DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(7), 1109-1119 (1990)



# EVALUATION OF DISSOLUTION CHARACTERISTICS OF AN ENCAPSULATED WATER SOLUBLE TABLET GRANULATION

A. V. Katdare,* K. O. Keller, J. J. Christoff
and J. F. Bavitz
Merck Sharp & Dohme Research Laboratories
West Point, PA 19486

## INTRODUCTION

Disintegrants are among the essential ingredients in conventiona tablet formulation. They promote water penetration and disruption of the tablet in dissolution media. Although different naturally occuring starches were commonly used in the past, newer disintegrants have won wide usage in recently (1-2). Numerous reports have been published describing the effect of different additives on drug release from capsules (3-6). Although the importance of the rate of deaggregation of the powder mass before dissolution has been pointed out (7) only a few reports dealt with the role of disintegranting agents in capsule formulation with some of the earlier studies reporting mixed results (8-10). A distinctive feature of the studies described is that it involves manually filled capsules with provides little compression of the contents. Such capsules are far more porous than machine filled

*To whom the correspondence be directed

counterparts, thus, there is negligible resistance to the swelling characteristics of disintegrants which promote deaggregation. This leaves wetting and moisture penetration as the determinants for deaggregation.

Capsule production has entered a new era in terms of modern automated high speed capsulating machines and now apprach the design of tablet presses. In the dosator-disk type encapsulating units the capsule contents formed into a plug are progressively compressed through a series of tamps. Recently, the effect of disintegrants on drug dissolution from capsules filled on such equipment was studied (11-13). The researchers reported that, in general, modified celluloses were most effective in enhancing drug dissolution followed in order by the modified starches, corn starch, and cross linked PVP. Low lubricant levels and soluble drug/excipients combinations also had a beneficial effect on drug dissolution. Compression force effects were evident in most cases; generally retarding the dissolution rate for insoluble excipient matrices and improving the rates for soluble counterparts. Interestingly inclusion of a superdisintegrant nullified the adverse effect attributed to compression caused by tamping.

Very recently, the mechanism of action of disintegrants in encapsulated mixtures was investigated using an instrumented machine (14-15). For this comparative evaluation, liquid uptake and swelling efficiencies were taken into consideration. These studies showed that the mechanism of action of disintegrants in these systems is rapid liquid absorption and swelling of disintegrant

particles into void spaces causing the compact/plug to disintegrate rapidly. The more critical evaluation also suggests that the wicking rate may be the limiting step in swelling efficiency and thus relates to the efficacy of the disintegrant.

## BACKGROUND

Recently supplies were requested of an antihypertensive drug for a double blind study in a capsule presentation. The drug is normally marketed as a compressed tablet. Its matrix consists of a water soluble excipient (lactose), a modified starch as a disintegrant, a stability enhancer and a lubricant. Precedent indicated that this tablet composition could be encapsulated and that the finished product would have physical properties, e.g. a dissolution rate not unlike a tablet.

Batches prepared by filling the tablet granulation in a #3 hard gelatin capsule with a dosator type capsulating machine, however, were found substandard with respect to dissolution rates. Preliminary investigations into such variables as mesh size distribution of the tablet granulation proved inconclusive and prompted the initiation of a more in-depth study described herein.

## OBJECTIVE

Thus the objective of this investigation was to study those physical variables believed to influence the physicochemical characteristics of this low dose water soluble drug in a lactose based matrix when encapsulated into hard gelatin capsule shells. These variables included:

a. Capsule shell composition

b. Capsule size

c. Residual granulation moisture content

d. Pressure of compaction (for formation of plugs)

e. Extragranular addition of a disintegrant

Evaluations were carried out by studying disintegration times and dissolution rates on finished capsules.

## EXPERIMENTAL

A common granulation of the low dose, water soluble drug in a lactose based formulation was used throughout the study. In one experiment, croscarmellose sodium (AcDisol) was added just before lubrication to study the effect of extragranular superdisintegrant on capsule dissolution characteristics.

In preparing the compacts of the granulation whenever known compression pressures of comparable magnitude that exist in conventional tablet presses were required, a Carver Press was utilized. A volume fill encapsulation machine was used to hand fill either the granulation or the compacts into the capsule shells. The resulting capsules were evaluated for weight uniformity, disintegration characteristics (with disks) and dissolution rates (USP II method) the latter with 10, 20, 30 minute sampling points. The independent variables studied included:

