M = mass of the reactive sample,
g = constant dependent on the furnace and sample holder geometry,
τ_s = thermal conductivity of the sample.

If the instrument is calibrated with a suitable standard, such as tin whose heat of fusion is 14 cal./Gm., then g and τ_s can be reduced to one constant, K, the heat transfer coefficient of the system.

K is determined for each thermocouple by means of the following equations which describe the response of the system:

$$\frac{\text{area}}{\text{Gm.}} = \frac{\text{area of fusion transition of tin} \times \text{range setting } (\mu\text{v.})}{\text{wt. of tin, Gm.}} \quad \text{(Eq. 2)}$$

$$\frac{\Delta H_f \text{ of tin (cal./Gm.)}}{\text{area/Gm.}} = \frac{\text{cal.}}{\text{area}} = \frac{\text{cal.}}{\text{mm.}^2} = K \quad \text{(Eq. 3)}$$

The heats of transitions can thus be determined by the following equation:

$$\Delta H_f = \frac{K \times \text{peak area in mm.}^2 \times \text{range setting } (\mu\text{v.})}{\text{sample wt., Gm.}} \quad \text{(Eq. 4)}$$

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Dissolution of Sodium Salicylate from Tablet Matrices Prepared by Wet Granulation and Direct Compression

By EDWARD MARLOWE* and RALPH F. SHANGRAW

A quantitative evaluation of dissolution of active ingredients from tablets is discussed. An investigation of filler-binder, lubricant, disintegrating agent, and hardness on the dissolution rate of sodium salicylate from tablet bases was studied by means of a 4 × 3 × 2 × 2 factorial experiment and analysis of variance. The utilization of a filler, spray-dried lactose, which required no preliminary granulation, gave significantly faster release rates than granulations prepared with acacia mucilage, starch paste, or ethylcellulose. The presence of a disintegrating agent notably affected the dissolution rate of the active ingredient, especially where wet granulation was employed. The release of sodium salicylate from several bases was a result of the interaction of many variables and was not dependent solely upon the effect of an individual component.

THE EFFECT of formulation and processing factors on the dissolution rate of active ingredients from compressed tablets has been the subject of a number of reports. Wensley (1), using a modification of the Gershberg-Stoll apparatus, investigated the effects of granulating agents and pressure on the dissolution rate of sodium bicarbonate tablets. Kadar and Walker (2) studied the *in vitro* release of sulfathiazole from compressed formulations using a modification of the U.S.P. XV tablet disintegration apparatus. The effects of particle density and neutral ionic and nonionic compounds on the dissolution rate of slightly soluble acidic drugs were determined by Parrott *et al.* (3). In a later study by the same workers (4) the influences of bases and buffers on rates of dissolution of acidic solids were investigated. Levy (5–7) studied the effect of formulation factors on the dissolution rate of the active ingredient. Included in the factors studied were the agitation intensity, granule size, starch concentration, compression pressure, and lubricants.

With the advent of new machines and materials, a great many tablets formerly prepared by wet granulation can now be manufactured by direct compression. Various direct compression fillers have been evaluated: spray-dried lactose by Gunsel and Lachman (8) and by Duvall *et al.* (9), microcrystalline cellulose by Reier and Shangraw (10), amylose by Kwan and Milosovich

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(11), and anhydrous lactose by Batuyios (12).

However, wet granulation continues to be widely employed, and proponents of this process argue that dissolution of active ingredients from granulated matrices is equal or may be superior to that from direct compression matrices. The object of this investigation was to study the individual effects and possible interactions of filler, binder, disintegrating agent, lubricant, and pressure on the release of an active ingredient from tablets prepared by wet granulation and compare such tablets with those made by direct compression. By means of statistical analysis, the magnitude of the individual factors as well as interactions were determined.

EXPERIMENTAL

Apparatus and Method—Many methods have been utilized for studying dissolution rates from tablets. The apparatus used in this study was similar to the one utilized by Patel and Foss in their studies on binding (13). A typical cell is shown in Fig. 1. Various membranes were studied in an attempt to find one which would give rapid equilibrium and at the same time provide adequate filtration. Many membranes were found to be unsatisfactory because they exhibited extremely long equilibrium times, possessed poor wet strengths, or gave rise to cloudy solutions. However, four thicknesses of a thin paper membrane[1] proved to overcome these difficulties. As no apparatus or procedure can exactly duplicate *in vivo* conditions, all dissolution studies are relative, and the most important considerations are ones of reproducibility, practicality, and reasonableness. The apparatus and method appeared to qualify in these respects.

