DFE pharma

Use of Primojel® and Primellose® in wet granulation

The pursuit of excipient excellence

Summary

Based on studies reported here, the inclusion of at least half of the disintegrant inside the granules is extremely important for formulations containing a high quantity of insoluble diluent. Use of all extragranular disintegrant in tablets based on dibasic calcium phosphate as the diluent gave tablets with unacceptably slow disintegration and dissolution.
For tablets based on soluble lactose as the diluent there was no effect of disintegrant location.
There was no apparent deleterious effect of wet granulation on the ability of Primojel ® or Primellose ® to promote tablet disintegration and drug dissolution.

1 Introduction

In the process of wet granulation there is the opportunity to add materials either in the actual wet granulation process (intragranular addition) or to the dried, milled granules resulting from wet granulation (extragranular addition). Addition of disintegrants to the intragranular and extragranular phases has been extensively reported, but without agreement on the best means of addition.

Table 1 shows a summary of some published results.

Table 1: *Summary of some literature findings*

Reference	Tablet description	Summary of results
1	Prednisone + lactose + sodium starch glycolate or croscarmellose sodium	Disintegration time typically in the range 1 – 2 minutes, irrespective of the disintegrant location
2	Naproxen + croscarmellose sodium	Dissolution faster with intragranular disintegrant compared to extragranular disintegrant.
3	p-aminobenzoic acid + naproxen or lactose or dicalcium phosphate + sodium starch glycolate or croscarmellose sodium or crospovidone	In general, dissolution fastest with extragranular disintegrant and slowest with intragranular disintegrant. Intermediate results with split intra- / extragranular addition.
4	Paracetamol + sodium starch glycolate or croscarmellose sodium	Disintegration and dissolution fastest for 50:50 intragranular : extragranular split than for either entirely intragranular or extragranular addition

The results are of course in part dependent on the actual formulations used in the studies.

The purpose of the work reported here is to study the use of Primojel ® (sodium starch glycolate type A) and Primellose ® (croscarmellose sodium) in wet granulated formulations containing predominantly soluble and insoluble fillers (lactose and dibasic calcium phosphate respectively) and diclofenac sodium as a soluble active.

2 Experimental section

2.1 Materials

Diclofenac sodium, dibasic calcium phosphate anhydrous, povidone and magnesium stearate were obtained from BUFA, The Netherlands
Lactose (Pharmatose ® 200), microcrystalline cellulose (Pharmacel ® 101), Primojel ® and Primellose ® are available from DFE Pharma.

2.2 Formulations

The formulations are shown in table 2.

Table 2: *Formulations used in this study*

Intragranular Component (mg/tab)	**1% total disintegrant**			**2% total disintegrant**			**4% total disintegrant**		
Diclofenac sodium	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
Diluent	190.0	190.0	190.0	187.5	187.5	187.5	182.5	182.5	182.5
Pharmacel ® 101	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
Povidone K25	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000
Disintegrant	2.500	1.250	0.000	5.000	2.500	0.000	10.000	5.000	0.000
Extragranular component (mg/tab)									
Disintegrant	0.000	1.250	2.500	0.000	2.500	5.000	0.000	5.000	10.000
Magnesium stearate	2.500	2.500	2.500	2.500	2.500	2.500	2.500	2.500	2.500
Total	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**

The diluent was either lactose monohydrate (Pharmatose ® 200M) or dibasic calcium phosphate anhydrous
The disintegrant was either sodium starch glycolate (Primojel ®) or croscarmellose sodium (Primellose ®)

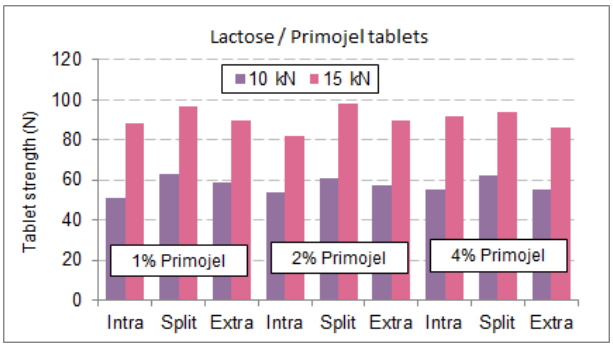
2.3 Preparation and testing of the formulations

