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FORMULATION AND PROCESSING FACTORS AFFECTING THE DISINTEGRATION OF HARD-SHELL GELATIN CAPSULES

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ABSTRACT

The effectiveness of disintegrants (Starch, Sodium Starch Glycolate, Microcrystalline Cellulose, cross-linked cellulose, cross-linked Polyvinylpyrollidone) and the influence of excipients such as the lubricant (Magnesium Stearate), glidant (Talc), insoluble and soluble compressible fillers (Calcium Phosphate, Dextrose), as well as processing factors such as the blending sequence of additives, and effects of light compaction (powder-slugs) on the disintegration of hard shell gelatin capsules were examined. It was found generally that wicking and swelling - type disintegrants were most effective at de-aggregating the encapsulated powder mass especially when Magnesium Stearate was present. The incorporation of Talc to the pre-mix (filler, disintegrant, lubricant) appeared to reduce disintegration times due to abrasion of the hydrophobic lubricant film. Tamped powder fills (slugs) took twice as long to disintegrate as loosely filled capsules, but

differences became negligible when disintegrants were included.

INTRODUCTION

Excipients which ensure the disintegration of solid dosage forms such as tablets have been well documented,[1-3] and generally categorized as swelling or wicking materials.

The disintegration behaviour of capsules has been largely neglected, as it is assumed that after ingestion, dispersion of the fill material would naturally follow. The fill formulation is usually designed to facilitate the encapsulation process by using excipients such as flowable fillers, glidants and lubricants. Hydrophobic loose, and tamped powder fills containing Talc and Magnesium Stearate, are likely to present problems with dispersion of the capsule's contents. Usually a "wet" powder plug is formed, and while this remains intact, drug release may be hampered. The inclusion of a disintegrant may thus be necessary to deaggregate the powder mass.

The disintegration of the capsule and the powder mass is dependant on a number of factors[4,5] besides the disintegrant, e.g. the solubility of the major component (drug or diluent), the presence of antiadherents, the medium in which it is disintegrated, capsule shell excipients, and processing factors such as the blending sequence and filling method.

MATERIALS AND METHODS

The general formulation used:

Disintegrant	5% m/m
Talc (glidant)	1% m/m
Magnesium stearate (lubricant)	0.5% m/m
Diluent to	100% (20 g)

These were blended as follows:

The disintegrant and diluent were blended in a V-blender for 7 minutes at 25 r.p.m. Magnesium stearate and Talc were added in combination to the above (unless otherwise stated) and blended for 3 minutes with the disintegrant-diluent mixture.

Preparation of capsules: Two methods of filling were used:

1) Loose fill - the powder mixture was filled manually into the clear capsules (Size 0) (Elanco). The capsule body was slightly over-filled and then levelled off flush with the rim using a spatula. The capsules were closed, dusted and weighed individually and collectively.

2. Compact fill - the powder fill was compressed into a loose slug using a Manesty F3 single punch tabletting machine, fitted with concave 8.5 mm diameter punches. This was operated manually at a low compression force. The powder mixture used in this case was blended traditionally, and consisted of Emcompress^{R} as the diluent. The slugs formed fitted exactly into size 00 capsule shells.

Diluents:

Dibasic calcium phosphate dihydrate: (Emcompress^{R}, Edward Mendell Co., Inc. Carmel N.Y.) was used in the size range <0.315 mm as an insoluble diluent.

A mixture composed of maltose-dextrose particles (Emdex^{R}, Edward Mendell Co. Inc., Carmel, N.Y.) was used in the size range 0.315 - 0.8 mm was used as a soluble diluent.

Disintegrants:

Croscarmellose Type A (AcDiSol^{R}, F.M.C Corp.)

Sodium Starch Glycolate (Primojel^{R}, F.M.C Corp.)

Maize Starch (Unilab)

Microcrystalline Cellulose (Avicel^{R}, F.M.C Corp.)