The plastic cell was assembled, 15 ml. of distilled water placed on each side of the membrane, and the entire assembly placed in a water bath maintained at 37°C. When the experimental temperature was reached, two tablets from each batch were inserted into one side of the cell. The cell was rotated in the water bath at a rate of 15 r.p.m. At specified intervals, 1-ml. samples were removed from the cavity on the other side of the membrane, appropriately diluted, and assayed spectrophotometrically.

The dissolution procedure is not as simple as would be desirable. The manual removal of samples and their assay are time consuming, and interruption of the rotation of the cell is necessary while samples are withdrawn. Even though the tablet remains immersed in the liquid and the removal procedure standardized, there is a chance for a slight distortion (reflected in a delay) in the dissolution profile. Obviously, an automatic sampler and analyzer would be advantageous.

Formulation and Preparation of Tablets—Sodium salicylate was chosen as an active ingredient due to its solubility characteristics and ease of assay. Test solutions were diluted with distilled water and absorbance read on a Beckman DU spectrophotometer at 296 mμ. It was found that approximately 6 min. were required to obtain equilibrium when a solution of sodium salicylate was placed into one side of the dissolution cell. Although a 6-min. equilibrium time is longer than might be ideally desirable, a high percentage of the drug does pass the membrane rapidly, and the delay is not unreasonable when comparable *in vivo* absorption conditions are considered.

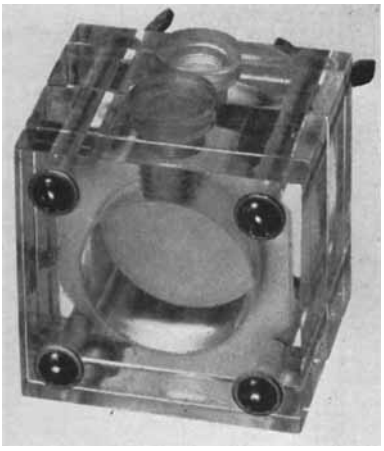

Fig. 1—Plastic dissolution cell.

Tablets were prepared containing 50 mg. of sodium salicylate made up to a total weight of 400 mg. with binder, lubricant, disintegrating agent, and filler. Two fillers (lactose and spray-dried lactose), three binding solutions (5% ethylcellulose in alcohol, 10% acacia mucilage, and 10% starch paste), and three lubricants (1% magnesium stearate, 1% hydrogenated vegetable oil,[2] and 3% of a soluble lubricant composed of a 1:1:2 ratio of DL-leucine, calcium benzoate, and polyethylene glycol 4000) were studied. Absence of a disintegrating agent was compared to 10% cornstarch. Since no granulation was necessary with spray-dried lactose, only 5% starch was added, and the difference in weight was made up with additional spray-dried lactose. The sodium salicylate, starch, and lubricant were blended with the spray-dried lactose, and tablets compressed directly.

The tablets prepared by wet granulation were manufactured by first blending the lactose, sodium salicylate, and one-half the starch (when present), and then moistening the powder blend with the appropriate binding solution. An attempt was made to maintain an equal amount of solid binder in the final granulation. The wet mass was forced through a No. 8 screen and allowed to dry overnight in an oven at 120°F. The dry granules were passed through a No. 12 screen and the lubricant and remaining starch blended into the mixture. Tablets were compressed to two different hardnesses (Strong-Cobb 3.5 and 6.5) on a Stokes model A-3 single punch tablet press.

Tablets were prepared utilizing all possible combinations of filler-binders (lactose–ethylcellulose, lactose–starch paste, lactose–acacia, and plain spray-dried lactose), lubricants, disintegrators, and hardnesses, giving a $4 \times 3 \times 2 \times 2$ factorial experiment with 48 batches of tablets. In order to

[1] Marketed as Tricolator by Tricolator Manufacturing Co., Inc., Bellmore, N. Y.

[2] Marketed as Sterotex by Capitol City Products, Columbus Ohio.