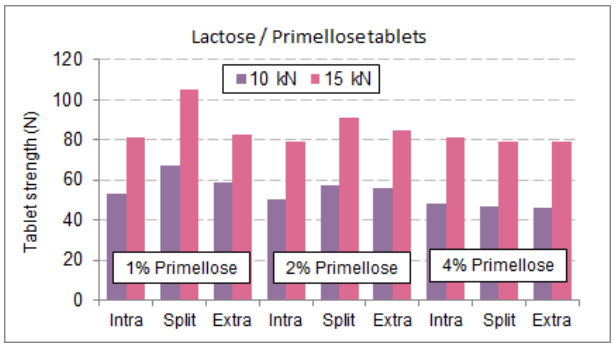
In all cases the batch size was 500g.
Intragranular components were added to a Procept Form-8 high shear granulator and granulated with purified water. The granules were fluid bed dried, screened through a 1mm mesh using an Erweka oscillating granulator and blended with the extragranular components using a Turbula mixer. The lubricated granules were tableted using a Kilian rotary press fitted with 9mm flat bevel edged tooling using compaction forces of 10 kN and 15kN.
Tablets were tested for crushing strength using a Schleuniger tester, disintegration time using standard USP apparatus and dissolution rate using 900 ml of purified water in USP apparatus 2 operated at 50rpm (lactose formulations) or 100 rpm (dibasic calcium phosphate formulations). Diclofenac was analysed by uv spectrophotometry at 276 nm. Only tablet compressed with 10 kN compaction force were dissolution tested.

3 Results and discussion

3.1 Tablet strength

Plots of tablet strength for the various formulations are shown below.





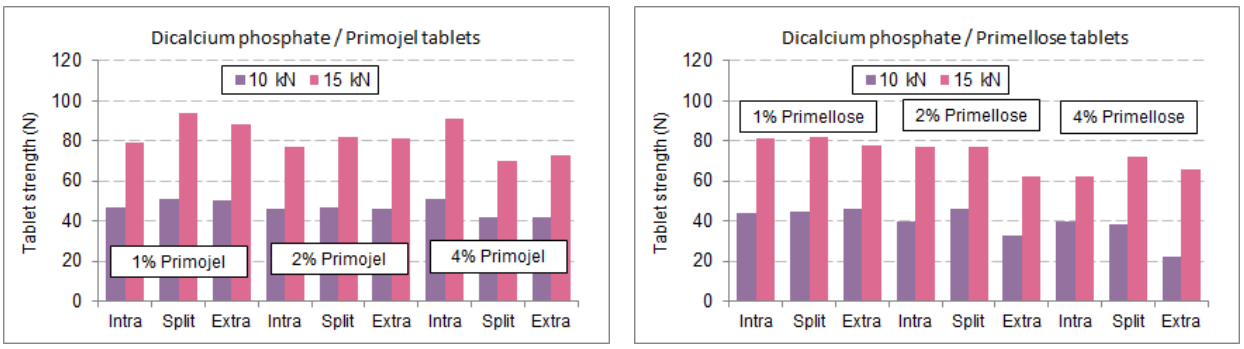


Figure 1: *Strength of tablets of various formulations*

There is very little influence of disintegrant type, disintegrant level or disintegrant location on tablet strength, except that 4% extragranular Primellose ® appears to give softer tablets when compressed with 10 kN compaction force.

3.2 Tablet disintegration

Figure 2 shows the disintegration of the lactose tablets. Not surprisingly the harder tablets made at higher compaction forces disintegrate more slowly. Increasing the total quantity of either Primojel ® or Primellose ® tends to decrease disintegration time, and Primellose ® appears to be slightly more effective than Primojel ®. However there is little or no effect of disintegrant location on disintegration time.

