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Unexpected Variable in the USP–NF Rotating Basket Dissolution Test

Keyphrases ☐ Dissolution test—rotating basket method ☐ Rotating basket dissolution test—vibration effect

Sir:

To increase our capability for dissolution-rate testing by the USP XVIII–NF XIII rotating basket method[1], we recently designed and constructed a mechanized apparatus capable of testing six dosage units simultaneously. To our surprise, this apparatus gave significantly longer dissolution times, especially at rotation speeds of 150 r.p.m. or less, than were obtained previously under the same conditions with a nonmechanized apparatus.

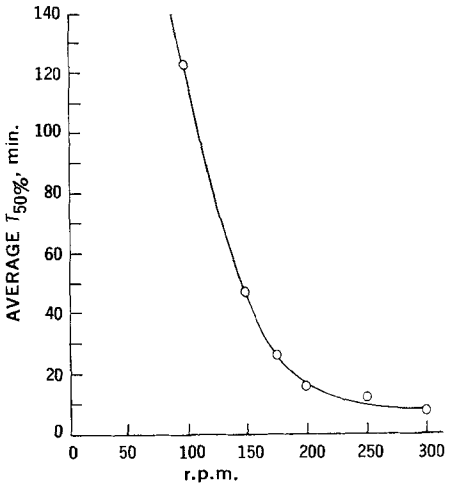

Figure 1—*Effect of rotation speed on dissolution rate of tolbutamide tablets USP, using the USP XVIII procedure with the mechanized apparatus.*

An investigation was undertaken to find the cause of this variation. Both pieces of apparatus conform to the requirements of the compendia (2, 3). By inspection, both permit smooth rotation of the basket assembly without perceptible wobble. The flask and stirrer assembly of the nonmechanized apparatus is mounted with a Fisher frame. The mechanized apparatus is of a unitized design; the six stirrers operate from a single-drive shaft; the flasks, held in place by a common manifold plate, rest on conical springs. The speeds of rotation for both pieces of equipment, as measured by a strobe light (or by counting revolutions at low speed), were well within the ±5% tolerance limits specified in the compendia. Both incorporate the same specified flask, which is sampled by a continuous flow system of the same pumping rate with similarly positioned inlet and outlet tubes of identical hold-up volumes.

Investigation finally revealed that a very subtle difference existed in the vibrational levels of the two pieces of equipment. Vibration was suspected when it was observed that the introduction of vibration by gentle tapping of the dissolution flask caused particles of a disintegrating tablet to spray from the basket; this was accompanied by an abrupt deflection in the dissolution profile toward higher percent dissolution. The vibrational levels associated with the two pieces of equip-

Table I—Effect of Vibration on Dissolution Times of a Single Lot of Tolbutamide Tablets USP by the USP Rotating Basket Method

Apparatus	Vibration[a] Displacement, mils	Vibration[a] Frequency, c.p.m.	Magnitude[b] of Vibration	Minutes for 50% Dissolution[c] 150 r.p.m.	300 r.p.m.
Nonmechanized unit	0.8	3600	Slightly rough	8.2	5.0
Nonmechanized unit, water pump off	0.2	3000	Very good	24	4.7
Mechanized unit	0.05	600	Extremely smooth	48	7.4

[a] Determined with Vibration Analyzer, model 600, International Research and Development Co., Columbus, Ohio. [b] From General Machinery "Vibration Severity Chart," International Research and Development Co., Columbus, Ohio. [c] Average of six tablets.

[1] The USP XVIII and NF XIII Method I dissolution test methods are identical, both being a modification of the method described by Pernarowski *et al.* (1).

ment were then tested with a vibration analyzer[2]. The analyzer probe was touched to various parts of the apparatus that contact the dissolution flask, and the vibration displacement and frequency values were recorded and averaged to give an estimate of the magnitude of vibration. These data are given in Table I, together with dissolution times obtained for a lot of tolbutamide tablets USP. Using the "Vibration Severity Chart" supplied by the manufacturer of the vibration analyzer, we rated the mechanized apparatus "extremely smooth" and the nonmechanized apparatus "slightly rough." Sources of vibration in the nonmechanized unit were traced to the benchtop, floor, and water circulator motor, with the latter being the principal source. When the circulator motor was turned off, the apparatus was rated "very good."