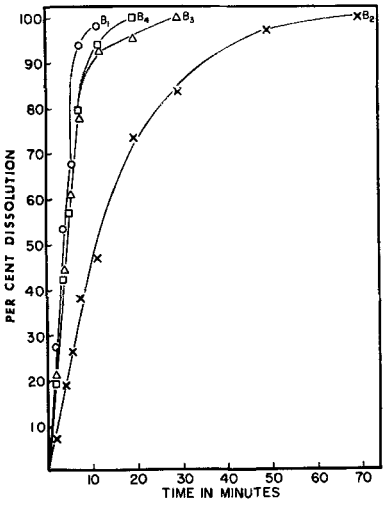

Fig. 2—Comparison of filler-binders in a tablet formula containing starch, magnesium stearate, and 3.5 S.-C. hardness. Key: B_1, *spray-dried lactose;* B_2, *ethylcellulose and lactose;* B_3, *acacia mucilage and lactose;* B_4, *starch paste and lactose.*

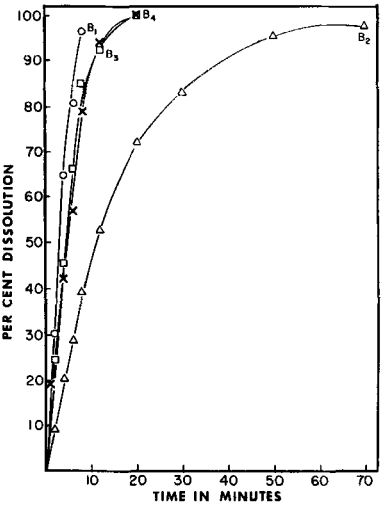

Fig. 4—Comparison of filler-binders in a tablet formula containing starch, hydrogenated vegetable oil, and 3.5 S.-C. hardness. Key: B_1, *spray-dried lactose;* B_2, *ethylcellulose and lactose;* B_3, *acacia mucilage and lactose;* B_4, *starch paste and lactose.*

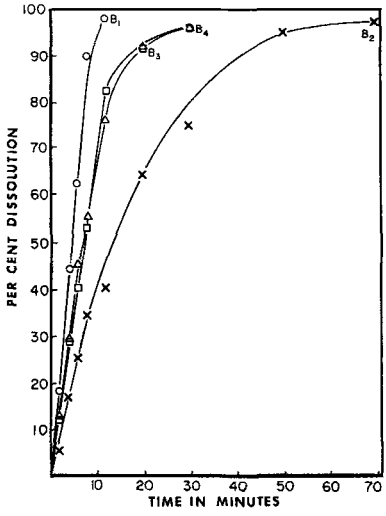

Fig. 3—Comparison of filler-binders in a tablet formula containing starch, magnesium stearate, and 6.5 S.-C. hardness. Key: B_1, *spray-dried lactose;* B_2, *ethylcellulose and lactose;* B_3, *acacia mucilage and lactose;* B_4, *starch paste and lactose.*

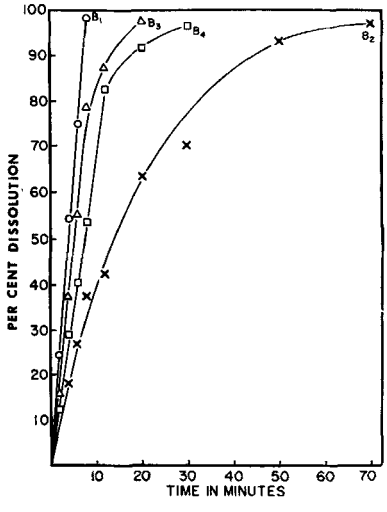

Fig. 5—Comparison of filler-binders in a formula containing starch, hydrogenated vegetable oil, and 6.5 S.-C. hardness. Key: B_1, *spray-dried lactose;* B_2, *ethylcellulose and lactose;* B_3, *acacia mucilage and lactose;* B_4, *starch paste and lactose.*

eliminate variables other than those under consideration, attempts were made to standardize the amount of active ingredient in each tablet as well as tablet weight and thickness.