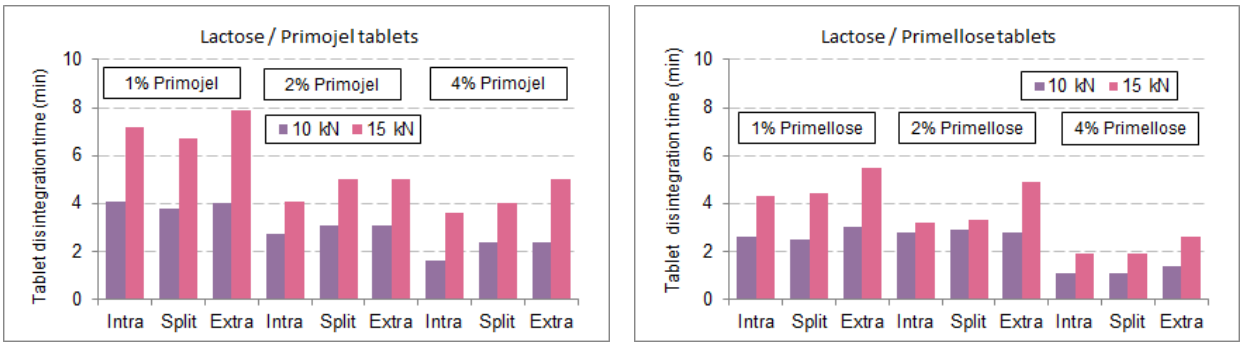


Figure 2: *Disintegration of lactose based tablets*

Figure 3 shows the equivalent data for the dibasic calcium phosphate tablets. For these tablets there is a very pronounced disintegrant location effect, and tablets containing only extragranular disintegrant tend to have prolonged disintegration times. Increasing the total amount of disintegrant decreases disintegration time, but it does not offset the location effect. The location effect is most pronounced for the tablets containing 1% Primellose where the disintegration time increases from 1 or 2 minutes (10 kN compaction force) for the intragranular and split locations to 18 minutes when the disintegrant is only extragranular.

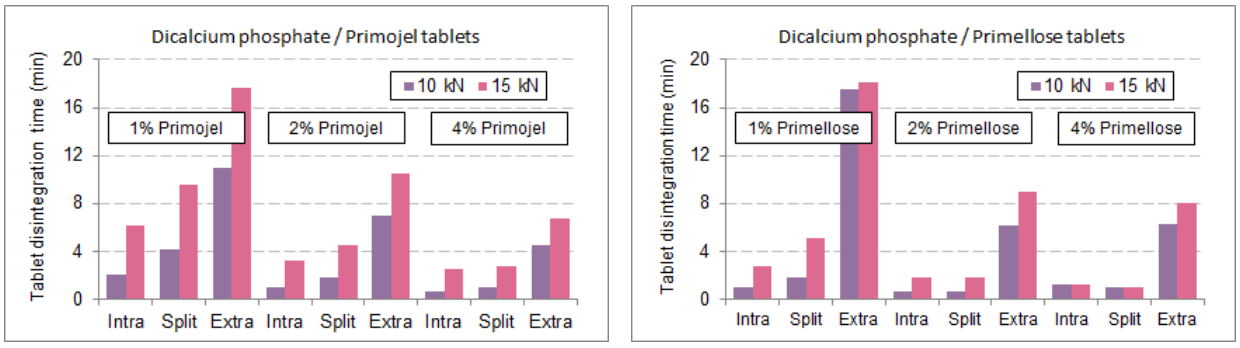


Figure 3: *Disintegration of dibasic calcium phosphate tablets*

3.3 Tablet dissolution

Dissolution of the lactose tablets containing 2% Primojel or Primellose are shown in figure 4. As can be seen, dissolution is rapid and essentially complete after 10 minutes for all the formulations. There is no apparent effect of disintegrant type nor of disintegrant location.

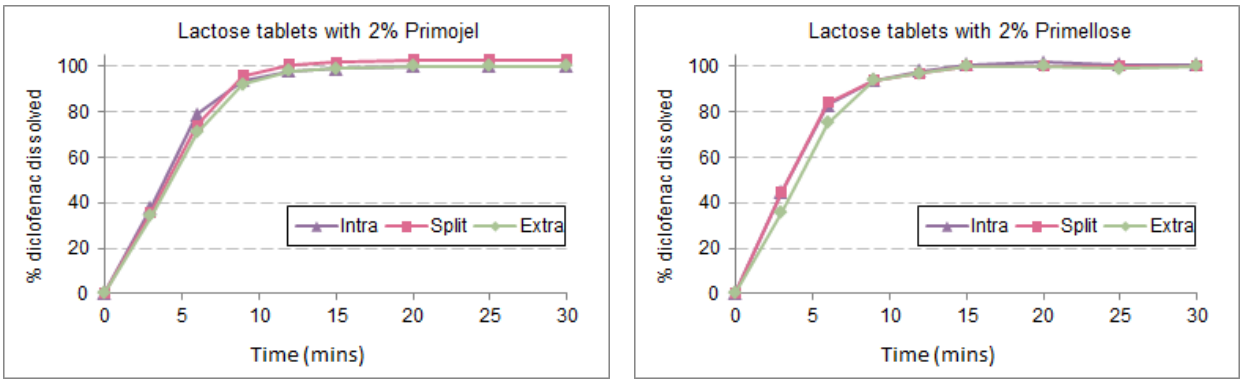


Figure 4: *Dissolution of tablets based on lactose with 2% Primojel or Primellose*

Dissolution profiles of all the tablets based on dibasic calcium phosphate are shown in figure 5. These tablets needed to be tested using USP apparatus 1 operated at 100rpm to disperse the formulation effectively in the vessel. For both disintegrants there is a clear location effect, in that tablets with only extragranular disintegrant dissolve much more slowly than those with intragranular disintegrant or those with disintegrant split between the two locations. There is little or no difference between intragranular or split disintegrant. Increasing the total quantity of extragranular disintegrant tends to improve tablet dissolution, but this is not nearly as effective as using at least 50% of the disintegrant inside the granules.
Primellose ® may be marginally more effective than Primojel ®, but for all tablets containing at least 50% intragranular disintegrant, the dissolution is essentially complete after 10 minutes.

