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Application of *Abelmoschus esculentus* in Soild Dosage Formulation 1: Use as a Binder for a Poorly Water Soluble Drug

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A gum extract from the pods of *Abelmoschus esculentus* (Ae) was evaluated as granulating agent for sulphaguanidine granules and tablets.The gum was employed at concentrations of 0, 2, 4 and 6% (w/w) and granules and tablets were prepared by the weight granulation method. Properties of granules and tablets evaluated as a function of the gum concentraion include: loose densities, flow rate and angle of repose, hardness and friability, disintegration time and dissolution profiles. Granules prepared with Ae possessed good flow characteristics and the polymer exhibited higher binding capacity in sulphaguanidine tablets than maize starch and gelatin at equivalent concentrations.The gum could be employed as a granulating agent in normal release sulphaguanidine tablets at concentration levels of 2 and 4% (w/w). Beyond these concentrations, sulphaguanidine tablets with relatively prolonged released profile was obtained.

Plant gums due to their rheological properties as viscosity imparting agents have found diverse applications in pharmacy in the formulation of both solid and liquid dosage forms. They are employed as suspending agents in formulations involving indiffusable materials and as binders in the formulation of granules and tablets. They are also useful as emulsifying agents in formulation of water-in-oil and oil-in-water emulsions. Acacia and tragacanth are examples of plant gums that have been utilized in this regard. The application of the following tropical plant gums as binders in tablet formulations have been reported mucuna gum[1], prosopis gum[2], detarium gum[3], cissus gum[4], and treculia gum[5].

Abelmoschus esculentus (Moench) is grown as a vegetable crop in the tropic, subtropic and warmer areas of the temperate zone where the mucilage from the fruit serves as a thickener in soup. Highly purified form of the gum has been evaluated as a plasma expander[6], as an intravenous circulating agent[7], and as an emulsifying agent[8]. Whereas a reasonable information is now available in literature on characterization and potential applications of this gum as a plasma expander and as an emulsifying agent in disperse systems, very little information is available on its potential application as a binder for granules and tablets. The only published work so far on the potential application of this gum as a binder in tablet formulation was on sodium salicylate, a highly water soluble drug that is no longer in therapeutic usage[9]. The present study, evaluated the binding properties of this gum in sulphaguanidine (a poorly, water soluble drug) granules and tablets relative to the binding properties of two standard binders: maize starch and gelatin.

EXPERIMENTAL

The following materials were used as procured from their manufacturers: sulphaguanidine, hydrochloric acid were obtained from Merck, Germany, Primogel from Generichem, New Jersey, While lactose, magnesium stearate, maize starch, acetone, gelatin were from Fluka AG. Germany.

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Extraction of the polysaccharride gum:

About 2 kg of fresh immature fruits of Ae (okra) were purchased from a local market. After removal of the seeds, the fresh immature fruits were sliced, homogenized and extracted with cold water containing 1% (w/w) sodium metabisulphate. The crude mucilage was centrifuged at 3000 rpm for 5 min and the gum was precipitated from the supernatant with acetone[5]. The precipitated gum was washed several times with acetone, air dried for 1 h and subsequently dried overnight in a desiccator. The dried gum was pulverized using an end runner mill and screened through a 0.25 mm stainless steeel sieve. This was stored in a well closed amber coloured specimen bottle till ready for use.

Preparation of Sulphaguanidine Granules and Tablets:

Four sulphaguanidine granule batches were prepared by the wet granulation method reported previous[5]. Each tablet contained, sulphaguanidine 250 mg, primogel, 3%, Ae, (0,2, 4 or 6%) magnesium stearate, 1% and enough quantity of lactose to obtain 300 mg tablet. Granule packing and flow indices such as loose denstities, hopper flow rate and angle of repose were evaluated using standard procedures[10]. Granules were compressed in an F-3 Manesty single punch electric tabletting machine after lubrication with appropriate quantity of magnesium stearate previously screened through a 0.20 mm stainless steel sieve. Compression was carried out using 0.95 cm tooling and at a fixed pressure setting equivalent to 450 kg force of the tabletting machine. Each tablet contained sulphaguanidine 250 mg, primogel 3%, magnesium stearate 1%, Ae gum 0, 2, 4 or 6% (w/w) and enough quantity of lactose to yield 300 mg tablets. A total of two hundred tablets were compressed per batch.