It is apparent from Table I that the effect of vibration on the dissolution rate of tolbutamide tablets USP is quite pronounced when the basket is rotated at 150 r.p.m., but it is almost insignificant when the basket is rotated at 300 r.p.m. In fact, for this lot of tablets the dissolution time obtained with the nonmechanized apparatus at 150 r.p.m. is about equivalent to that obtained with the mechanized apparatus at 300 r.p.m.

Some insight into the effect of vibration may be gained from a dissolution time–revolutions per minute profile. The profile shown in Fig. 1 was obtained, using the mechanized apparatus, for the same lot of tablets for which data are presented in Table I. Note that the slope is quite steep at 150 r.p.m. but quite flat at 300 r.p.m. Since additional vibration has the same effect on dissolution as additional rotation speed, it becomes immediately apparent why the effect of vibration is much more pronounced at 150 r.p.m. than at 300 r.p.m.

We have found that the shape of the dissolution time–revolutions per minute profile varies considerably from product to product, and to a lesser extent, from lot to lot of the same product. Therefore, control of vibration is more important for some products than for others. Undoubtedly, the nature of ingredients and the disintegration characteristics of the formulation are important factors.

It is not the purpose of this communication to cast doubt on the value of the USP and NF rotating basket dissolution test. In fact, we believe that this test holds much promise for the control of lot-to-lot dissolution-rate uniformity. However, if meaningful interlaboratory or even intralaboratory comparisons are to be made using this test, such variables as the one we have discussed must be identified and controlled.

When establishing dissolution specifications for products using the rotating basket method, the data presented here suggest two courses of action: either vibration must be carefully controlled within a specified limit as defined by an objective vibration test procedure, or its effects must be reduced by rotating the basket at sufficient speed.

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[2] Model 600 Vibration Analyzer, International Research and Development Co., Columbus, Ohio.

Preparation and Characterization of Lincomycin Cyclamate

Keyphrases ☐ Lincomycin cyclamate—synthesis, characterization ☐ Cyclamate interference—lincomycin therapy

Sir:

In recent studies, small quantities of the synthetic sweetening agents, sodium or calcium cyclamate[1], were shown to reduce the absorption of the antibiotic lincomycin hydrochloride to 25–30% of control values obtained in the absence of these agents (1). This activity was observed during carefully controlled clinical pharmacology studies, in which blood levels and/or urinary excretion were measured, in the development of a pediatric syrup of this antibiotic. It was found that depression in absorption of lincomycin occurs not only when the cyclamate is present with the antibiotic in the syrup ingested by both adults and children but also when the antibiotic is taken as the syrup and the cyclamate is ingested in the form of a diet drink[2], and mixing of the two fluids occurs in the human stomach. One molar equivalent of cyclamate essentially produced maximum depression of absorption of lincomycin hydrochloride, whereas no interference was found with the absorption of tetracycline hydrochloride.

In view of the obvious hazard to lincomycin therapy posed by the apparent interference of common cyclamates, we investigated the possibility of a metathetic reaction leading to precipitation of lincomycin cyclamate. Lincomycin cyclamate was expected to be easily precipitated from aqueous media by analogy with the known sparingly soluble hexadecylsulfamate and octadecylsulfamate salts of lincomycin (2) and from the fact that cyclamate salts have been prepared and characterized from several widely used classes of drugs such as antihistaminic, autonomic, myospasmolytic, central stimulant, neuroleptic, antitussive, antibiotic, and local anesthetics (3).

To our surprise, no precipitate formed when nonsaturated aqueous solutions of equivalent quantities of lincomycin hydrochloride were treated with either sodium or calcium cyclamate. Slightly impure linco-

[1] Sucaryl.
[2] Such as Diet-Rite Cola or Like.