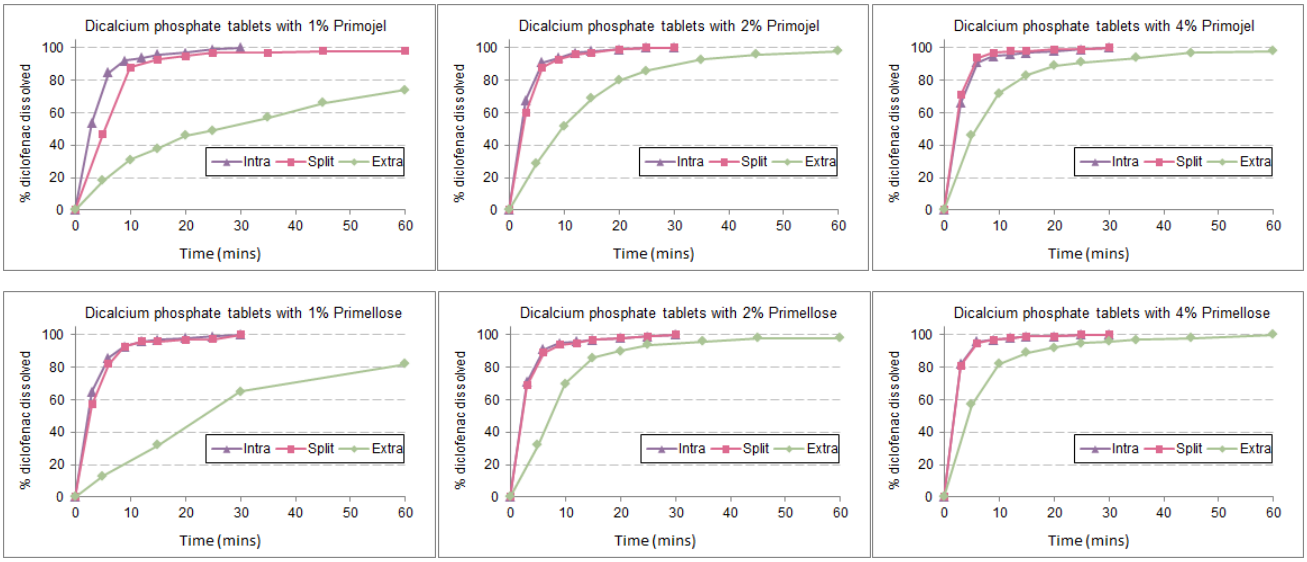


Figure 5: *Dissolution of tablets based on dibasic calcium phosphate with different levels of disintegrant*

The difference between the properties of tablets based on lactose or dibasic calcium phosphate is almost certainly a reflection of the difference in solubility of the two diluents. During disintegration testing of the calcium phosphate tablets containing only extragranular disintegrant, it was seen that the outer part of the tablet would disintegrate readily but an inner core that disintegrated slowly remained in the disintegration apparatus. This is consistent with an explanation where disintegration proceeds from the outside of the tablet as water penetrates, until the penetrating water front reaches an area of the tablet resulting from

granule to granule contact with no intervening extragranular disintegrant. At this point water ingress slows dramatically. The effect is not seen with the lactose tablets because the solubility of lactose means that the water front can continue to penetrate into the tablet.

4 Conclusion

The combination of choice of diluent (which is the majority of these tablet formulations) and disintegrant location can have a profound effect on tablet disintegration and dissolution properties. For tablets containing high levels of insoluble calcium phosphate and only extragranular disintegrant, then disintegration and dissolution of tablets are unacceptably slow.
Increasing the total amount of extragranular disintegrant has an effect on disintegration and dissolution, but inclusion of at least 50% of the disintegrant inside the granules has a much greater effect.
For tablets based on soluble lactose there is no apparent effect of disintegrant location on either tablet disintegration or dissolution of diclofenac sodium.
The ability of both Primojel ® and Primellose ® to promote tablet disintegration and drug dissolution does not appear to be affected by wet granulation.

References

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