Compressed tablets were evaluated for friability using the Erweka friabilaltor (TAR model) operated at 25 rpm for 100 revolutions, hardness, (n=10) using Monsanto hardness tester, disintegration time using a Manesty single unit disintegration assembly (n=6) and dissolution profile using an Erweka DT-D dissolution assembly fitted with a paddle operated at 50±1 rpm. The disintegration and dissolution media were freshly prepared 0.1M HCl maintained at 37±1°. Drug analysis in the dissolution experiment was carried out at 259 nm in a SP8-100 Pye-Unicam Uv-vis spectrophotometer. Granules and tablets containing the same concentrations of maize starch or gelatin were similarly prepared and evaluated.

RESULTS AND DISCUSSION

The extracted and purified Ae gum is cream coloured and odourless. The gum is composed mainly of monosaccharide units of galactose, rhamnose and galacturonic acid[11-13]. Relatively many studies on the mucilage of this material have been published[11-16]. These studies, however, presented varying results and ratios of the monosaccharide compositions. This could be attributed to uncertainty in the homogeneity and mucosity of the mucilage, and difference in these factors presumably may account for the disagreements in these published results.

The bulk density of the granules containing Ae showed slightly increase with increase in the gum concentration (Table 1). The bulk density of granules containing maize starch or gelatin did not follow a similar trend. There was a general increase from the bulk densities to the tapped densities of the granules as a result of filling of void spaces and densification. The increase is desirable because increase in tapped density is usually an advantage in capsule and tablet technology because of reduced volume of fill[16]. With the exception of the control batch, granules containing Ae exhibited better hopper flow rate than those containing maize starch or gelatin. From Table 1, the angle of repose values do not follow any regular trend and do not correlate with the hopper flow rates. This behaviour sometimes occurs because flow rate and angle of repose depend on, among other things, on the method adopted in their deternination. Consequently, a correlation can not always be expected to exist between the two parameters, a finding which was earlier reported by Lachman *et al.*[17] and confirmed in a recent study[18]. However, angle of repose values of $<40^0$ indicate good flow[19], and since the angle measures interparticulate forces, it still remains one of the very commonly used parameters for evaluating granule flow. All the granule batches could be considered to be free flowing on the basis of their angle of repose values. The existence of low inerparticulate frictions and good flow characteristics of the granule was further confirmed by relatively low values of Hausner's quotients and compressibility indices (Table 1).

The effect of binder type and concentration on the mechanical properties of sulphaguanidine tablets are presented in Table 2. Tablets containing Ae exhibited a near linear increase in hardness and binding capacity with increase in the binder concentration. Binding capacity is

TABLE 1: SOME MICROMERITIC PROPERTIES OF SULPHAGUANIDINE GRANULES

	Parameter					
	B.D.	T.D.	F.R.	A.R.	H.Q.	C.I.
	g cm^{-1}	g cm^{-1}	g s^{-1}	(degree)	-	-
Ae						
0.0	0.50	0.51	7.04	30.68	1.02	1.96
2.0	0.57	0.63	6.60	26.40	1.11	9.52
4.0	0.59	0.69	5.81	27.73	1.17	1.44
6.0	0.61	0.67	5.46	23.40	1.10	9.0
Maize Starch						
2.0	0.56	0.61	5.67	25.34	1.09	8.20
4.0	0.61	0.71	4.71	29.39	1.16	14.10
6.0	0.59	0.67	4.98	29.05	1.14	12.00
Gelatin						
2.0	0.61	0.67	6.0	26.48	1.10	9.00
4.0	0.56	0.63	5.39	33.59	1.13	11.10
6.0	0.63	0.63	5.51	30.50	1.13	11.10

B. D. represents bulk density, T. D. denotes Tapped density, F. R. is flowrate, H. Q. represents Hausner's quotient and C. I. is the compressibility index.

the ratio between hardness and thickness of the tablet and this parameter has been utilized in the comparision of the efficiency of binders[5,20]. Comparatively, the mecahnical properties of the tablets shown in Table 2 indicate that Ae is superior to the traditional binder maize starch and equivalent to gelatin as binder in sulphaguanidine tablets. With exception of granules containing 6% (w/w) of Ae, all the other tablet batches were friable (Table 2).