Cross-linked Polyvinylpyrrolidone (Polyplasdone^{R} G.A.F. Corp.).

Disintegration Test: Capsule disintegration times were measured in 900 ml of distilled water at 37.5°C. The Disintegration Test was performed using an Erweka ZT6 Disintegration Tester, with a six-tube reciprocating basket-rack assembly (30 cycles/minute). The disintegration time was recorded after all the contents of the capsule had passed through the screen.

The capsules were restrained using an open mesh nylon net (mesh opening of 4 mm x 4 mm), secured over the top of the basket-rack assembly with an elastic band.

RESULTS AND DISCUSSION

The capsules disintegrated by first splitting open, almost uniformly at one of the ends, often with the release of an air bubble. Goodhart et al[6] made similar observations, but Jones et al[7] observed that the capsule ruptured "at the weakest point", namely the radius or seal. The liberation of air on rupturing could be of importance. Capsules generally contain a large volume of air, and when raised to 37°C this air is likely to expand. This expansion may aid the rupturing of the capsule and perhaps, particularly in loose-filled capsules, the dispersion of the powder. As all disintegration is delayed until the capsule has ruptured, the importance of this step should not be overlooked.

From Table 1 it may be seen that in the absence of a disintegrant, (control) Emdex^{R} capsules took about four minutes to disintegrate, while Emcompress^{R} capsules, on average, took about eighteen minutes longer. This result therefore complies with the general observations that, if

Table 1 - Disintegration times of Emdex® and Emcompress® preparations containing Magnesium Stearate 0.5%m/m, and disintegrant 5%m/m.

	CONTROL®	STARCH®	PRIMOJEL®	AVICEL®	AcDiSoL®
EMDEX®					
Ave. weight	0,54g	0,55g	0,56g	0,54g	0,55g
Ave. time (mins:sec)	4:01	2:37	4:17	2:19	2:52
Range (mins:sec)	2:50-5:25	2:28-2:46	3:16-6:28	2:08-2:25	2:36-3:10
EMCOMPRESS®					
Ave. weight	0,64g	0,67g	0,67g	0,64g	0,65g
Ave.Time (mins:sec)	22:07	4:20	4:24	8:46	2:24
Range (mins:sec)	17:43-28:50	3:00-6:34	3:43-6:00	6:18-15:36	1:54-4:05

the capsule contents are soluble, disintegration rates are generally faster and a disintegrant is unnecessary.

With AcDiSol® and Primojel® the differences in disintegration times for the soluble and insoluble fills were negligible, whereas with Starch and Avicel® the Emcompress® took respectively double and treble (approximately) the disintegration time of the Emdex® fill. Primojel® and AcDiSol® both have a powerful swelling action when wetted, in comparison to Starch and Avicel®, and this may explain the different effects. Although in these loose-filled capsules there is no compaction to hinder disintegration, the hydrophobic magnesium stearate film is capable of slowing the wetting and subsequent disintegration of the fill material[8].

From Table 2 it may be seen that magnesium stearate has a severe retarding action on the disintegration of

Table 2 - The disintegration times of Emcompress^{R}/ Disintegrant blends containing 0,5%m/m and 0%m/m Magnesium Stearate.

	CONTROL^{R}	STARCH^{R}	PRIMOJEL^{R}	AVICEL^{R}	AcDiSoL^{R}	POLYPLASDONE^{R}
0,5%m/m magnesium stearate Ave. Mass	0,64g	0,67g	0,67g	0,64g	0,65g	0,60g
Ave. time (mins:sec)	22:07	4:20	4:24	8:46	2:24	4:31
Range (mins:sec)	17:43-28:50	3:00-6:34	3:43:6:00	6:18-15:36	1:54-4:05	3:43-4:45
0%m/m magnesium stearate Ave. Mass	0,56g	0,67g	0,66g	0,61g	0,64g	0,61g
Ave. time (mins:sec)	1:19	2:18	2:08	1:52	2:01	1:53
Range (mins:sec)	1:04-1:33	1:47-2:45	1:40-2:47	1:39-2:20	1:41-2:18	1:41-2:15

Emcompress^{R} alone. This action is reduced by all disintegrants, although some, as seen previously, are more effective than others.

