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COMPARATIVE EVALUATION OF FOUR DISSOLUTION APPARATUS

(Mrs.) M. R. Baichwal*, S.G.Deshpande and U.C.Shetty

Department of Chemical Technology,
University of Bombay, Bombay 400 019,
India.

*Presently at : C.U. Shah College of Pharmacy,
S.N.D.T. Women's University, Bombay 400 049.

ABSTRACT

Four dissolution methods, the rotating basket, the rotating paddle, the rotating basket with paddle and the stationary basket-rotating paddle, were evaluated using capsules and non-disintegrating pellets of salicylic acid. The agitation intensity produced by the rotating basket method was very low and differed significantly throughout the vessel. However, it did not differ significantly at different positions in the stationary basket-rotating paddle method. This method offered considerable advantages and hence appears to be a suitable alternative to the existing compendial methods which have limitations for evaluation of dosage forms which tend to float on the dissolution medium.

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INTRODUCTION

Satisfactory determination of dissolution rates of a drug product either in tablet or capsule form under indentical experimental conditions is difficult to achieve with the existing compendial methods. Though the rotating basket method is capable of evaluating both the dosage forms, it suffers from the disadvantage that the homogeneity of the bulk of the dissolution medium is not attained within a reasonable time. This was observed earlier by Withey (1) and Carstensen et al (2,3) with non-disintegrating pellets. With the rotating paddle method the dissolution of some dosage forms like capsules, beads, pellatized formulations etc. presents a problem because of their tendency to float on the dissolution medium. USP XX states that "a small loose piece of non-reactive material such as wire or glass helix may be attached to dosage units that would otherwise float". However, we have observed that even a sufficiently loose wire helix interferes in the opening and disintegration of the capsule. Such a procedure, apart from being cumbersome, poses the problem of reproducibility and accurate placing of dosage forms. In addition, tablets, capsules and other dosage forms cannot be evaluated by this method under identical experimental conditions.

Though, however, the use of rotating filter-stationary basket method developed by Shah et al (4) would circumvent these problems it has been reported (5) that this method gives more variable results and is quite difficult to use compared with either the rotating basket or the rotating paddle apparatus. Alternatively, an assembly with a stirring element in which a stirrer is attached to the stirring shaft above the basket and used by Pernarowski et al (6) or Lin et al (7) or the magnetic basket method of Shephered et al (8) could overcome the limitations of the compendial methods. However, a promising method appears to be one suggested earlier by Langenbucher and Moeller (9) which is a simple modification of the existing official methods. This simply involves an introduction of a stationary basket above the paddle; a design somewhat similar to the one used by Cook et al (10). Such a method was recently used by Gonzalez and Golub (11) for evaluation of Theo-Dur Sprinkle pellets.

This study presents a comparative evaluation of four dissolution methods. These methods were evaluated for (i) homogeneity of the dissolution medium and reproducibility of the method employing salicylic acid capsules for dissolution and (ii) the agitation intensity produced in each method at predetermined different

positions in the dissolution vessel. Dissolution of non-disintegrating pellets of salicylic acid was followed for this purpose (12).

Results of this study indicate the poor agitation intensity at low stirring speed (50 rpm) as well as variation in agitation intensity as a function of the position in the dissolution vessel irrespective of the stirring speed in case of the rotating basket method. On the other hand, this study clearly demonstrates the hydrodynamic superiority of the stationary basket-rotating paddle apparatus.

METHODS

Apparatus

The four types of dissolution equipments used were: (A) Rotating basket (RB) of USP XX (apparatus I). (B) Rotating paddle (RP) of USP XX (apparatus II). In this method, wire helix of two different dimensions were used to sink the capsule. One was long (L.C.) with 5 turns covering the capsule whereas the other one was short (S.C.) with only two turns. The coil was made from a stainless steel wire of 0.2 mm diameter. (C) Rotating basket with paddle (RBWP). This was similar to the RB apparatus and in addition had a paddle attached to the stirring rod 0.8 cm above the basket (Fig. 1a) (D) Stationary basket-rotating paddle (SBRP). This

