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Prediction of physical properties of a novel polysaccharide controlled release system. I.

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Abstract

TIMERx is a novel polysaccharide-based controlled release matrix technology. The matrix consists of the synergistically interacting polysaccharides xanthan gum and locust bean gum in the presence of a third component, often dextrose, and other tertiary components. The physical properties and compression characteristics of this system were studied using conventional characterisation equipment and by the assessment of the tensile strength of compacts produced on an instrumented tablet press. The granulation method had a profound influence on granule properties and compact strength. Dry mixing of the relevant components led to the production of weak compacts. Granulation in a fluid bed granulator produced hollow granules of low bulk density which produced relatively weak compacts. Only high speed mixer granulation produced tablets with the strength required for pharmaceutical processing. Subsequent studies indicated that the nature and concentration of secondary and tertiary components added to the granulation can further influence the nature of granules produced and tablets manufactured from them. The particle size of granules, and the distribution around the mean, also appear to be important. It is concluded that the physical properties of granules and tablet depend on a number of factors not easily delineated using conventional statistics.

Keywords: Xanthan gum; Locust bean gum; Controlled release; Hydrophilic matrix; Tableting

1. Introduction

In recent years it has been shown that several polysaccharide-based technologies have the potential to join the semi-synthetic material hydroxypropylmethylcellulose (HPMC), which is widely used for this purpose (Hogan, 1989), as systems for controlled release. Xanthan gum, alone and in conjunction with other polysaccharides (Lu et al., 1991; Talukdar and Plaiziervercammen, 1993), alginates, sodium carboxymethylcellulose (scmc) and chitosan are among those which have been shown to have controlled release properties in vitro, and, in a more limited number of cases, in vivo.

It can be shown that these materials, given appropriate treatment, can, like HPMC, be used as direct compression excipients, for instance scleroglucan (Rizk et al., 1993), ethylcellulose

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(Upadrashta et al., 1993) and chitosan (Knapczyk, 1993). However there has been relatively little research done on the factors which influence the compactibility of these materials (Waaler et al., 1992).

TIMERx is a novel controlled release system containing the semi-synthetic bacterial polysaccharide xanthan gum and the synergistically interacting plant polysaccharide locust bean gum, along with secondary and tertiary components (Baichwal and Staniforth, 1991; Baichwal and Staniforth, 1992a; Baichwal and Staniforth, 1992b). It has been shown to be an effective controlled release excipient in vitro and, in a number of circumstances, in vivo (McCall and Baichwal, 1994). The basic properties of the system were the subject of a recent review (Staniforth and Baichwal, 1993).

It has previously been demonstrated that the properties of matrices based on xanthan gum alone can be influenced by granulation (Hodson et al., 1994). The purpose of this study was to investigate some of the processing and formulation factors which may influence the physical properties of and compactibility of different customised granulations of TIMERx.

2. Methods and materials

2.1. Materials

The following materials were obtained from commercial sources and used as received: xanthan gum (Ticaxan, TIC gums, Belcamp, MD), locust bean gum (TIC gums, Belcamp, MD), dextrose (Clintose, Essex Grain, Newark, NJ), calcium sulphate (Compactrol, Mendell, Patterson, NY), ethylcellulose (Ethocel, Dow Chemical, Midland, MI) and sodium stearyl fumarate (PRUV, Mendell, Patterson, NY). Fresh distilled water was used as the granulating fluid and ethanol, of USP grade, was used to make the ethylcellulose slurry.

2.2. Powder mixing and granulation

Dry powder mixtures of components were obtained by mixing for 10 min on a V-cone mixer. Fluid bed granulation of powders was carried out in an Aeromatic Strea 1 running at room temperature. Distilled water was added at a flow rate of 10 ml/min by the top spray process, to a concentration of 15% w/w.

Granulation was carried out in a Baker-Perkins 10-l high shear mixer. The same amount of granulation fluid was slowly added to the mixing vessel. All granulations were dried using a fluid bed drier (Aeromatic Strea 1) with an inlet temperature of 70°C. Granules were passed through a 20 mesh screen to remove agglomerated granules.

