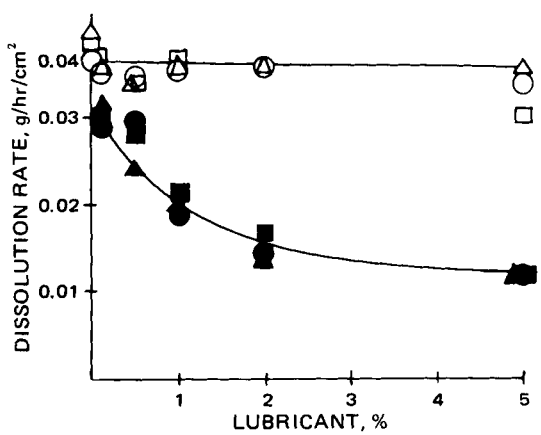

Figure 6—*Effect of particle size at various concentrations of lubricants on dissolution rate of salicylic acid compressed at 1135 kg. Key: □, 40/60-mesh size with talc; ○, 80/100-mesh size with talc; △, 140/200-mesh size with talc; ■, 40/60-mesh size with magnesium stearate; ●, 80/100-mesh size with magnesium stearate; and ▲, 140/200-mesh size with magnesium stearate.*

[1] Lot 733828, certified, Fisher Scientific Co.
[2] Lot 43904, USP, fine crystals, J.T. Baker Chemical Co.
[3] Carver press, model C.
[4] Lot A22, Matheson, Coleman and Bell.
[5] Purified, Fisher Scientific Co.
[6] Lot ENB, USP, Mallinckrodt.
[7] Lot WRHN, Mallinckrodt.
[8] Lot 3204560, J. T. Baker Chemical Co.

Table III—Effect of Compression Force on Dissolution Rate of 80/100-Mesh Equimolar Mixture of Aspirin and Salicylic Acid Containing 5% Starch Compressed into a 1.27-cm Disk

Compression Force, kg	Rate of Mass Loss[a], g/hr		Dissolution Rate, g/hr/cm²	
	Aspirin	Salicylic Acid	Aspirin	Salicylic Acid
910	0.059	0.035	0.047	0.028
1820	0.058	0.035	0.046	0.028
2730	0.060	0.034	0.048	0.028
3640	0.060	0.035	0.047	0.028
4550	0.060	0.034	0.040	0.026
5450	0.057	0.033	0.045	0.026
6360	0.063	0.036	0.049	0.028
7270	0.057	0.034	0.047	0.027
8190	0.060	0.036	0.048	0.029
9100	0.055	0.034	0.044	0.027

[a] Average of two determinations.

produced a slower dissolution rate of disks compressed of salicylic acid, aspirin, and an equimolar mixture of aspirin and salicylic acid. Similarly, an increase in concentration of calcium stearate, glyceryl monostearate, and stearic acid decreased the dissolution rates of disks of an equimolar mixture of aspirin and salicylic acid (Figs. 2 and 3).

These data seem to confirm the axiom that a sufficient quantity of a lubricant should be used to optimize tablet manufacture but that its concentration in a compressed tablet should be as low as practical to prevent a marked slowing of dissolution. With magnesium stearate, a concentration of 0.5% decreased the dissolution rates of salicylic acid and aspirin from compressed disks by approximately 20 and 7%, respectively, and decreased the dissolution rates of aspirin and salicylic acid from disks compressed of an equimolar mixture of aspirin and salicylic acid by approximately 33 and 27%, respectively.

Stearic acid, 1.0%, decreased the dissolution rates of aspirin and salicylic acid from compressed disks of an equimolar mixture of aspirin and salicylic acid by approximately 7 and 10%, respectively. Glyceryl monostearate, 0.5%, decreased the dissolution rates of aspirin and salicylic acid from compressed disks of an equimolar mixture of aspirin and salicylic acid by approximately 32 and 10%, respectively. Calcium stearate, 0.5%, decreased the dissolution rates of aspirin and salicylic acid from compressed disks of an equimolar mixture of aspirin and salicylic acid by approximately 20 and 40%, respectively.

