

Superdisintegrants:

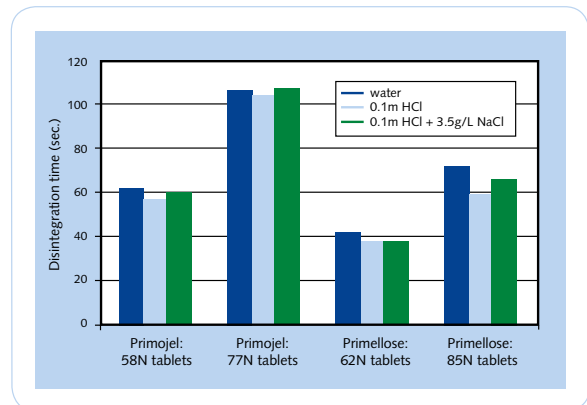
effect of pH on
performance.

DMV-Fonterra Excipients
The ingredients of success



Summary

Formulations of atenolol wet granulated tablets formulated with Primojel, and diazepam directly compressed tablets formulated with Primojel and Primellose have been examined for test medium pH effects on disintegration and dissolution. The diazepam tablets were also examined for ionic strength effects. The results showed no effect of medium composition on disintegration or dissolution of the tablets, and it is concluded that Primojel and Primellose can act as medium pH and ionic strength independent superdisintegrants.



Introduction

Both Primojel (sodium starch glycolate, SSG, figure 1) and Primellose (croscarmellose sodium, CCS, figure 2) are cross-linked, carboxymethylated polymers of potato starch (in the case of Primojel), or cellulose (in the case of Primellose).

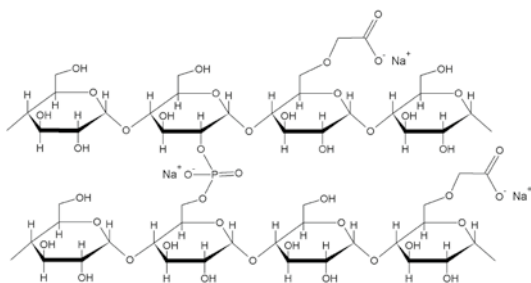


fig. 1: Primojel schematic.

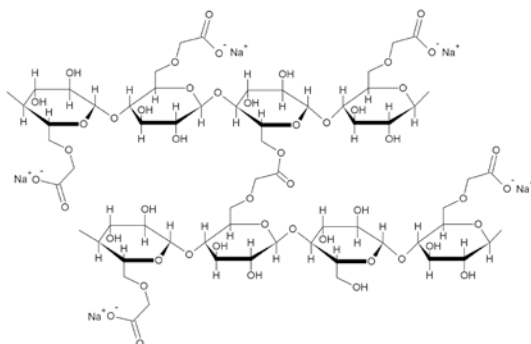


fig. 2: Primellose schematic.

The carboxymethyl substituent can take the form of the carboxylic acid or the anion depending on the pH of the surrounding medium, acidic media favouring the acid and neutral to alkaline media favouring the anion. It has been reported that both the liquid uptake rate⁽¹⁾ and the settling volume^(1,2) of sodium starch glycolate are affected by the pH of the test medium, a lower pH reducing both of these properties. These findings may give rise to a concern that the effectiveness of these two superdisintegrants

may be compromised if the tablet disintegration or dissolution test is carried out at low pH. A number of publications have examined the effect of pH on disintegration or dissolution of tablets containing various disintegrants including sodium starch glycolate or croscarmellose sodium, and the data are summarized in table 1.

Vadas et al⁽³⁾ studied a number of disintegrants in spray dried lactose tablets using water (pH 6.0), USP simulated gastric fluid (pH 1.5) and USP simulated intestinal fluid (pH 7.5) as disintegration media. The results show that, whilst the tablets without disintegrant disintegrated faster at lower pH, the addition of 3% croscarmellose sodium both shortened the disintegration time and removed the pH dependence.

Gordon et al⁽⁴⁾ found that superdisintegrants tended to give faster dissolution of p-aminobenzoic acid (as a model for a drug) in pH 7.4 phosphate buffer than in 0.01M hydrochloric acid (pH 2) when incorporated by wet granulation. This observation was noted for the three superdisintegrants studied (sodium starch glycolate, croscarmellose sodium and crospovidone) incorporated at 2%, and did not appear to depend on the location of the superdisintegrant (intragranular, extragranular or split) nor on the filler (lactose or dicalcium phosphate).

Sakr et al⁽⁵⁾ studied the disintegration of directly compressed hydrochlorothiazide tablets and found that increasing the concentration of croscarmellose sodium greatly decreased the disintegration time. The effect of pH was reduced as the croscarmellose concentration was increased, and at higher concentrations the pH effect was minimized. The disintegration time versus disintegrant concentration profiles from this reference are shown in figure 3.