2.3. Bulk characterisation of granules

Poured and tapped densities of powders and granules were assessed on a Vankel Vanderkamp tap density meter. Five hundred taps were used before characterising the tapped density. Carr's ratio was assessed using the following formula (Eq. (1)):

$$\textit{Carr's ratio} = \frac{\textit{Tapped density} - \textit{poured density}}{\textit{Tapped density}} \times 100 \quad (1)$$

Sieve sizing was carried out on Ro-Tap apparatus, for 10 min. The following sieves were used:

Sieve No (USP)	Mesh size (μm)
20	850
40	425
60	250
100	150
140	106
200	75

Mean particle size was assessed from the above using Eq. (2):

$$\textit{Mean sieve diameter} = \frac{\Sigma nd}{\Sigma n} \quad (2)$$

and the size diameter standard deviation was calculated from Eq. (3):

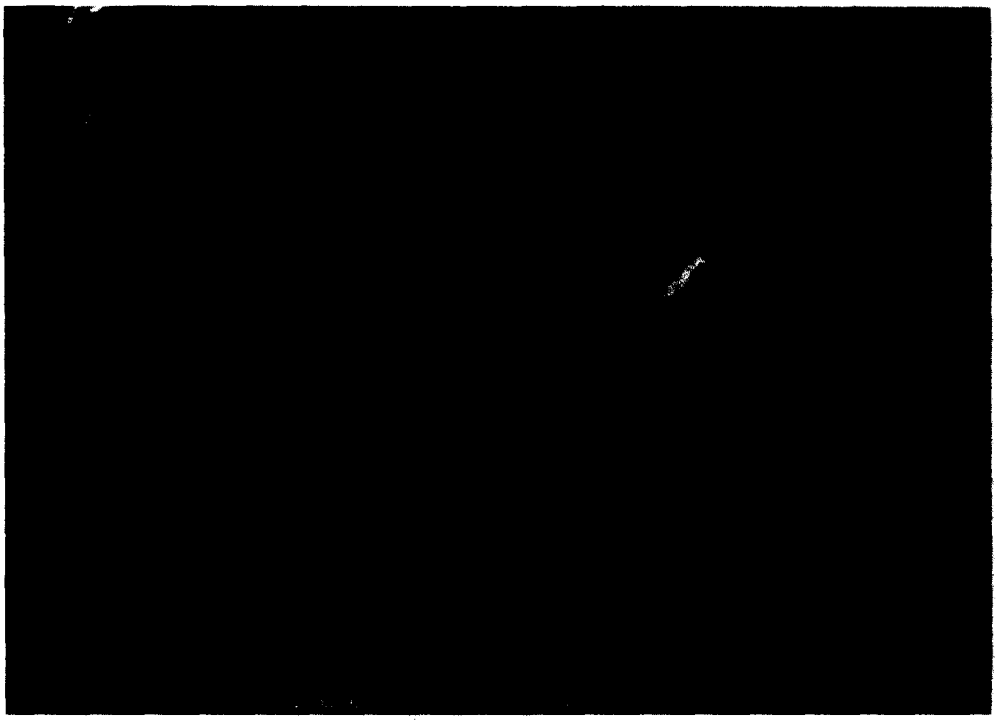

Fig. 1. Electron micrograph of granule produced in fluid bed granulator. Undifferentiated dextrose crystals and xanthan gum (see Fig. 2) can be seen.

$$\sigma = \frac{\sqrt{\Sigma(x - \bar{x})^2 d\Phi}}{\Sigma d\Phi} \quad (3)$$

where x is the particle size of each fraction and $\bar{x}$ was the mean particle size. In those cases where a particular size fraction was used to assess the compressibility, the standard deviation was set to zero.

2.4. Tableting and tablet characterisation

Sodium stearyl fumarate (1%) was mixed with all formulations for 5 min prior to tableting. Compacts were manufactured on a six-station Korsch AH100 press, with five stations blanked off, running at 25 rev./min. Tablets were manufactured to a target weight of 250 mg using 3/8" flat-faced tooling. For the dry mixed powders it was necessary to use a powder feeder but all other formulations were free flowing powders and filling by gravity was sufficient.

Tableting parameters were monitored using the Korsch compression system. Upper punch force was used as the main indicator of compression force. Compression parameters and standard deviations were taken from 10 tableting cycles.

Tablet crushing strength and size parameters were measured on an Erweka (Model TBH 30MD) tester. Results are the mean of 10 tests. Tensile strength (in MPa) was then calculated from Eq. (4):

$$Tensile\ strength = \frac{2 \times hardness\ (N)}{\pi \times T \times D} = MPa \quad (4)$$

where T and D and the thickness and diameter (in mm), respectively.

2.5. Electron microscopy of granules

Desiccated granules were examined on a Jeol T330 microscope running at 15 kV, following sputter coating on an Edwards sputter coater.