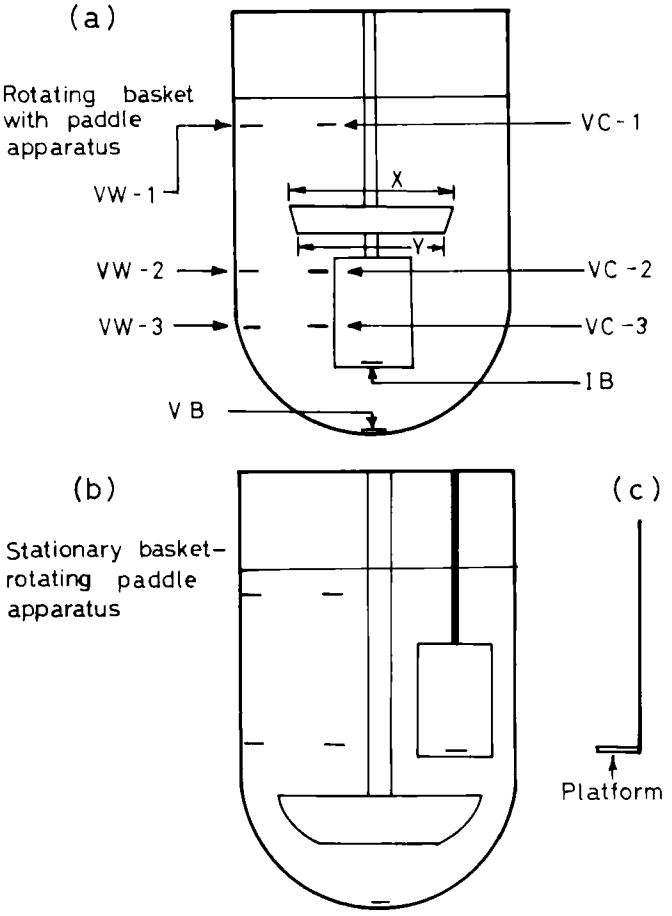

FIGURE 1

Schematic Diagram of the Dissolution Apparatus and Positions at which Agitation Intensity was Determined.

VW=Position near the wall of the vessel; VC=position near the centre of the vessel, 3.8 cm from the vessel wall. Levels 1,2 and 3 = 1, 6.5 and 8,5 cm below the surface of the dissolution medium. x = 6 cm; y = 5.5 cm

assembly was a modification of the RP apparatus. A basket (USP specifications) was positioned 1.5 cm above the paddle, mid-way between the stirring rod and wall of the dissolution vessel with a separate shaft attached to the cover of the vessel.

Dissolution of Capsules

This was studied in 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5°C at 50 rpm. The dissolution fluid samples were withdrawn simultaneously from two levels, at 1 and 7.5 cm below the surface of the dissolution medium and mid-way between the wall of the dissolution vessel and the stirring shaft. Each capsule contained an accurately weighed (100mg) quantity of salicylic acid granules prepared by wet granulation with starch paste as the binder.

Dissolution of Pellets

These experiments were also conducted in pH 6.8 phosphate buffer at 37 ± 0.5°C at three stirring speeds, namely, 50,100 and 150 rpm for RB method and 50, 75 and 100 for other three methods. The agitation intensities produced at various positions in the vessel were investigated by placing the pellets at specific positions with an additional shaft attached to the cover of the vessel. There was a small platform(Fig.1c) at one end of the shaft on which the pellets were

stuck with a water-resistant adhesive tape. The intensity was determined at three levels viz at 1, 6.5 and 8.5 cm below the surface of the dissolution medium near the vessel wall (positions VW-1, VW-2, VW-3 in Fig. 1a) as well as near the centre of the vessel that is, 3.8 cm from the vessel wall (positions VC-1, VC-2, VC-3 in Fig. 1a). The agitation intensity was also determined at the base of the vessel (VB) and in the basket (IB).

Agitation intensity was determined at the above 8 positions with RB and RBWP methods (Fig.1a), at 6 positions with SBRP method (Fig. 1b) and at 5 positions with RP method (all positions as in SBRP except position IB). While determining the agitation intensity at VB and IB positions, one surface of the pellet was covered with the adhesive tape, so that the surface area available for dissolution by such an arrangement was not different from that at the other positions. The non-disintegrating pellets (600 mg) were prepared on a hydraulic press at a constant pressure. In all the above experiments dissolution was carried on till only about 5% of the drug dissolved. Thus the surface area available for dissolution could be assumed to have remained practically constant during an experiment.

RESULTS

Dissolution of Capsule

In order to study the homogeneity of the dissolution medium, the drug concentration from the upper sampling level was subtracted from that at the lower sampling level. The mean (n = 6) difference so obtained at each sampling time for each of the apparatus was compared statistically by one-way ANOVA. These results are recorded in Table 1. By following such a procedure the variation in dissolution process from capsule to capsule did not interfere in the comparative evaluation. The first order dissolution rate constants (K_1) were calculated from the regression slope ($-K_1/2.303$) of the semi-logarithmic plot of per cent drug retained *versus* time (Table 2).