Results and Treatment of Data—The per cents of dissolution of sodium salicylate from the various tablet formulations are shown in Figs. 2–8. Tablets prepared by direct compression with spray-dried lactose uniformly exhibited more rapid dissolution patterns. In all cases except where no disintegrating agent was employed (Fig. 8), dissolution was complete within 12 min. This includes the uniform delay necessary for equilibrium which is inherent in the experimental method employed. All tablets prepared by wet granulation displayed slower release rates, particularly during the latter stages. The ethylcellulose binding solutions gave the slowest release rates in all cases where disintegrating agents were employed, but no real differences could be noted when a disintegrating agent was not used. In general, an increase in tablet hardness retarded dissolution, while the presence of starch dramatically increased it.

In order to give the data mathematical significance

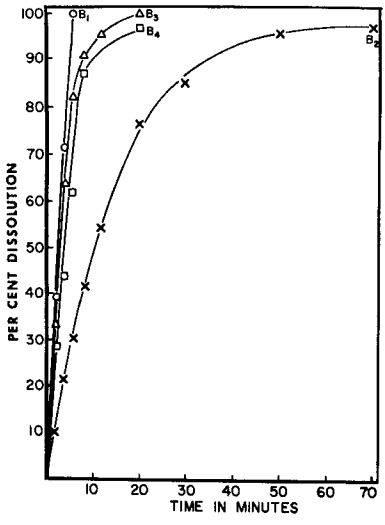

Fig. 6—Comparison of filler-binders in a tablet formula containing starch, soluble lubricant, and 3.5 S.-C. hardness. Key: B_1, *spray-dried lactose;* B_2, *ethylcellulose and lactose;* B_3, *acacia mucilage and lactose;* B_4, *starch paste and lactose.*

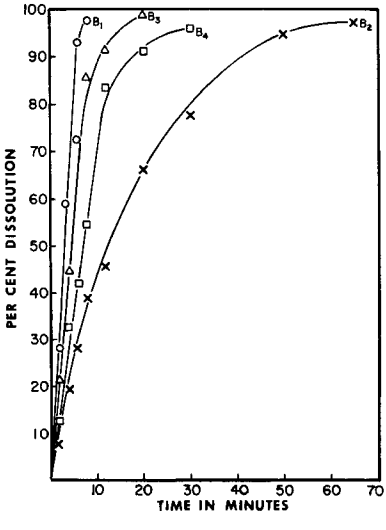

Fig. 7—Comparison of filler-binders in a tablet formula containing starch, soluble lubricant, and 6.5 S.-C. hardness. Key: B_1, *spray-dried lactose;* B_2, *ethylcellulose and lactose;* B_3, *acacia mucilage and lactose;* B_4, *starch paste and lactose.*

and to point up interactions between formulation components, an analysis of variance was carried out. The method used for analysis was a $4 \times 3 \times 2 \times 2$ factorial experiment representing four filler-binders, three lubricants, two disintegrating agents, and two compression hardnesses. In order to make use of all the data collected at all nine time intervals, it would have been necessary to calculate a $9 \times 4 \times 3 \times 2 \times 2$ factorial experiment. Because this would have been cumbersome to handle and necessitate the use of a computer, a single time was selected.

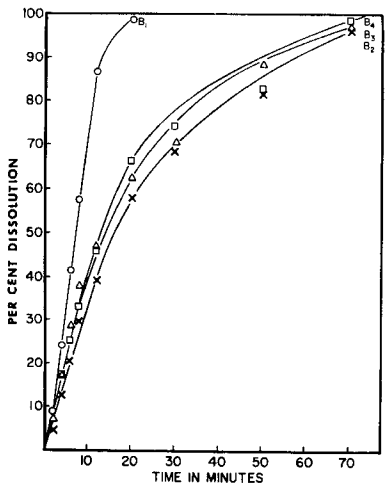

Fig. 8—Comparison of filler-binders in a tablet formula containing no starch, magnesium stearate, and 6.5 S.-C. hardness. Key: B_1, *spray-dried lactose;* B_2, *ethylcellulose and lactose;* B_3, *acacia mucilage and lactose;* B_4, *starch paste and lactose.*

The 8-min. per cent dissolutions chosen as data from that time interval were influenced less by the membrane equilibrium time and had not reached 100% for most formulations. The analysis of variance is shown in Table I.