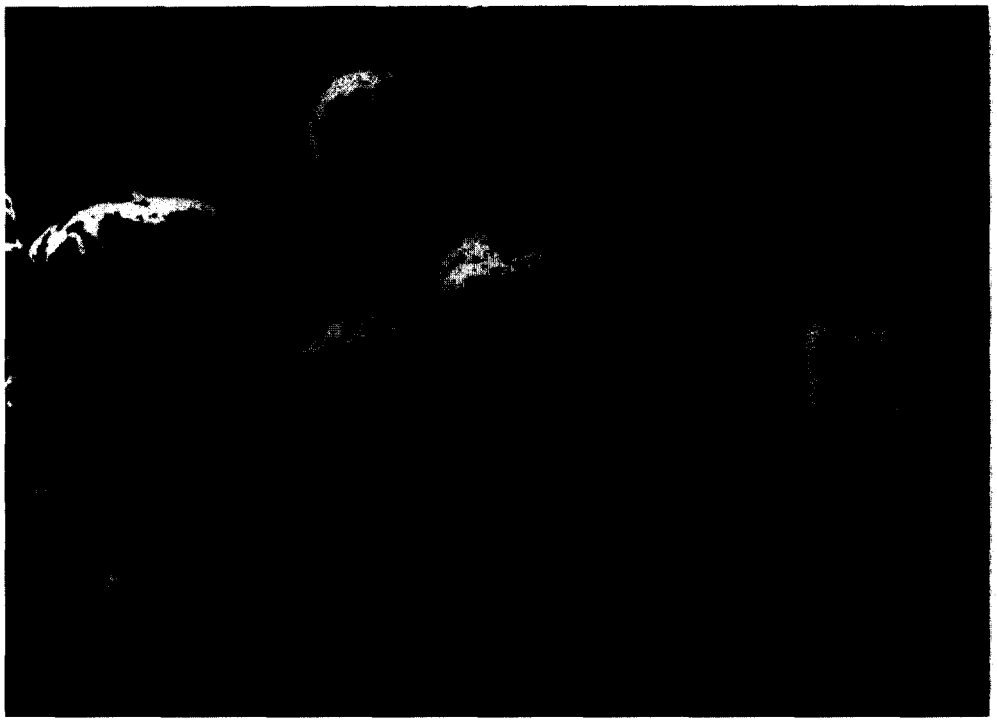

Fig. 2. Electron micrograph of xanthan gum particles.

2.6. Statistical analysis of results

Statistical analysis was carried out with the Minitab program (V9, Minitab corporation). Post-ANOVA analysis was carried out according to the Newman-Keuls procedure (Hochberg and Tamhane, 1987).

3. Results

3.1. Influence of granulation method on bulk properties of granules and compact strength of tablets

Initial formulation was carried out on mixes containing 25% xanthan gum, 25% locust bean gum and 50% dextrose.

Electron micrographs of granules prepared in the fluid bed granulator and the high speed mixer granulator, and dried by the same method, appeared to indicate a number of significant differences between the two formulations. The fluid bed granulated particles (Fig. 1) apparently have a heterogenous structure, with the individual components of the mix, e.g. pendular dextrose crystals and xanthan gum particles (Fig. 2), being visible in the granule. This may suggest that during the wetting phase of the granules the individual components of the mix were not sufficiently dispersed in the aqueous phase and that the agitation provided by the fluid bed drier was not sufficient to bring the components to an intimate mix. At higher magnification (Fig. 3), it can be seen that the fluid bed granulated particles contained significant hollow regions, of sizes greater than 10 μm, suggesting that the fluid bed granulation process, as might be expected, incorporates significant amounts of air into the granules. This is further indicated by the low bulk density of these granules (Table 1).