Dissolution of Pellets

The agitation intensities produced in each of the dissolution assemblies were compared by the zero-order dissolution rate constants Ko. When the same pellet is tested, the variation in Ko could be considered to reflect only the variation in diffusion layer thickness as a function of the hydrodynamics of the apparatus. This is so because other parameters like diffusion coefficient, solubility of the drug in the dissolution medium and surface area available for dissolution are maintained constant. Hence the

TABLE 1

Mean Difference* in per cent Drug Concentration From Upper and Lower Sampling Levels for the Different Apparatus at Various Sampling Time.

Apparatus	2 min	4 min	6 min	8 min	10 min
1. Rotating basket	5.8	6.6	7.2	7.3	4.1
2. Rotating paddle					
a. Long coil	1.2	0.8	2.4	1.2	1.5
b. Short coil	1.0	1.0	1.5	0.7	1.4
3. Rotating basket with paddle	1.0	1.0	1.0	1.3	1.3
4. Stationary basket-rotating paddle	1.2	1.4	1.1	2.6	3.4
Computed 'f'	3.0	13.5	8.4	13.2	1.7

f = 2.78 at 95% confidence level. $V_1 = 4$, $V_2 = 24$

* Each value is a mean of 6 observations.

comparison of Ko value obtained from the different apparatus used and from different positions in the same apparatus indirectly reflects the agitation intensities produced in each of the methods or in a single method at different positions in the vessel. The zero order kinetics of the dissolution was confirmed by analysis of variance of the regressions of amount of drug dissolved versus time. The Ko values were calculated from the regression slope (Table 2).

TABLE 2

Dissolution Rate Constants* and Coefficient of Variation for Dissolution of Non-disintegrating Pellets (Position VB) and Capsules of Salicylic Acid.

Apparatus	For Pellet Ko(mg/min)	For Capsule $K_1(min^{-1})$
1. Rotating basket	1.0683 (5.83)	0.0741 (12.25)
2. Rotating paddle	2.863 (3.85)	
a) Long coil	-	0.1036 (45.60)
b) Short coil	-	0.0750) (47.99)
3. Rotating basket with paddle	2.3774 (5.12)	0.1019 (8.30)
4. Stationary basket-rotating paddle	2.4056 (4.43)	0.1304 (11.74)

Values in parentheses indicate coefficient of variance

*Each value is a mean of 6 observations

DISCUSSION

Homogeneity of the Dissolution Medium

These results (Table 1) confirmed the earlier observations made by Withey (1) and Carstensen et al (2,3) for dissolution of non-disintegrating pellets. As seen from the data in Table 1 the mean difference in drug concentration from the two sampling levels was always higher for the RB method. This difference

was significant (p=0.05) at 2,4,6 and 8 min. and during this period about 40% of dissolution took place in RB method. However, with the values at longer duration of time this difference was insignificant. In other three apparatus, however, complete homogeneity in the dissolution medium could be obtained at the same stirring speed (50 rpm).

Reproducibility of the Methods

Though the values for coefficient of variance (CV) of the Zero-order dissolution rate constant (Ko) differed only slightly for all the apparatus indicating comparable variability, a high variation was seen (Table 2) for capsule dissolution rate constant (K_1) in case of RP method only (CV = 45.60 and 47.99). This clearly indicates that the wire helix used to sink the capsule plays a vital role in causing high variability with this method. In absence of the wire helix, the capsule actually broke open within 15 to 45 sec. However, in presence of the helix the disintegration was hindered and it varied from 15-120 sec. The size of the wire helix did not have any significant (p=0.001) effect on the dissolution profiles (K_1) as well as on the variability (Table 2).

Comparison of the Methods

The zero-order dissolution rate constant (Ko) and hence the agitation intensity in the RB method inside

the basket (Position IB) did not differ appreciably from that in the RBWP and SBRP methods at similar positions (IB) and in the RP method at position VB. But such a comparision may not be proper because once the capsule breaks open most of the material is outside the rotating basket. Hence it is desirable to compare the agitation intensities produced in the RB method at various positions outside the basket with those at similar positions in the other methods. Such a comparison reveals that the agitation intensity produced by RB method at all positions (except IB) was significantly ($p=0.001$) less than that in other three methods at similar positions. Values representing such a comparison for one position (VB) is shown in Table 2. The rank-order of the apparatus as per decreasing agitation intensity may be considered as RP > SBRP ≈ RBWP > RB. In fact the agitation intensity produced by RB even at 150 rpm ($Ko \approx 2.1991$) was less than that produced by other apparatus at 50 rpm.