DISCUSSION

From Table I it can be seen that filler-binders and presence of a disintegrating agent are significant at a 5% level. This was to be expected from visual examination of the data. No two factor interactions were significant at the 5% level which can be attributed to the large mean squares associated with the three factor interactions, two of which (binder–hardness–disintegrating agent and binder–disintegrating agent–lubricant) were significant. These are exactly the same three factor interactions found significant by Kwan *et al.* (14) in their study using disintegration times as end points. By utilization of a t test, it was shown that spray-dried lactose and acacia–lactose give significantly different mean availability times. The calculated t value was 3.93 as compared to a significant value at 95% of 2.02. Since acacia–lactose gave the second fastest availability rate, it can be concluded that spray-dried lactose is significantly superior to the other filler-binders tested in this study.

Analysis of variance was then repeated utilizing only the data obtained from the three filler-binders which required prior granulation, *i.e.*, acacia–lactose, starch–lactose, and ethylcellulose–lactose. The binder effect previously obtained was no longer significant, indicating no substantial difference between acacia, starch, and ethylcellulose. This can be attributed to the lack of differences when no disintegrating agent is employed, as it appears obvious that when a disintegrating agent is used (Figs. 2–7) ethylcellulose gives a much slower release rate. The same three factor interaction, binder–hardness–disintegrating agent, again was shown to be significant. More important, the two factor interaction, binder–disintegrating agent,

TABLE I—ANALYSIS OF VARIANCE OF PER CENT DISSOLUTION OF SODIUM SALICYLATE AFTER 8 min.

Source	d.f.	Mean Sq.	*F*vs I[e]	*F*va R[f]	$F_{.05}$	$F_{.10}$
B[a]	3	611,879	4.65[g]		2.88	2.25
H[b]	1	49,729	<1.00			
D[c]	1	628,148	4.77[g]		4.12	2.86
L[d]	2	43,373	<1.00			
B × N	3	12,124	<1.00			
B × D	3	62,733	2.62[h]		3.20	2.44
B × L	6	8,200	<1.00			
H × D	1	22,576	<1.00			
H × L	2	1,504	<1.00			
D × L	2	617	<1.00			
B × H × D	3	11,774		13,41[g]		
B × H × L	6	624		<1.00	4.76	3.29
B × D × L	6	11,061		12.60[g]	4.28	3.05
H × D × L	2	445		<1.00		
Residual	6	878				
Total	47					

[a] Three filler-binder combinations. [b] Four hardness. [c] Five disintegrating agents. [d] Six lubricants. [e] *F* determined by the combined mean square of the interactions. [f] *F* determined by the mean square of the residual. [g] Significant at 5% level. [h] Significant at 10% level.

became significant. This can be attributed to the large effect the disintegrating agent had on the acacia and starch granulations as opposed to the small effect on the ethylcellulose.

Tablet hardness did not have a significant effect in either study. However, hardness did appear to affect the rate of dissolution from those formulations containing starch. Analysis of variance of 8-min. dissolution data from all tablets containing starch was calculated. Hardness still did not show up as a significant factor, although the binder–hardness interaction was extremely significant. One of the reasons for lack of significance was the softness of tablets obtained from both pressure settings. It is probable that tablets of both hardnesses possessed sufficient pore spaces to promote capillary water penetration and subsequent tablet rupture. The high interaction term can be attributed in large measure to the little effect hardness had in spray-dried lactose tablets, even in the presence of starch.

In order to further substantiate that the presence of a disintegrating agent was significant, a *t* test was carried out on the mean per cent dissolution of sodium salicylate from 6-min. samples containing starch and no starch. The difference between the means was found to be significant, the calculated *t* value being 2.64 as compared to a table value of 2.01 for significance at the 95% level.

One further study was conducted to show the importance of binders on dissolution for all values of time. In this case, the per cent availabilities of all the filler-binders were compared at different time intervals, keeping pressure constant (high), lubricant the same (magnesium stearate), and including starch in the formulations. Analysis of variance indicated that binders were even more significant when compared over all the time intervals. Of course, time showed up highly significant as would be expected.