Inclusion of a glidant: The effect of including an abrasive hydrophobic excipient, such as talc, on the disintegration times may be noted from Table 3.

In all cases but Starch and AcDiSol^{R} the disintegration time was decreased. It is noteworthy that in the absence of a disintegrant (control), the presence of talc reduces the disintegration time substantially. Mechtershiemer et al[5] suggested that this may be due to talc abrading the hydrophobic magnesium stearate film.

The mixing sequence

The control powder-mixture was used to investigate the effects of talc and the mixing sequence on magnesium stearate's influence on disintegration. The powder mixtures were prepared as follows:

Table 3 - The disintegration times for the capsules containing Emcompress®, Talc 1%m/m , Magnesium Stearate and the various Disintegrants:

	CONTROL®	STARCH®	PRIMOJEL®	AVICEL®	AcDiSoL®	POLYPLASDONE®
0% TALC						
Ave mass(g)	0,64	0,67	0,67	0,64	0,65	0,60
Ave time (mins:sec)	22:07	4:20	4:24	8:46	2:24	4:31
Range (mins:sec)	17:43-28:50	3:00-6:34	3:34-6:00	6:18-15:36	1:54-4:05	3:43-4:45
1% TALC						
Ave Mass(g)	0,65	0,66	0,66	0,63	0,64	0,60
Ave time (mins:sec)	4:05	4:32	2:31	5:31	3:41	2:49
Range (mins:sec)	3:40-4:43	2:42-6:54	2:10-3:09	3:50-7:45	2:48-4:20	2:02-4:30

1. Emcompress® Blended together for 3 minutes.
   Talc 1% m/m
   Magnesium stearate 0,5%m/m Blended with the above for 3 minutes.
2. Emcompress® Blended together for 3 minutes.
   Magnesium stearate 0,5%
   Talc 1% m/m Blended with the above for 3 minutes.

These two blends were then compared with the control blend, which was prepared by blending all three excipients together for three minutes. From Table 4 it may be noted that if talc is included subsequently to the magnesium stearate, the disintegration time is decreased (3:39) due to talc abrading the hydrophobic magnesium stearate film. When magnesium stearate was added sub-sequently to talc, the disintegration time was relatively long, (5:47)

Table 4 - The disintegration tests performed on Emcompress^{R}, where the excipients, Talc (1% m/m) and Magnesium Stearate (0,5% m/m) have been incorporated using different blending sequences:

	SIMULTANEOUS ADDITION OF TALC AND MAGNESIUM STEARATE	TALC ADDED SUBSEQUENT TO MAGNESIUM STEARATE	MAGNESIUM STEARATE ADDED SUBSEQUENT TO TALC.
Average time (mins:sec)	4:05	3:39	5:47
Range (mins:sec)	3:40-4:43	3:24-4:07	4:17-9:58
Average Mass	0,65g	0,66g	0,68g

implying that the Emcompress^{R} particle, and any talc adhering to it, was coated with the magnesium stearate. The disintegration time however, was still shorter than that of Emcompress^{R} and magnesium stearate alone in the absence of talc (22 minutes).

This aspect of the investigation was extended to include two disintegrants, namely AcDiSol^{R}, and Avicel^{R} (5% m/m). The Emcompress^{R} was initially blended with the relevant disintegrant for seven minutes, then either magnesium stearate (0,5% m/m) or talc (1,0% m/m) was included and blended for three minutes, and finally the outstanding excipient was added with a further three minute blending period. The results are recorded in Table 5.

