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SELECTION OF OPTIMUM DISSOLUTION TEST METHODS IN DOSAGE FORM DESIGN

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ABSTRACT

The rate limiting factors involved in release of a drug from a tablet are generally accepted to be the disintegration of the tablet followed by the subsequent dissolution of the drug from the dispersed granules.

The development of new potencies of an existing tabletted product by weight multiplication was found to result in non-conformance to established specifications for the product not formulation related.

In addition to a study of the rate limiting factors mentioned above compendial dissolution tests were also compared. Apparatus II was shown to produce more rapid and consistent results than Apparatus I in this investigation and this test is recommended as the one of choice where large volume compacts are involved.

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INTRODUCTION

Part 320.22(d) (2) Title 21 of the Code of Federal Regulations sets forth several criteria for waiver of evidence of in-vivo bioavailability as these relate to the registration of certain drug products.

The object of these studies was to formulate higher strengths of an existing, marketed, dosage form keeping the active and inactive ingredients proportionally similar so as to meet the conditions outlined in the above regulations. This would permit petitioning the Food and Drug Administration (FDA) to waive the requirement for submission of in-vivo bioavailability of the new higher strength products.

The existing product is marketed as a tablet in potencies of 150 mg and 200 mg both in unique shape. Size, quality control and marketing considerations; however, dictated a more conventional capsule shape for the higher strengths (300 mg and 400 mg).

While the marketed products consistently met a dissolution specification of 85% drug in solution in 30 minutes using United States Pharmacopoeia apparatus I operated at 100 revolutions per minute early tests results indicated that the higher potencies would not consistently do so.

Disintegration times, for all strengths were rapid, usually less than one minute, with residence times in the dissolution basket of the same time order. It was observed, however, that during the dissolution test, agitational effects of the basket were insufficient to keep all of the solid granules making up the

tablet, particularly those in the higher potencies, in motion. This allowed most of the wetted granules to settle to the bottom of the dissolution flasks where they but slowly dispersed with time. As a consequence, dissolution rates were slower than anticipated and not consistent with accepted standards for the product.

It is recognized that two rate limiting processes are involved in the release of a drug from a tablet: (1) disintegration of the tablet and (2) dissolution of the drug from the solid granules.

Attempts at determining the time course of disintegration have been reported (1,2). Dissolution processes have been extensively studied (3,4) and operational characteristics of dissolution testing systems compared (5,6,7). Other factors influencing dissolution behavior, such as effects of compression force (8,9) particle size (10) and lubricants (9) influencing dissolution rate have also been examined.

While many of the above factors were studied in this investigation much of the effort was directed toward increasing residence time in the dissolution basket and improving the dispersion of the granules layering at the bottom of the dissolution flask.

EXPERIMENTAL

The compositions of the formulations studies were:

	Ingredient	I (in % w/w)	II (in % w/w)	III (in % w/w)
1.	Sulindac USP	59.5	59.5	59.5
2.	Microcrystalline Cellulose NF	36.6	36.6	36.6

3.	Corn Starch, NF	-	2.9	2.4
4.	Pregelatinized Starch, NF	2.9	-	-
5.	Magnesium Stearate, NF	0.7	0.7	1.2
6.	Purified Water, USP	q.s.	q.s.	q.s.

The mixtures for subsequent tabletting were made as follows:

Formulation I: The active drug, microcrystalling cellulose and pregelatinized starch were mixed[1]. Purified water was added then mixed for 10 minutes. The granulation formed was dried by vacuum in the mixer, comminuted[2] to a desired mesh distribution, then lubricated[3] with magnesium stearate.

Formulations II and III: The active drug and microcrystalline cellulose were mixed[4] and sieved[5]. The mixture was then granulated with a starch suspension. The granulation was wet-sized[2] then dried overnigh[6] at 50°C. After drying the granulation was again milled[2] to an appropriate mesh distribution then lubricated[7] with magnesium stearate.

All blends were compressed on a single station press.[8]

RESULTS AND DISCUSSION

Formulation I when prepared as described above yields a granulation where typically 84% is below 120 mesh. When compressed into tablets dissolution values are as summarized in Table I.

During the dissolution test it was noted that all tablets disintegrated rapidly with the fine granules easily filtering

Table I

Dissoution Rates of Tablets Compressed From Granulation

84% < 120 Mesh

Measurement	Potency (mg) 150	200	300	400
Dissolution Rate[a] (% of label claim at 30 minutes)				
$\bar{X}$	94	96	84	77
(Range)	(90-99)	(91-102)	(80-88)	(63-84)

[a]USP Apparatus I, 100 R.P.M.

through the basket. Agitational effects sufficient to keep most granules of the lower potencies in motion, were inadequate in preventing a significant portion of the granulation generated by the higher potencies from settling to the bottom of the flask where they remained undisturbed during most of the test.