Ref.	Tablet 'active'/filler	Process	Superdisintegrant	Effect on disintegration time (DT) or dissolution rate (Disso)
3	None/spray dried lactose	DC	None 3% CCS	DT: pH1.5 < water < pH7.5 DT: Insensitive to pH
4	p-aminobenzoic acid/ lactose or dicalcium phosphate	WG	None 2% SSG 2% CCS	Disso: Insensitive to pH Disso: faster at pH 7.4 than pH 2.0 for both fillers and both superdisintegrants.
5	Hydrochlorothiazide/ MCC + Calcium phosphate (50:50)	DC	None 0.2% to 4% CCS	DT: 0.1M HCl < water DT: 0.1M HCl < water at low CCS concentration.

table 1: Literature data on the effect of pH on the performance of SSG and CCS.

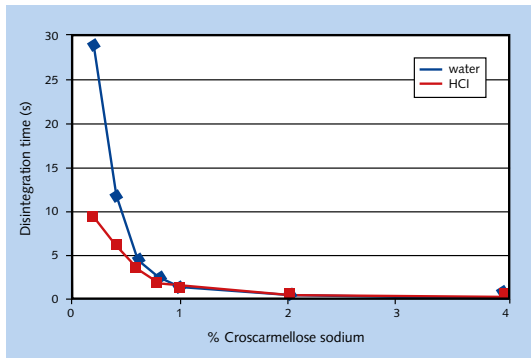


fig. 3: Hydrochlorothiazide tablet disintegration data from Sakr et al⁽⁵⁾.

Thus the literature data do not give a consistent picture of the effect of pH on the performance of sodium starch glycolate or croscarmellose sodium.

An additional performance factor may be the effect of sodium chloride. Bolhuis et al⁽⁶⁾ found that purification of a series of experimental sodium starch glycolates tended to increase their sedimentation volumes. When used at 4% in lactose or dicalcium phosphate placebo tablets, purification also slightly shortened the tablet disintegration time. Purification in this case consisted of removal of sodium chloride by washing with ethanol/water, and the sodium chloride content of Primojel lies in between the experimental unpurified and purified samples.

The purpose of the studies reported here is to assess the effect of pH on disintegration and dissolution of tablets containing Primojel and Primellose in a range of different test media. Additionally in one experiment the effect of increasing the ionic strength of one test medium by addition of sodium chloride was investigated.

Experimental section

Three tablet formulations were employed in this study. First a typical wet granulation formulation containing 50mg of atenolol per tablet and employing Primojel as the superdisintegrant (table 2), and secondly, typical direct compression formulations containing 2mg of diazepam per tablet and employing Primellose or Primojel as the superdisintegrant (table 3).

Atenolol tablet preparation

Component	mg/tablet	%w/w
Atenolol	50.00	33.33
Pharmacel 101	71.00	47.33
Povidone (K=30)	0.15	0.10
Primojel	3.00	2.00
Pharmacel 102 (a)	18.35	12.23
Primojel (a)	6.00	4.00
Magnesium stearate (a)	1.50	1.00
Total	150	100

(a): Extragranular excipient.

table 2: Atenolol 50mg formulation.

The atenolol tablets were made at a batch size of 10,000 tablets by wet granulation of the atenolol, Pharmacel 101 and intragranular Primojel with an aqueous solution of Povidone in a planetary mixer followed by fluid bed drying. The dried granules were screened, blended with the extragranular Pharmacel 102 and Primojel for 20 minutes followed by magnesium stearate blending for 5 minutes. Tablets were compressed at two hardnesses (46N and 86N) using 7mm round, normal concave punches.

Atenolol dissolution was performed using USP apparatus 2 operated at 50rpm, and dissolved atenolol was determined by hplc with uv detection at 226nm. Disintegration and dissolution testing were performed in three different media, namely 0.1M hydrochloric acid, 0.1M pH 4.6 acetate buffer, and pH 6.8 phosphate buffer (simulated intestinal fluid USP without enzymes).

Diazepam tablet preparation

Component	mg/tablet	%w/w
Diazepam	2.00	0.80
SuperTab 14SD	118.40	47.36
Pharmatose 100M	118.40	47.36
Primellose or Primojel	10.00	4.00
Magnesium stearate	1.25	0.50
Total	250	100

table 3: Diazepam 2mg formulations.

The diazepam tablets were made by blending the diazepam, SuperTab 14SD, Pharmatose 100M and Primojel or Primellose in a Turbula mixer followed by the magnesium stearate. Tablets were compressed using 9mm round, flat bevel edged punches to target hardnesses of 60N and 80N.

Diazepam dissolution was performed using USP apparatus 2 operated at 50rpm, and dissolved diazepam was determined by uv at the wavelength of maximum absorbance in each medium.