The variation in agitation intensity as a function of position was as follows :

RB Method

Marked difference in the agitation intensities were noticed at different positions in the vessel. The intensity was significantly ($p = 0.001$) low at all the three levels (Fig.2a) near the wall of the

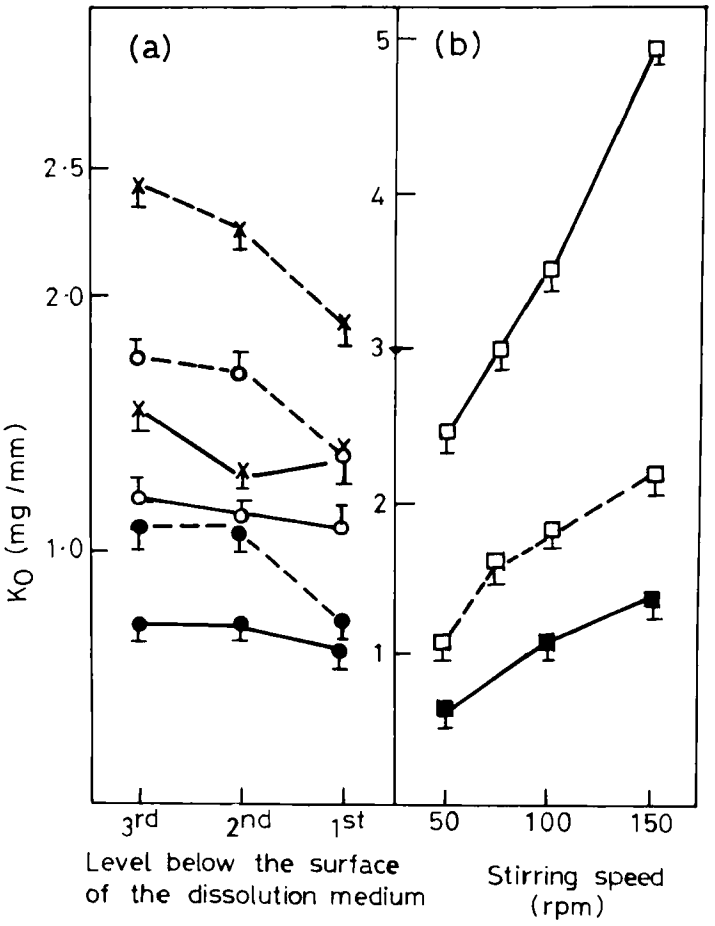

FIGURE 2

Plot of Zero Order Dissolution Rate Constant versus
(a) Level at which Agitation Intensity was Determined
(b) Stirring Speed, for the Rotating Basket Apparatus

(●——●) VW 50 rpm
(●- - -●) VC 50 rpm
(○——○) VW 100 rpm
(○- - -○) VC 100 rpm
(×——×) VW 150 rpm
(×- - -×) VC 150 rpm
(□——□) IB
(□- - -□) VB
(■——■) VW-1

vessel (positions VW), at the central position VC-1 and at the base of the vessel (VB). From the graphs presented in Fig. 2 the following points are noteworthy. (A) The reduction in agitation intensity was to the extent of 15-25% at VW-1, 30-40% at VW-2 and VW-3 at all the stirring speeds as compared to the corresponding VC positions.(B) A vertical gradient in agitation intensity was observed at the centre of the vessel (VC). It dropped by about 32% (Fig. 2a) at 50 rpm and 20% at 100 and 150 rpm at position VC-1 as compared to other positions namely VC-2 and VC-3. (C) Similarly, there was a reduction of about 45-55% at the base of the vessel (VB) as compared to that in the basket (Fig.2b). (D) However, the agitation intensity did not differ significantly ($p = 0.001$) at (a) positions VW-1, VW-2 and VW-3 and at (b) VC-2 and VC-3. This was observed at all the stirring speeds.

RP and RBWP Methods

In these methods agitation intensity was same ($p = 0.001$) at all the positions except at VC-1 for RP method and at VC-1 and VB for RBWP apparatus. The intensity was higher at VC-1 by about 35, 30, 15% and 17, 14, 16% as compared to VW-1 position for the two apparatus at 50, 75 and 100 rpm respectively (Fig.3). Similarly, there was an increase in agitation intensity of about 19-28% at the base of the vessel (VB) in RBWP method as compared to that at position IB.