Under the premise that larger granules would remain in the dissolution basket longer and thus remain in motion and in more contact with the liquid media, Formulation I was prepared to yield a granulation where only 4% of the granules were less than 120 mesh.

Dissolution rates from tablets compressed from the coarser granulation were:

Table II

Dissolution Rates of Tablets from Granulation Containing Granules 96% > 120 Mesh

Measurement	Potency (mg) 300	400
Dissolution Rate[a] (% of label claim at 30 minutes)		
$\bar{X}$	66	84
(Range)	(61-70)	(81-88)

[a]USP Apparatus 1, 100 RPM

While the coarser granules produced an improvement in the dissolution rate of the 400 mg potency this was not true with the 300 mg potency. Furthermore neither reached a mean of 85% dissolved in 30 minutes (Standard for this Product).

In another attempt at increasing residence times in the dissolution basket Formulation 1 was compressed into extremely hard tablets. (Note: Tablet crushing strengths exceeded the capacity of conventional testers and a motorized stress/strain device was used to make the measurement.)

At this point in the investigation USP Apparatus II was also employed in the evaluation of dissolution rates. Data generated with this apparatus are in Table III.

These results reveal that longer residence times in the dissolution basket obtained by increasing tablet hardness improved dissolution rates. More significantly, however, a further

Table III

Dissolution Rates and Crushing Strength Values of Tablets Compressed to Increase Residence Times in Dissolution Basket

Measurement	Potency (mg) 300	400
Dissolution Rate (% of label claim at 30 min.)		
$\bar{X}$ (Range)	82 (76-86)[a]	90 (84- 93)[a]
	95 (93-97)[b]	96 (92-102)[b]
Tablet Crushing Strength (Kp)	15.7	15.5

[a]USP Apparatus 1 100 RPM 30 minutes

[b]USP Apparatus 2 50 RPM 45 minutes

increase in dissolution rates occurs when USP Apparatus II is used.

While these data show that dissolution rates were likely more dependent on conditions in the test procedure than the formulation itself, formulation and process variables were studied in further trials.

Formulations II and III, for example, gave the following results.

The data again indicate that USP Apparatus II generally produce more rapid dissolution rates than Apparatus I. They also indicate that Formulation III dissolves somewhat more rapidly than Formulation II and that the dissolution rates of neither formulation are significantly influenced by tablet hardness.

Table IV

Dissolution Rates of Tablets Prepared

to Different Crushing Strengths

Measurement	Potency (mg) 300	
Tablet Crushing Strength (Kp)	12	18
Dissolution Rate		
9% of Label Claim at 30 min.)		
$\bar{X}$ (Range)	97(71- 81)[a,c]	78(74- 85)[a,c]
	93(98- 95)[a,d]	96(92-100)[a,d]
	89(81-109)[b,c]	89(85- 98)[b,c]
	--------	105(102-112)[b,d]

Measurement	Potency (mg) 400	
Tablet Crushing Strength (Kp)	12	18
Dissolution Rate		
9% of Label Claim at 30 min.)		
$\bar{X}$ (Range)	76(73- 80)[a,c]	80(78- 87)[a,c]
	86(80- 90)[a,d]	101(97-107)[a,d]
	92(83-102)[b,c]	89(86-101)[b,c]
	--------	104(102-106)[b,d]

[a]USP Apparatus I 100 rpm 30 minutes
[b]USP Apparatus II 50 rpm 45 minutes
[c]Formulation II
[d]Formulation III

CONCLUSION

Of the three formulations studied only Formulation III gave acceptable dissolution rates using the USP Apparatus I. The corresponding rates, by USP Apparatus II were acceptable. Modifications in procedure or formulation did not significantly alter the dissolution rates, using USP Apparatus I for Formulations I and II, therefore, the "Basket Method" may not be appropriate for rapidly disintegrating tablets since their residence time in the basket is short. Furthermore, the disintegrated tablets form a solid mass at the bottom of the dissolution flask, which is not easily dispersed by the spinning basket. In instances such as these USP Apparatus II - "The Paddle Method" should be considered as the one of choice.

FOOTNOTES

[1]Nauta Mixer - Day Mixing Co., Wilmington, DE 19810

[2]Model D6 - Fitzpatrick Co., Elmhurst, IL 60126

[3]Double Cone Blender, General Machine Co., Inc., Newark, NJ

[4]Readco Mixer, Model 20, Read Standard Corp., York, PA

[5]Centri Sifter Model KOB, Kason Corp., Newark, NJ 07108

[6]Tray Dryer, Model 38A, F. J. Stokes, Warminster, PA

[7]Twin Shell Blender, Patterson Kelley Co., Inc., E. Stroudsburg, PA

[8]Manesty Model F3, Thomas Engineering Co., Hoffman Estates, IL

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