1) Capsule shell composition

   1.1 #3 size white opaque capsule shells from Capsugel=control

   1.2 #3 size transparent uncolored capsule shells

   1.3 #3 size opaque capsule shells other than those supplied by Capsugel

2) Capsule size

   2.1 size #3 = control

2.2 size #2

2.3 size #4

3) Granulation moisture content

3.1 'As-is' = control

3.2 Reduced (by storing the granulation at low humidity)

3.3 Elevated (by storing the granulation at high humidity)

4) Compaction pressure to form plug

4.1 1.5 ton

4.2 2.0 ton

4.3 2.5 ton

4.4 3.0 ton

4.5 3.5 ton

5) Disintegrant content

5.1 with intragranular disintegrant = control

5.2 with extragranular addition (5 mg of croscarmellose sodium)

## RESULTS AND DISCUSSION

The results of the physicochemical testing are in Table 1. Capsule weights were found acceptable for all lots prepared, never varying by more or less than 6% from the mean weight. Disintegrating times, likewise, while within acceptable limits were not indicative of differences among the lots. Dissolution rates at 10, 20 and 30 minutes expressed as % drug dissolved as expected proved most revealing. At the top of Table 1 listed are the dissolution rate results of the tablet made from the granulation that is used throughout this study. The tablets dissolved uniformly

TABLE - 1 PHYSICO CHEMICAL PROPERTIES OF CAPSULES

| Description of the Capsule Type | Mean Wt mg (range) N=20 | Range of Disintegration Times Min' Sec" N=6 | % Dissolved (Label Claim) & Range (N=6) 10 min | 20 min | 30 min |
|---|---|---|---|---|---|
| Control Tablet | 231 (230-233) | 1'10" - 1'56" | 98 (95-100) | 98 (97-100) | 98 (96-100) |
| Control (#3 size capsule) | 281 (266-291) | 1'20" - 2'0" | 40 (32-56) | 62 (48-89) | 76 (63-106) |
| #3 Coloress Transparent | 284 (269-298) | 1'40" - 4'20" | 10 (0-32) | 25 (11-52) | 34 (19-69) |
| #3 Opaque (Diff. Supplier) | 284 (269-296) | 1'30" - 2'20" | 31 (18-40) | 56 (38-74) | 69 (50-83) |
| #2 Size | 291 (274-301) | 1'30" - 1'45" | 47 (25-70) | 68 (44-85) | 75 (54-90) |
| #4 Size | 266 (261-272) | 1'00" - 1'45" | 68 (51-86) | 93 (90-94) | 95 (92-97) |
| Reduced Moisture | 275 (270-291) | 1'00" - 1'55" | 43 (35-58) | 69 (63-83) | 79 (72-92) |
| Elevated Moisture | 269 (258-281) | 1'50" - 2'15" | 17 (8-38) | 34 (21-47) | 46 (31-57) |
| 1.5 Ton Pressure | 276 (273-283) | 1'00" - 1'30" | 44 (23-65) | 90 (83-95) | 95 (89-100) |
| 2.0 Ton Pressure | 279 (274-283) | 1'00" - 1'55" | 65 (47-95) | 100 (97-105) | 100 (97-103) |
| 2.5 Ton Pressure | 277 (273-281) | 1'40" - 2'15" | 74 (49-88) | 94 (91-97) | 95 (91-97) |
| 3.0 Ton Pressure | 275 (272-279) | 1'30" - 2'10" | 63 (38-77) | 98 (94-101) | 96 (94-98) |
| 3.5 Ton Pressure | 277 (272-282) | 1'30" - 2'00" | 51 (25-75) | 106 (103-109) | 103 (97-106 |
| Extragranular Croscarmellose | 271 (265-275) | 1'05" - 2'30" | 90 (86-94) | 92 (86-95) | 92 (88-96) |

fast and with very low variability. The control formulation in white opaque #3 size capsule shells supplied by Capsugel showed slow dissolution rates with wide variability at the 30 minutes sampling point. A colorless, transparent #3 size capsule shell included to study the effect of capsule shell composition especially with respect to capsule shell fillers had dissolution rates somewhat slower with less uniformity than the control. This observation suggested that the capsule shell composition could have some minor influence on the dissolution characteristics of the drug. Opaque size #3 capsule shells, from a supplier other than Capsugel, were essentially the same as control.

In evaluating capsule size, it was observed that #3 (i.e. control) and #2 capsules allow a relatively loose powder fill. Not unexpectedly, both of these capsule lots have similar dissolution rates as control. Size #4 capsules, produce a more densely compacted mass and dissolved at a faster rate with lower variability and this was consistent with early results. This observation further implied that the porosity of the powder plug may be inversely related to dissolution rate.

To study the residual moisture content of the granulation, samples were exposed to high humidity conditions at room temperature for 48 hours in a desiccator containing monobasic ammonium phosphate or to low humidity condition in a desiccator containing silica gel. Moisture contents were determined by loss on drying measurements at the end of 48 hours with the following results. The control granulation had 1.1% moisture, that exposed to low humidity had 0.9% moisture and that exposed to high humidity had 5.5% moisture.