Once the disintegrants were included, differences were observed and the longest disintegration times were those recorded when talc and magnesium stearate were added simultaneously, as opposed to when magnesium stearate was added subsequently to talc. This difference was only of significance with Avicel^{R}.
(Without talc, the Emcompress^{R}, Avicel^{R}, magnesium stearate mixture had an average disintegration time of 8,75

Table 5 - The effect of sequence of addition of Talc and Magnesium Stearate on the disintegration of capsules containing Emcompress^{R}, and either Ac-di-Sol^{R} or Avicel^{R} as indicated:

	SIMULTANEOUS ADDITION OF TALC AND MAGNESIUM STEARATE		TALC ADDED SUBSEQUENTLY TO MAGNESIUM STEARATE		MAGNESIUM STEARATE ADDED SUBSEQUENTLY TO TALC	
	AVICEL^{R}	AcDiSol^{R}	AVICEL^{R}	AcDiSol^{R}	AVICEL^{R}	AcDiSol^{R}
Average time (mins:sec)	5:31	3:41	3:16	3:12	3:36	3:35
Range (mins:sec)	3:50-7:45	2:48-4:20	2:57-4:04	2:57-3:26	3:00-4:20	2:23-5:13
Average Mass	0,63g	0,64g	0,61g	0,64g	0,62g	0,64g

minutes). This phenomenon was not, however, observed for the AcDiSol^{R} blends, where the average disintegration time had increased by about a minute, irrespective of the sequence of addition of the talc. A possible explanation for this behaviour lies in the different mechanisms of action of the two disintegrants.

The effects of compaction on the Disintegration Time

In the pharmaceutical industry most capsules are now filled using automatic, high-speed filling machines, which compress the powder mixture into slugs during the process. Slugs were prepared using Emcompress^{R}/talc (1%m/m)/magnesium stearate (0,5%m/m) blends with 5%m/m of the respective disintegrants, and filled into size 00 capsule shells.

From Table 6 it may be seen that without a disintegrant the powder slug took more than twice as long to disintegrate as the loose powder mass. However, differences in the disintegration times between the slugs and the loose powder fills became negligible in the presence of any of the disintegrants investigated.

Table 6 - The disintegration times of the various powder blends, when the fill material occurs as a tamped slug, and as loose powders:

DISINTEGRANT	COMPACT SLUGS		LOOSE FILL	
	MASS	AVERAGE TIME (RANGE) in mins:secs	MASS	AVERAGE TIME (RANGE) in mins:sec
CONTROL^{R}	0,85g	9:45 (6:36-12:02)	0,89g	4:10 (2:58-4:59)
STARCH^{R}	0,85g	3:10 (3:00-3:40)	0,89g	3:47 (3:20-4:39)
PRIMOJEL^{R}	0,86g	2:50 (2:30-3:19)	0,90g	2:40 (2:31-3:30)
AVICEL^{R}	0,81g	5:52 (4:26-8:42)	0,85g	5:14 (4:24-5:42)
AcDiSoL^{R}	0,83g	3:00 (2:43-3:30)	0,86g	3:20 (3:09-3:28)
POLYPLASDONE^{R}	0,79g	2:58 (2:26-3:35)	0,82g	3:09 (2:43-4:05)

CONCLUSIONS

In the formulations tested, the disintegrants with powerful swelling and wicking ability were generally the most effective, e.g. AcDiSol^{R} and Primojel^{R}. Starch has only moderate ability in this regard, and Avicel^{R} relies mainly on physiochemical bonding (and therefore a degree of compression) for its activity. The diversity of capsule formulations hinders the accurate prediction of an effective disintegrant.

Process factors such as the mixing sequence and method of encapsulation (i.e as loose powders or a slug) have been shown to have an effect on disintegration.

The inclusion of a disintegrant in the capsule formulation is therefore necessary if the powders have been encapsulated as a compacted slug or lubricated with a hydrophobic excipient.

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