Dissolution and disintegration testing were performed in three media, namely deionised water, 0.1M hydrochloric acid, and 0.1M hydrochloric acid plus 3.5g/L of sodium chloride.

Results and discussion

Atenolol tablet properties

The physical properties and disintegration times (DT) of the atenolol tablets are given in table 4, and dissolution after 15 minutes in three test media is given in table 5 as the mean and RSD of 6 tablets. Dissolution profiles are also shown graphically in figures 4 and 5.

Property	46N tablets	86N tablets
Mean weight (mg)	154	149
Thickness (mm)	3.96	3.68
Hardness (N)	46	86
Friability (%)	0	0
DT in HCl (s)	100	544
DT in acetate (s)	116	522
DT in phosphate (s)	172	554

table 3: Diazepam 2mg formulations.

% dissolved after 15 minutes in each medium (RSD)	46N tablets	86N tablets
0.1M HCl	98 (1.7)	92 (5.1)
pH 4.6 acetate	94 (3.0)	95 (1.3)
pH 6.8 phosphate	95 (3.0)	94 (2.2)

table 5: Dissolution of atenolol tablets.

The tablets all have good physical properties. The 46N tablets disintegrate more slowly in phosphate buffer than in the other media, but this effect is not seen at the higher hardness. The harder tablets also disintegrate more slowly in all media, and this is reflected in the slower dissolution of the harder tablets at the first time point. But dissolution is rapid for all the tablets and it is clear from figures 4 and 5 that there is no pH dependence.

Diazepam/Primellose tablet properties

The physical properties and disintegration times for these tablets are given in table 6. Dissolution after 15 minutes in the three test media is given in table 7 as the mean and RSD of 6 tablets, and also shown graphically in figures 6 and 7.

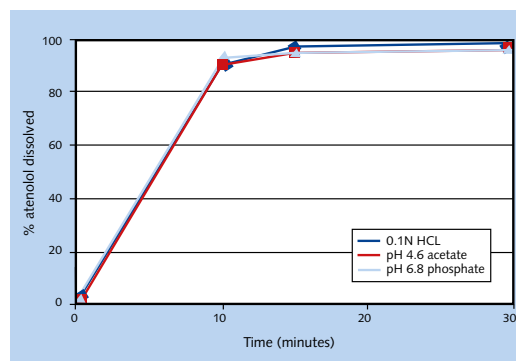


fig. 4: Dissolution of 46N atenolol tablets.

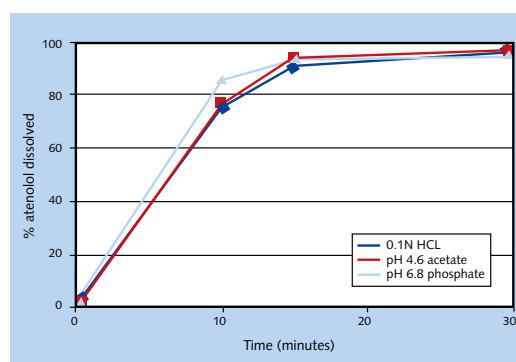


fig. 5: Dissolution of 86N atenolol tablets.

Property	62N tablets	85N tablets
Thickness (mm)	2.98	2.87
Hardness (N)	62	85
DT in water (s)	42	72
DT in HCl (s)	38	59
DT in HCl + NaCl (s)	38	66

table 6: Properties of diazepam tablets with Primellose.

% dissolved after 15 minutes in each medium (RSD)	62N tablets	85N tablets
Water	90 (1.8)	103 (6.3)
HCl	101 (2.4)	103 (2.9)
HCl + NaCl	95 (1.7)	97 (3.7)

table 7: Dissolution of diazepam tablets with Primellose.

From the data it is clear that there is no pH or ionic strength effect on either the dissolution or disintegration of directly compressed diazepam tablets formulated with 4% Primellose as superdisintegrant. Harder tablets have a slightly longer disintegration time, but comparison of figures 6 and 7 does not reveal an effect of hardness on dissolution.

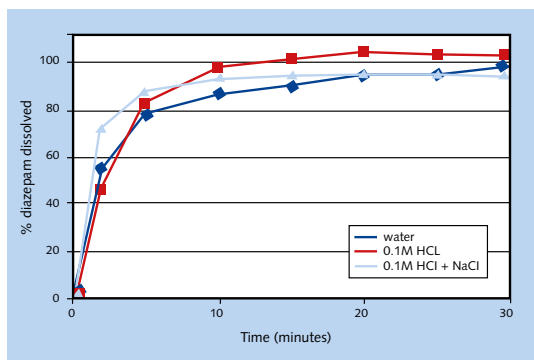


fig. 6: Dissolution of 62N diazepam tablets with Primellose.