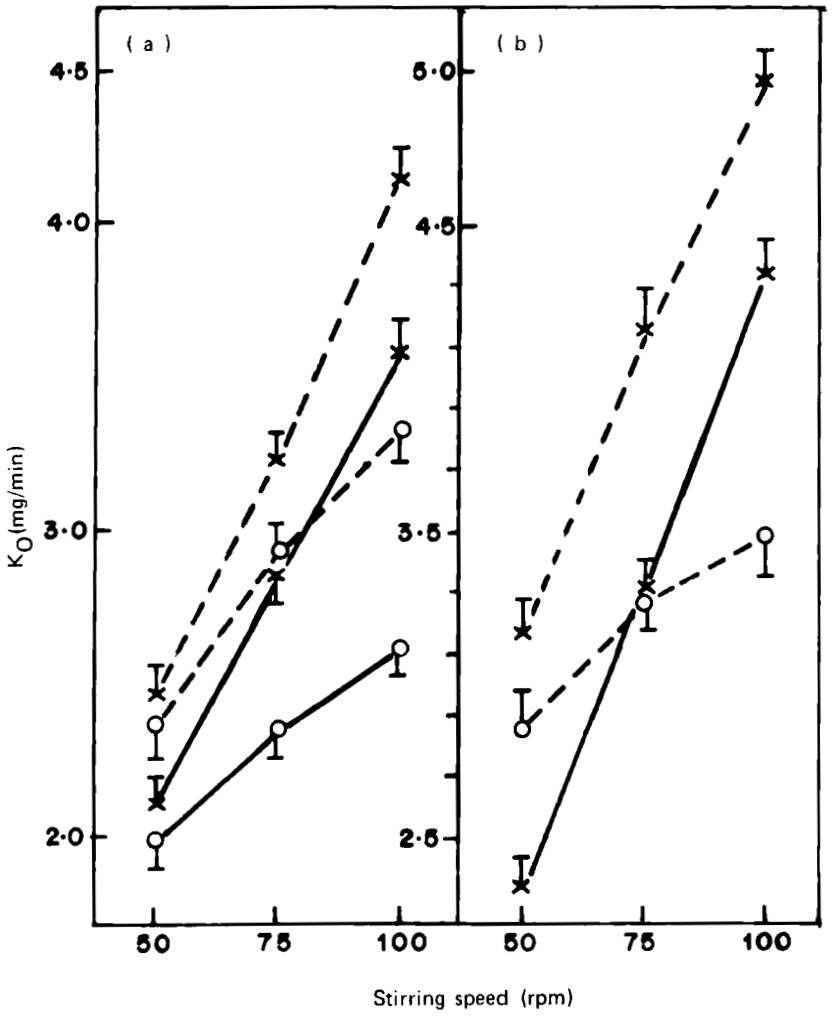

FIGURE 3

Plot of Zero Order Dissolution Rate Constant versus Stirring Speed at Different Positions.
(a) Rotating basket with paddle apparatus
(b) Rotating paddle apparatus

(X——X) VW-1
(X- - -X) VC-1
(O——O) IB
(O- - -O) VB

SBRP Method

It was interesting to note that the agitation intensity produced in this method did not differ significantly ($p=0.001$) at all the positions in the vessel and at all the stirring speeds.

CONCLUSIONS

Considering the various aspects studied it may be concluded that the stationary basket-rotating paddle method appears to be superior to other methods in view of the following points :

This method can be used to evaluate both tablets and capsules under identical experimental conditions which is not possible with the rotating paddle method.

It produces sufficient agitation intensity to give homogeneity in the dissolution medium even at low rpm of 50, unlike in the rotating basket method where homogeneity is a problem. Studies at as low a rpm as possible are desirable to detect small formulation differences in products (13,14). Hence the chances of small formulation differences being masked are reduced considerably by using this method.

As the agitation intensity is not significantly different throughout the vessel, particles or granules which come out of the basket and remain at different levels in the vessel will not be subjected to differe-

ntial agitation intensity as in the case of other three methods.

The sieving action and clogging of the mesh, which causes serious problems in the rotating basket (7,8,15) is brought down considerably with the use of the stationary basket.

All dosage units can easily be introduced and placed accurately.

Thus stationary basket-rotating paddle method which offers several advantages over the rotating basket and rotating paddle method which have some limitations,deserves serious consideration for adopting it as an official method for evaluating dissolution rates of various solid dosage forms.

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