The dissolution rates of capsules containing granulation exposed to low humidity are similar to the control. Since their residual moisture levels were similar, these data are not unexpected. The capsules containing the granulation exposed to high humidity dissolved slower. It is postulated that the disintegrant in the granulation absorbs moisture upon exposed to high humidity, swells and expands the overall mass of the powder. Since the compact remains confined by the capsule shell, the disintegration characteristics of the dosage form are lost and this results in a slower rates of dissolution.

Application of as little as 1.5 tons pressure on the plug improved the dissolution rates significantly where 95% of the labelled claim dissolved in 30 minutes. Changing pressures in increments of 0.5 tons produced some further improvement in dissolution rates, and improved the uniformity at the 20 and 30 minute sampling points. The somewhat higher variability observed at the 10 minute point is consistant with the variability in wetting and dissolution properties of capsule shells themselves. It is apparent that once the compacted contents (plugs) are free from the capsule shell, disintegration and dissolution occurs uniformly and rapidly just like in case of corresponding tablets.

The improvement in dissolution rates of capsules containing compacted plugs (using pressure) can be related to elastic deformation, granule fracture and reduction in compact porosity. If the matrix is not sufficiently compacted as in the control or the size #2 capsules the disintegrant swells upon exposure to moisture

and has sufficient void space for expansion. As a result, it is unable to cause any disruption of the compacted mass. Disintegration and dissolution rates thus result solely due to slow erosion. The disintegration and dissolution rates observed with tablets compressed from the same granulation further substantiate this hypothesis. These observations suggest that an acceptable tablet granulation may not always be suitable for encapsulating particularly when it is impossible to apply pressures near those that are used in tabletting operation.

The capsules made from granulation containing croscarmellose sodium (and without application of measurable pressure) disintegrated rapidly and dissolved uniformily at a rapid rate with most of the drug dissolved within 10-15 minutes. Since studies have shown that croscarmellose exerts its disintegrant action through enormous swelling efficiency and improved wicking. These attributes seem to nullify the variability of capsule shell dissolution.

## CONCLUSIONS

While the capsule shell composition and moisture are shown to affect dissolution rates of an encapsulated tablet granulation of a water soluble drug in a lactose based matrix, compaction pressure is shown to have a more pronounced effect on dissolution characteristics. An extragranular addition of a superdisintegrant is also shown to improve the dissolution characteristics most significantly.

## ACKNOWLEDGEMENT

The authors would like to acknowledge the analytical support received from Quality Control Laboratories of MSD and MSDRL. Also,

most grateful thanks to Mr. Karl Schafer for supplying the tablet granulation needed for the study.

## REFERENCES

1. Shangraw, R.F., Mitrevej, A. and Shah, M., Pharm. Tech., 4(10), 419-57, 1980.
2. Shangraw, R.F., Wallace, J.W. and Bowers, F.M., Pharm. Tech., 5(10), 44-60, 1981.
3. Whithey, R.J. and Mainville, C.A., J. Pharm. Sci., 59, 1120-1126, 1969.
4. Newton, J.M., Rowley, G. and Tornblom, J.F.V., J. Pharm. Pharmacol., 23, 452-453, 1971.
5. Newton, J.M. and Razzo, F.N., J. Pharm. Pharmacol., 29, 294-297, 1977.
6. Mehta, A.M. and Augsburger, L.L., Int. J. Pharm., 7, 327-334, 1981.
7. Aguiar, A.J., Wheeler, L.M., Fusari, S. and Zelmer, J.E., J. Pharm. Sci., 57, 1844-1850, 1968.
8. Shah, P.T. and Moore, W.F., J. Pharm. Sci., 59, 1034-1036, 1970.
9. Goodhart, F.W., McCoy, R.H. and Ninger, F.C., J. Pharm. Sci., 62, 304-310, 1973.
10. Samyn, J.C. and Jung, W.Y., J. Pharm. Sci., 59, 169-175, 1970.
11. Botzolakis, J.E., Small, L.E. and Augsburger, L.L., Int. J. Pharm., 12, 341-349, 1982.
12. Botzolakis, J.E. and Augsburger, L.L., J. Pharm. Pharmacol., 36, 77-84, 1984.
13. Shah, B., Augsburger, L.L. and Marshall, K., J. Pharm. Sci., 76(8), 639-645, 1987.

14. Botzolakis, J.F. and Augsburger, L.L., Drug Dev. Ind. Pharm., 14(1), 29-41, 1988.

15. Botzolakis, J.E. and Augsburger, L.L., Drug Dev. Ind. Pharm., 14(9), 1235-1248, 1988.