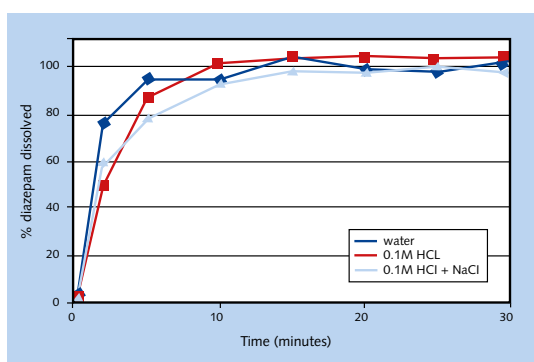


fig. 7: Dissolution of 85N diazepam tablets with Primellose.

Diazepam/Primojel tablet properties

The physical properties and disintegration times for these tablets are given in table 8. Dissolution after 15 minutes in three test media is given in table 9 as the mean and RSD of 6 tablets, and also shown graphically in figures 8 and 9.

Property	58N tablets	77N tablets
Thickness (mm)	2.95	2.87
Hardness (N)	58	77
DT in water (s)	62	106
DT in HCl (s)	57	104
DT in HCl + NaCl (s)	60	107

table 8: Properties of diazepam tablets with Primojel.

% dissolved after 15 minutes in each medium (RSD)	58N tablets	77N tablets
Water	95 (5.4)	96 (7.9)
HCl	103 (0.6)	103 (2.7)
HCl + NaCl	93 (2.9)	99 (4.3)

table 9: Dissolution of diazepam tablets with Primojel.

Physical properties are again good. Compared to the tablets containing Primellose, the Primojel tablets exhibit a slightly slower disintegration time, but this parameter is still perfectly acceptable and always under 2 minutes.

The disintegration and dissolution data for diazepam tablets formulated with 4% Primojel do not exhibit a pH effect, or an ionic strength effect. Harder tablets have a longer disintegration time, but this is not reflected in the dissolution results.

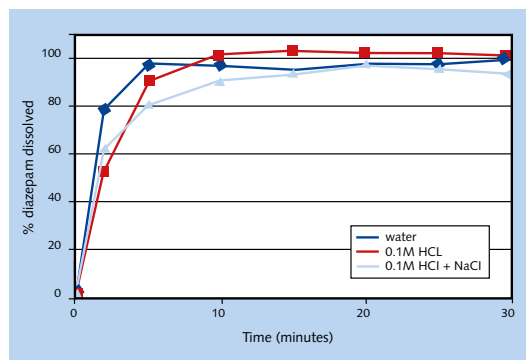


fig. 8: Dissolution of 58N diazepam tablets with Primojel.

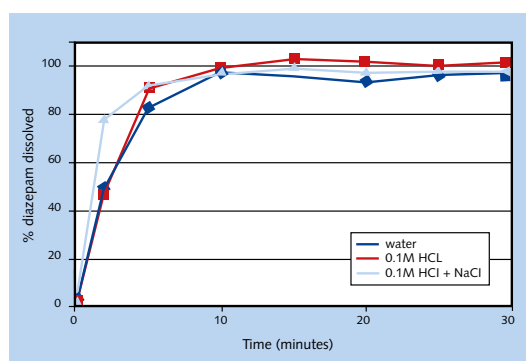


fig. 9: Dissolution of 77N diazepam tablets with Primojel.

General discussion

This study did not reveal a dependence of disintegration or dissolution on the pH of the medium. The superdisintegrants were used at 4% in the diazepam tablets, and the Primojel was used at 6% in the atenolol tablets. These levels are higher than those used in the study of Gordon et al⁽⁴⁾, and superdisintegrant concentration was found to influence the pH effect in the study of Sakr et al⁽⁵⁾. Superdisintegrant concentration is therefore a possible explanation for the differences observed between studies.

Addition of sodium chloride to the test media in this diazepam tablet study did not affect the disintegration or dissolution of the tablets. This contrasts with the data reported by Bolhuis et al⁽⁶⁾ where removal of sodium chloride from the experimental sodium starch glycolates slightly improved disintegration performance. High local concentrations of sodium chloride within the individual modified superdisintegrant grains may be responsible for the slightly worse performance of the unpurified experimental products. These high local concentrations are not found when sodium chloride is added to the test media.

Conclusions

In the studies reported here, directly compressed diazepam tablets formulated with 4% Primojel or Primellose exhibited disintegration and dissolution data that did not depend on the media used. Both superdisintegrants were effective. Atenolol tablets made by wet granulation with Primojel as the superdisintegrant were also unaffected the dissolution medium. It is concluded that Primojel and Primellose can act as pH independent and ionic strength independent superdisintegrants.

References

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