In order to make a more meaningful study, the disintegration times of all batches prepared were determined by the U.S.P. XVI method. An analysis of variance of the mean disintegration times was computed. The same single effects, filler-binder and disintegrating agents, appeared significant at the 95% level as well as the two factor interaction of filler-binder and disintegrating agent. However, no three factor interactions were significant due to the fact that the residual or error term against which three factor interactions were tested was large. This can be attributed to the large inherent error in disintegration time determinations which arise from indistinct end points and operator variability. The statistical analysis of the U.S.P. disintegration results failed to demonstrate the interplay between component variables present in normal formulations and reflected in *in vitro* release data.

In an attempt to summarize the preceding experiments, the mean dissolution per cents for 8-min. samples and the mean disintegration times are presented in Tables II and III. Both tables denote analogous results indicating that an 8-min. dissolution test gives the same indications of component effects as much longer disintegration times. The spray-dried lactose showed superior release rates followed by acacia–lactose, starch–lactose, and ethylcellulose–lactose.

In order to present these dissolution data in a manner which more closely approximates disintegration times, an attempt was made to determine the mean 100% dissolution times. However, this end point did not always give good comparable data as can be seen from the dissolution curves in Figs. 2–8. Thus, the times necessary for samples to reach 80% dissolution were chosen for comparison and the means of these values are presented in Table IV. These figures substantiate the same order of dissolution previously described. However, the difference between acacia and starch as binders is negligible. It is quite apparent from Tables III and IV that the time for 80% availability appears to differ significantly from the mean disintegration time. Even taking into consideration a delay in equilibrium time, the dramatic increase in the amount of time necessary to obtain only 80% dissolution points up the inadequacy of the U.S.P. XVI disintegration method for determining active ingredient release patterns.

One of the objects of this investigation was to study the effect of a water-soluble lubricant com-

TABLE II—AVERAGE PER CENT DISSOLUTION OF 8-min. SODIUM SALICYLATE SAMPLES

Filler-Binder		Pressure		Disintegrators		Lubricants	
Spray-dried lactose	88.8	Low	62.0	No starch	47.4	Mg stearate	53.2
5% Ethylcellulose and lactose	34.6	High	55.6	Starch	70.2	Hydrogenated vegetable oil	59.7
10% Acacia mucilage and lactose	59.3					Soluble lubricant	63.5
10% Starch paste and lactose	52.4						

TABLE III—MEAN DISINTEGRATION TIMES (sec.) OF SODIUM SALICYLATE TABLETS

Filler-Binder		Pressure		Disintegrators		Lubricants	
Spray-dried lactose	221	Low	404	No starch	662	Mg stearate	689
5% Ethylcellulose and lactose	922	High	641	Starch	382	Hydrogenated vegetable oil	446
10% Acacia mucilage and lactose	435					Soluble lubricant	370
10% Starch paste and lactose	510						

TABLE IV—AVERAGE TIME (sec.) OF 80% DISSOLUTION OF SODIUM SALICYLATE

Filler-Binder		Pressure		Disintegrators		Lubricants	
Spray-dried lactose	390	Low	1122	No starch	1644	Mg stearate	1290
5% Ethylcellulose and lactose	1992	High	1320	Starch	798	Hydrogenated vegetable oil	1260
10% Acacia mucilage and lactose	1266					Soluble lubricant	1104
10% Starch paste and lactose	1230						

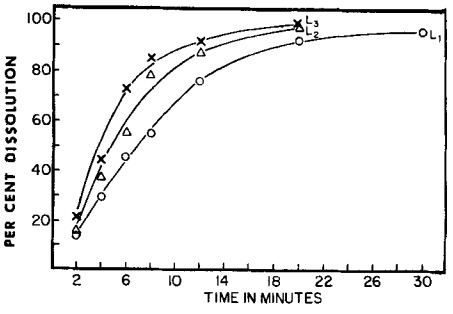

Fig. 9—Comparison of lubricants in a tablet formula containing acacia mucilage, starch, and 6.5 S.-C. hardness. Key: L_1, *magnesium stearate;* L_2, *hydrogenated vegetable oil;* L_3, *soluble lubricant.*

posed of a DL-leucine, polyethylene glycol 4,000, and calcium benzoate on the availability of active ingredients. It was hoped that the soluble lubricant would increase dissolution over the more conventionally used stearates. However, lubricant variation did not appear significant in any of the studies. As shown in Fig. 9, which represents the data in a typical formulation containing starch, acacia–lactose, and compressed at high pressure, the soluble lubricant exhibited the fastest dissolution rate, followed by hydrogenated vegetable oil and then magnesium stearate. This pattern, although showing only slight differences, was consistent throughout all the work.