Talc behaved differently from other hydrophobic lubricants. As shown in Fig. 4, the dissolution rates of disks compressed from salicylic acid, aspirin, and an equimolar mixture of aspirin and salicylic acid were essentially independent of concentrations of talc as great as 5%. It could be postulated that the stearates soften and spread under compression to provide a more coherent coverage of the matrix than talc.

If many hydrophobic lubricants slow dissolution, highly water-soluble lubricants, such as the polyethylene glycols, conversely could enhance

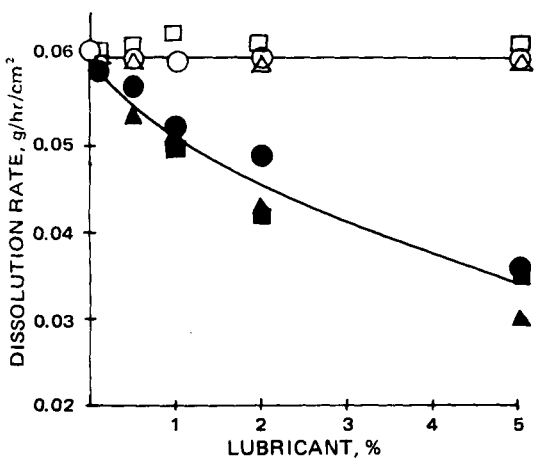

Figure 7—*Effect of particle size at various concentrations of lubricants on dissolution rate of aspirin compressed at 1135 kg. Key: □, 40/60-mesh size with talc; ○, 80/100-mesh size with talc; △, 140/200-mesh size with talc; ■, 40/60-mesh size with magnesium stearate; ●, 80/100-mesh size with magnesium stearate; and ▲, 140/200-mesh size with magnesium stearate.*

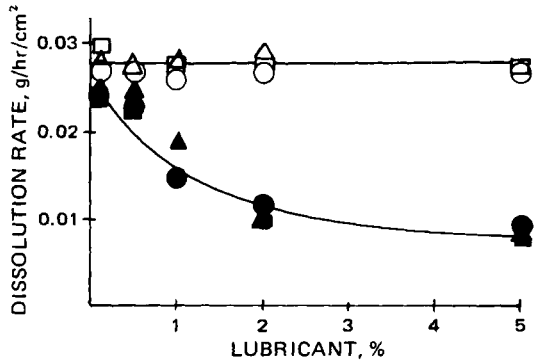

Figure 8—*Effect of particle size at various concentrations of lubricant on dissolution rate of salicylic acid from equimolar mixture of aspirin and salicylic acid compressed at 1135 kg. Key: ○, 40/60-mesh size with talc; □, 80/100-mesh size with talc; △, 140/200-mesh size with talc; ●, 40/60-mesh size with magnesium stearate; ■, 80/100-mesh size with magnesium stearate; and ▲, 140/200-mesh size with magnesium stearate.*

dissolution by increased wetting of, and better solvent penetration into, the mass (19). This enhancement did not occur with polyethylene glycol 4000. As shown in Fig. 3, the dissolution rates of disks compressed of an equimolar mixture of aspirin and salicylic acid were not affected by concentrations of polyethylene glycol 4000 as great as 5%. It may be that, to enhance dissolution, a lubricant must be simultaneously a water-soluble and surface-active substance.

Starch is a multipurpose excipient in commercial tablets; it is a good glidant and antiadhesive material, an excellent disintegrating agent, and an excellent binding agent (25). The dissolution rates from disks compressed at 1135 kg from an equimolar mixture of aspirin and salicylic acid were increased as the concentration of starch was increased (Fig. 5). It is difficult to apply the methodology used to determine intrinsic dissolution rates of nondisintegrating masses to compressed masses containing starch because the swelling of the starch causes flaking. As flaking occurs with a progressive roughening of the surface, the total surface of the solid exposed to the dissolution medium is increased. However, in the early period before gross flaking, the dissolution rates were more rapid as the concentration of starch was increased. Although the methodology is not absolute, it permits a comparison of the influence of various excipients on dissolution rate from compressed multicomponent masses.

Since starch has more than a single function in a tablet and swells mechanically when wet (26), the effect of compression force might influence characteristics of a tablet containing starch (27). The dissolution rates from disks compressed of an equimolar mixture of aspirin and salicylic acid containing 5% starch were determined at compression forces from 900 to 9100 kg. The dissolution rates were independent of the compression force (Table III).