The mean disintegration time of the various tablet batches are shown in Table 3. Ae produced tablets with relatively long disintegration times far above the time limit

TABLE 2: MECHANICAL PROPERTIES OF SULPHAGUANIDINE TABLETS

	BinderType and Concentration (% w/w)									
Parameter	Ae				maize starch			Gelatin		
	0.0	2.0	4	6	2	4	6	2	4	6
Hardness	2.25± (0.55)	3.12± (0.58)	5.32± (0.91)	8.84± (0.70)	3.23± (0.60)	4.22± (0.50)	4.25± (0.92)	5.55± (1.07)	5.97± (2.0)	6.70± (1.70)
Binding Capacity Kg / cm	6.82	8.91	14.38	23.26	8.73	12.06	12.14	15.86	16.58	19.14
Friability	5.0	3.22	3.22	0.0	9.01	6.25	3.33	6.25	3.22	2.56

values in bracket represent standard deviations (SD)

TABLE 3: DISINTEGRATION TIME OF SULPHAGUANIDINE TABLETS

Binder type and Con (% w/w)	DisintegrationTime (min)		
	Ae	maize starch	gelatin
0.0	3.83±0.77		
2.0	62.50±2.51	2.70±0.67	23.17±2.36
4.0	72.30±3.75	5.0±1.26	32.83±3.19
6.0	98.50±1.52	2.17±0.39	63.50±1.38

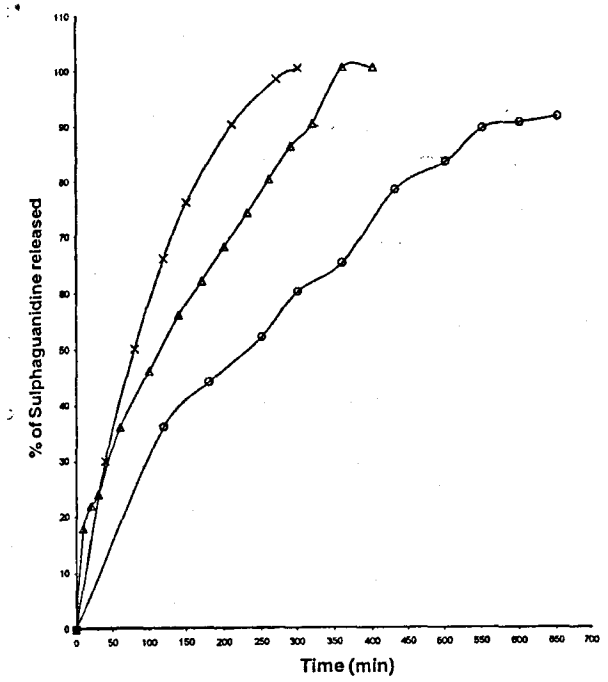

Fig. 1: Dissolution profile of sulphaguanidine from tablets. Tablets prepared with 2% w/w (-X-) or 4% w/w (-Δ-) or 6% w/w (-O-) *Abelmoschus esculentus* gum were subjected to dissolution studies in 0.1M HCl. Samples were withdrawn at different time intervals and drug content was analysed spectrophotometrically.

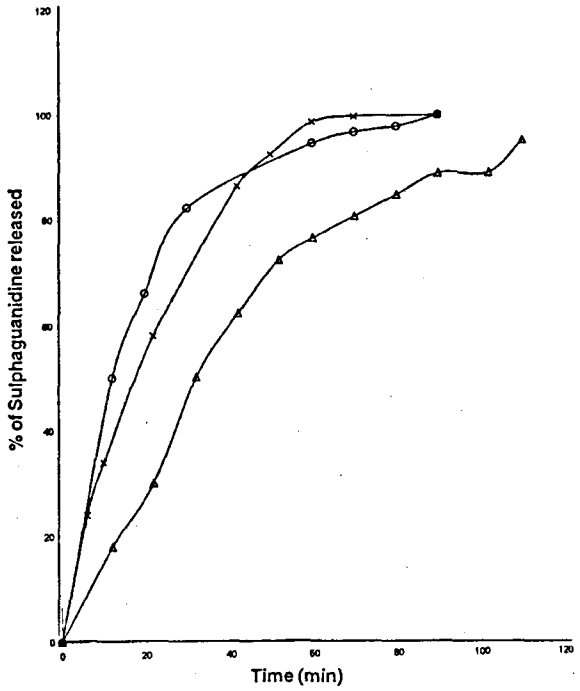

Fig. 2: Dissolution profile of sulphaguanidine from tablets. Tablets prepared with 2% w/w (-X-) or 4% w/w (-Δ-) or 6% w/w (-O-) starch were subjected dissolution studies in 0.1M HCl. Samples were withdrawn at different time intervals and drug content was analysed spectrophotometrically.