The results of the investigation indicate that for this particular active ingredient and the various factors studied, direct compression uniformly gives rise to faster dissolution rates than wet granulation. In addition, direct compression is clearly less time consuming and requires less equipment than wet granulation. On the other hand, both acacia and gelatin gave tablets which exhibited acceptable dissolution profiles when a disintegrating agent was present, indicating that wet granulation is still an effective means of preparing powders for compression. It appears, however, that economics alone will lead to a steady decrease in the utilization of wet granulation procedures, and the process will eventually be confined to those drugs which cannot be adapted to direct compression techniques.

SUMMARY AND CONCLUSIONS

1. An apparatus and procedure for the determination of the *in vitro* dissolution of active ingredients from tablets is described.

2. The effect of filler-binders, lubricants, disintegrating agents, and hardness on the dissolution of sodium salicylate from tablet bases was studied by means of a $4 \times 3 \times 2 \times 2$ factorial experiment.

3. Tablets prepared by direct compression with spray-dried lactose exhibited faster dissolution rates for sodium salicylate than tablets prepared by wet granulation.

4. Dissolution of an active ingredient from a tablet matrix is generally not dependent solely on the effect of a single component or production

specification, but is the result of the interaction of many variables.

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Preliminary Investigation of the *Z*-Value Measure of Relative Solvent Polarity in Micellar Solubilization

By STEVEN G. BJAASTAD and NATHAN A. HALL

The *Z*-value method for determining solvent polarity has been applied to surfactant solutions containing camphor and 2-heptanone. The surfactants used were partially purified polysorbate 80, potassium laurate, and dodecyltrimethylammonium chloride. As the surfactant concentration increased the *Z*-value decreased, indicating that the solubilized ketones encountered an environment of decreasing polarity. In the polysorbate 80 system 2-heptanone appeared to be solubilized deeper in the micelle interior than camphor. Both ketones in 0.2 *M* potassium laurate solutions were solubilized in more highly polar environments than in 0.2 *M* dodecyltrimethylammonium chloride solutions.

SURFACTANTS, as agents for making aqueous solutions of poorly water-soluble substances, continue to be of interest in pharmaceutical as well as many other systems. The solute is considered to be solubilized by the less polar micellar pseudophase, and this type of solubilization has been shown to affect the chemical and biological properties of the solubilizate. Compounds are thought to be solubilized in various regions of the micelle: on the surface, in the palisade layer, or in the lipophilic micellar core (1, 2). It is logical to assume, therefore, that solubilized molecules would encounter regions of varying polarity.

Riegelman *et al.* (3) have shown that the ultraviolet absorption spectra of solubilized compounds alter upon solubilization and have drawn certain conclusions regarding the micellar region of solubilization from the spectra of solubilized systems. The ultraviolet spectral investigations of Sasaki *et al.* (4) indicated that the micellar interior in solubilized systems does contain some water.

Although polarity is reflected by a number of measurements on bulk liquids, such as dielectric constant and refractive index, the correlation of such measurements with the liquid's solvent properties has been shown to have many limitations. No single measurement appears to be valid in more than a general way for predicting solubility and the effect of a given solvent on the properties of its solutions. Several investigators have attempted to improve the situation by developing empirical methods to assess the relative polarity of a series of solvents (5–9). One of these, the *Z*-value method developed by Kosower (9), appeared to be promising enough for use in examining micellar solubilized systems and was the subject of this study.

Based upon the assumption that the first layers of solvent around a molecule or ion will be appreciably different in dielectric constant from that measured for the bulk solution, Kosower originated the *Z*-value method for measuring the relative polarity of the layer of solvent molecules immediately surrounding the solute molecule (cybotactic region). The *Z*-value was defined as the energy of electronic transition corresponding to the charge-transfer absorption band of 1-ethyl-4-carbomethoxy pyridinium iodide. The shift of this band to longer wavelengths, occurring with solvents of decreasing polarity, was found to correlate well with other phenomena, such as rates of hydrolysis and keto–enol equilibria, which were known to be sensitive to solvent polarity. Subsequently, many substances were found to exhibit solvent-sensitive absorption spectra and

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