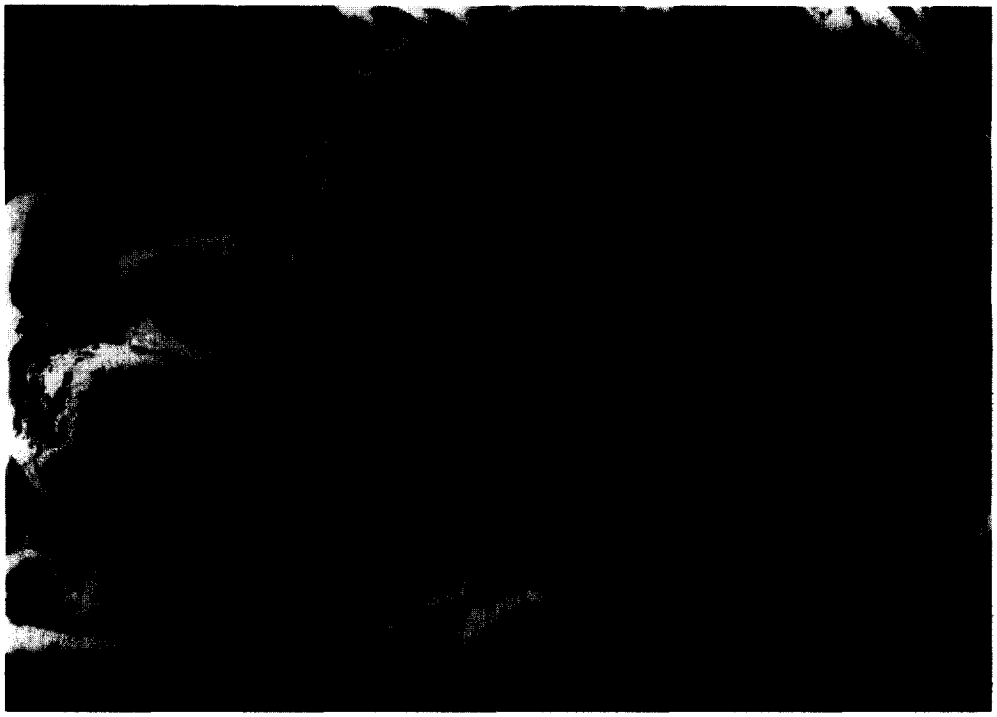

Fig. 3. Electron micrograph of granule produced in fluid bed granulator, demonstrating the presence of pores of magnitude greater than 10 μm.

Electron micrographs of granules prepared in the high speed mixer granulator (Fig. 4) showed that, on a macroscopic scale, these were more homogenous in structure, perhaps suggesting that, with the addition of the same amount of water, the components were getting wetter and that the greater shear provided by this granulator allowed the components of the mix to interact more intimately in the formation of the granule. Examination of these granules at higher magnification showed that their surfaces were relatively smooth but failed to show any apparent air spaces or hollowness. The granules did have significantly higher bulk density, suggesting that the incorporation of air into these particles was lower.

The bulk properties of the granules prepared by each method, and the properties of a dry mix containing the components of the granulation, are given in Table 1. The properties of compacts manufactured from these powders are given in Table 2. One way ANOVA demonstrated that there were significant ($P < 0.05$) differences between the groups of tablets manufactured from each technique at each pressure. Separate analysis of each group also demonstrated that increasing compaction force led to a significant ($P < 0.05$) increase in the strength of the compacts.

The results indicate that, in order to produce a strong compact, a granulation stage for the components is necessary. The high speed granulation method appears to be superior in terms of producing strong tablets. Given that the fluid bed granulation method apparently incorporates a large amount of air into the granules it should not be surprising that these granules do not produce strong tablets. Also, given the heterogenous nature of the granules it is unlikely that the dextrose, which may act as a binder in the formulation, is

Table 1
Bulk properties of granules and powders processed by different granulation methods

Granulation method	Particle size (μm)	σ_{sd}	Poured density (g/cm^3)	Tap density (g/cm^3)	Carr's ratio
None	71.9	8.87	0.618	0.790	21.77
Fluid bed	121.3	7.42	0.358	0.468[a]	23.50
High speed mixer granulation	380.5	18.78	0.529	0.587	9.86

[a]Consolidation occurred by rearrangement of particles and by disintegration of weak particles.

sufficiently intimate with the polysaccharides to provide the necessary degree of binding. All subsequent formulations were produced in the high speed mixer granulator.

3.2. Influence of the secondary component on the bulk properties of granules and tablets manufactured from them

The evidence from the previous section suggests that the secondary component, in this case dextrose, may have a part to play in the strengthening of the compact. To investigate this hypothesis the secondary component was altered. Six formulations containing the same amounts of polysaccharide (50%) but different proportions of dextrose and another filler, calcium sulphate, were prepared by the same method. The bulk properties of these granules are given in Table 3. It can be seen that, as the proportion of calcium sulphate increases the bulk density increases, this is a function of the differing bulk densities of dextrose and calcium sulphate.

Table 4 gives the properties of tablets manufactured from the above formulations. One way ANOVA demonstrated that there were significant ($P < 0.05$) differences between the tensile strength of different formulations at each approximate compaction force. Further analysis showed that the compaction force had a significant ($P < 0.05$) influence on the compact strength obtained.

It would appear from the data that, in terms of the secondary components, the formulation of the granulation can significantly influence the compact strength of tablets manufactured from them. Examination of the data suggests that those formulations which contain a mixture of components are weaker than those with single components.