of 15 min specified for uncoated tablets in the British pharmacopoeia. A similar behaviour occurred with gelatin, while tablets containing maize starch disintegrated within 5 min. It appear from the result of disintegration times test that use of Ae as a binder for a poorly water soluble drug may require a higher concentration of a 'super' disintegrant such as primogel. When the gum was employed at concentrations below 2% (w/w), tablets with poor mechanical properties were obtained. This seems to suggest that the minimum concentration of the gum that could produce tablets of reasonable mechanical properties (at least from hardness point of view) is 2% (w/w).

The dissolution profiles of the different batches of sulphaguanidine tablets are shown in Figures 1-3. From figure 1, there was complete release of sulphaguanidine from tablets containing 2 or 4% (w/w) of Ae within 6 hours. At 6% (w/w) concentrations of the gum relatively prolonged released of the drug occurred and the dissolution curve followed a prolonged release pattern.

In gel forming polyers such as Ae gum, rate of drug release is governed by diffusion and leaching of the gelled layers. This process may be slowed by gelation which may hinder further fluid penetration into the tablet. As gel forming polymers imbibe fluid, gelled layers are formed which slows the rate of medium diffusion into the tablet. Ae gum hydrates very slowly, and this may account for the relatively slow release of sulphaguanidine from the tablets. The release so sulphaguanidine from tablets containing either of the three binders Ae gum, maize starch and gelatin were compared using the concept of t_{50} and t_{70} (time taken for 50 and 70% of the drug to be released). From table 4, it is evident that faster release of the drug occurred from tablets containing maize starch or gelatin. From the t_{50} and t_{70} values of tablets containing Ae gum, it is evident that at concentrations beyond 4% (w/w), the polymer may not be suitable for normal release sulphaguanidine tablets. There is the indication here that this polymer may be a potential hydrophilic matrix for prolonged release formulations at concentrations above 4% (w/w). This has currently been investigated and will constitute a separate report.

TABLE 4: T_{50} AND T_{70} VALUES OF SULPHAGUANIDINE

	Ae			maize starch			gelatin		
	2	4	6	2	4	6	2	4	6
t_{50}	80	120	230	19	30	10	44	56	64
t_{70}	130	200	390	29	49	22	72	86	96

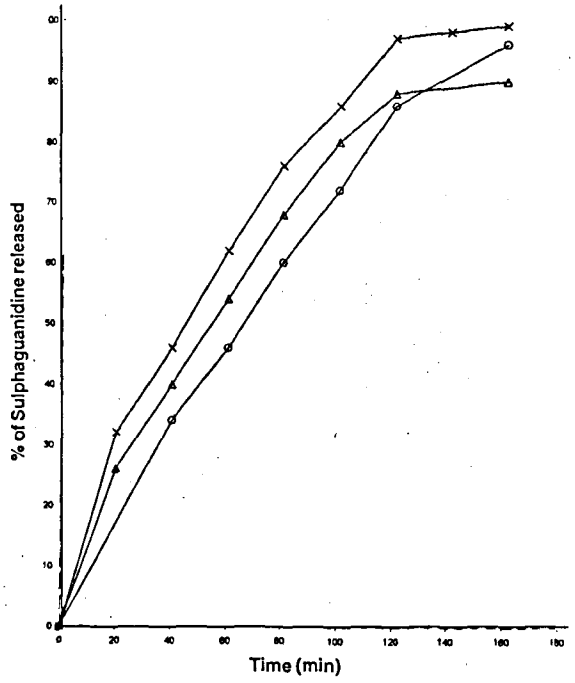

Fig. 3: Dissolution profiles of sulphaguanidine from tablets. Tablets prepared with 2% w/w (-X-) or 4% w/w (-Δ-) or 6% w/w (-O-) gelatin were subjected dissolution studies at different time intervals and drug content was analysed spectrophotometrically.

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