Influence of Lubricants on Dissolution Rate of Disks Compressed from Different Sized Particles—The influence of the concentration

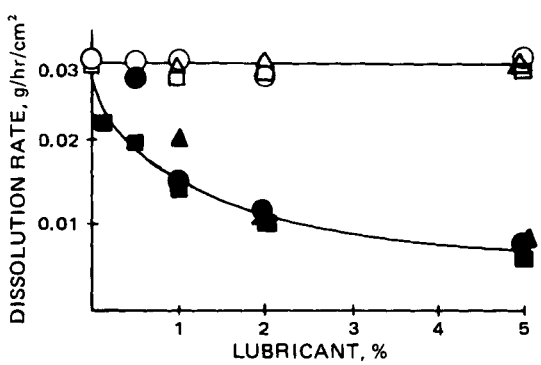

Figure 9—*Effect of particle size at various concentrations of lubricant on dissolution rate of aspirin from equimolar mixture of aspirin and salicylic acid compressed at 1135 kg. Key: ○, 40/60-mesh size with talc; □, 80/100-mesh size with talc; △, 140/200-mesh size with talc; ●, 40/60-mesh size with magnesium stearate; ■, 80/100-mesh size with magnesium stearate; and ▲, 140/200-mesh size with magnesium stearate.*

of a lubricant on the dissolution rate of a mass compressed at a given force was demonstrated for particles of 80/100-mesh size fraction. It is conceivable that a given weight of a lubricant may be distributed differently when blended with particles of different sizes and that different distributions may influence the dissolution of the compressed mass.

The dissolution rates of disks compressed at 1135 kg of 40/60-, 80/100-, and 140/200-mesh size fractions of salicylic acid containing 0.1–5% talc are shown in Fig. 6. The presence of talc in a concentration as great as 5% and the use of three size fractions of salicylic acid did not significantly alter the dissolution rates of the compressed disks. Similar results with talc were obtained from disks composed of aspirin (Fig. 7) and of an equimolar mixture of aspirin and salicylic acid (Figs. 8 and 9). The use of three size fractions of aspirin and an equimolar mixture of aspirin and salicylic acid with concentrations of talc from 0.1 to 5% did not alter the dissolution rates.

The dissolution rates of disks compressed at 1135 kg of 40/60-, 80/100-, and 140/200-mesh size fractions of salicylic acid, aspirin, and an equimolar mixture of aspirin and salicylic acid containing 0.1–5% magnesium stearate are shown in Figs. 6–9. As observed with talc, the dissolution rate, when using magnesium stearate, was independent of the size of the particles used to prepare the compressed disks.

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Recommendations to Eliminate Subjective Olfactory Methods from Compendial Identification Tests

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Abstract □ Substitution of IR and UV absorption spectroscopy and use of the various test papers listed in the compendia provide satisfactory means of identifying drugs and other substances that presently require subjective odor identification.

Keyphrases □ Compendial odor identification tests—substitution of IR and UV spectroscopic methods recommended □ IR spectroscopy—recommended as substitute for compendial odor identification tests □ UV spectroscopy—recommended as substitute for compendial odor identification tests

Many identification tests in USP XIX (1) and NF XIV (2) monographs rely on detection of odors produced either by the test substance itself or by its reaction products. Olfactory methods are inherently undesirable, both because of the possible toxic nature of the inhaled substances and because all such tests are markedly and unpredictably influenced by such subjective and idiosyncratic factors as the experience and discriminatory powers of the analyst, sensory fatigue, and the presence of masking odors.

Compounding the subjective nature of such olfactory testing, a varied terminology is used to describe the odors actually produced. Tables I and II list the various terms used in USP XIX and NF XIV, respectively.

For many drug substances, the IR spectrum is distinctive and can be compared to a curve in the literature. Final identification is made by comparing the unknown spectrum with a curve obtained from a reference standard prepared similarly and run under the same conditions and, preferably, on the same instrument. One advantage of the IR spectrophotometer is the ease with which it handles samples in the solid, liquid, or gaseous state. Commercial test papers or those described in the compendia (USP XIX, p. 760) are also useful for confirming the identity of several gases evolved in monograph identity tests.