3.3. Influence of particle size and particle size distribution on the bulk properties and compact strength of tablets manufactured from a grade of TIMERx

A customised grade of the system, chosen for its superior controlled release characteristics, was divided into different particle sizes by sieving. In addition to the components previously outlined, the material contains ethylcellulose. The ethylcellulose is added as an alcoholic slurry during the granulation phase of processing. Electron microscopy of the sample showed that the granule had similar morphology to the high speed mixer granulated sample above. Closer examination of the particles (Fig. 5) previously smooth components of the granule. It is known that hydrophilic materials can migrate to the surface of granules during the process of fluid bed drying so it would appear possible that this honeycomb structure can be attributed to the ethylcellulose.

Fig. 5 gives the bulk properties of the bulk material and the fractions separated by sieving while Table 6 gives the tensile strength of tablets manufactured from these fractions. Statistical analysis of the results showed that particle size had a significant (one way ANOVA, $P < 0.05$) influence on the compact strength at each compression force. Further analysis showed that compaction force had a significant affect on compact strength.

4. Discussion

The evidence presented here indicates that a number of factors can influence the compact

Fig. 4. Electoron micrograph of granules produced in a high speed mixer granulator. The surface of each component of the granule appears smooth.

strength of grades of this controlled release system. It would appear that the granulation method critically influences the compact strength of tablets produced. The inclusion of air by the fluid bed granulation process would lead to the weakening of the compacts. Secondly the dextrose component appears unable to act as a binder under these circumstances. That the sugar does

Table 2
Properties of tablets manufactured from granules prepared from different granulation techniques

Granulation method	Mean upper punchforce (kN)	Mean tablet weight (mg)	Tensile strength (MPa)
None	9.87	225[a]	0.000
	19.683	247	0.400
	29.538	261	0.540
	38.408	257	0.550
Fluid bed	9.818	246	0.000
	19.740	245	0.490
	29.944	256	0.820
	38.408	250	0.890
High speed mixer granulator	10.067	245	0.250
	19.943	264	0.980
	30.088	255	1.400
	40.203	243	1.510

[a]Tablets were too friable to hold together at required weight.

Table 3
Influence of secondary component on the bulk properties of granules produced by high speed mixer granulation

Form No.	Secondary component(s)	Particle size (μm)	σ_{sd}	Poured density (g/cm^3)	Tap density (g/cm^3)	Carr's ratio
1	Dextrose 50%	289.2	16.73	0.538	0.649	17.10
2	Dextrose 40%, calcium sulphate 10%	240.6	16.79	0.583	0.743	19.21
3	Dextrose 30%, calcium sulphate 20%	254.5	20.32	0.664	0.820	19.02
4	Dextrose 20%, calcium sulphate 30%	233.7	18.86	0.732	0.857	14.58
5	Dextrose 10%, calcium sulphate 40%	298.5	20.26	0.761	0.870	12.53
6	Calcium sulphate 50%	278.4	35.51	0.761	0.905	13.70

Table 4
Tensile strength of compacts manufactured from granules containing different amounts of secondary components

Formulation No.	Mean upper punch force (kN)	Mean tablet weight (mg)	Tensile strength (MPa)
1	10.423	251	0.330
	20.297	251	0.661
	29.851	247	1.023
	38.776	249	1.186
2	10.075	247	0.000
	19.636	249	0.586
	29.826	249	0.967
	38.668	249	1.102
3	10.134	250	0.000
	20.020	250	0.447
	29.761	258	0.761
	38.611	257	1.005
4	10.125	258	0.000
	19.154	265	0.418
	30.002	267	0.745
	38.817	265	0.840
5	10.058	247	0.000
	19.778	252	0.480
	29.964	254	0.530
	40.677	254	0.762
6	9.838	246	0.431
	20.285	246	0.927
	29.717	246	1.174
	38.527	246	1.335

act as a binder can be shown from compressing granules manufactured from the xanthan gum and locust bean gum components alone. These compacts have very poor tensile strength, even at high compression forces (Challinor et al., 1994).

The statistical analysis of the data also suggests that the nature and proportion of the secondary component of granulation and the particle size of the granules can be of importance in determining the strength of compacts produced.

Fig. 5. Electron micrograph containing TIMERx A formulation. Much of the surface is covered in a thin film of material.

This analysis, however, is unable to give a complete picture of the compaction process. For instance, whilst it is possible to relate particle size to compact strength in the case of TIMERx A, the overall correlation between these two parameters is poor. No simple statistical parameter was able to elucidate the overall links between the bulk properties of each material and grade of the system and subsequent tensile strength of granules produced from them.

5. Conclusions

Using the methods outlined, it is possible to demonstrate that granulation method and other parameters have a significant influence on the tensile strength of this controlled release system. The correlation between these parameters and those which influence drug release from the system has yet to be carried out.

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