FORMULATION STUDIES ON THE HOT WATER LEAF EXTRACT OF FICUS SUR (MORACEAE): EFFECT OF INSOLUBLE DILUENTS ON COMPACTION CHARACTERISTICS.

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ABSTRACT

The hot water extract of the leaves of Fiscus sur, a saprophytic plant widely available in most parts of Africa and used in GIT disorders was formulated into tablets. The compaction behaviour of the extract with 2 insoluble diluents - heavy magnesium carbonate and aerosil was studied using the Heckel equation. The results showed that the equation was useful in explaining the compaction characteristics with most of the formulations having type B deformation characteristics, an indication that they would produce strong compacts. In some cases the presence of the extract changed the type B deformation pattern of heavy magnesium carbonate to type C. The particle size of the granulates was also useful in explaining some of the observations.

Keywords: Fiscus sur, leaf extract, compaction behaviour, Heckel equation, Aerosil, heavy magnesium carbonate.

INTRODUCTION

Fiscus sur (Moraceae) is a saprophytic plant widely available in the South, West and Eastern parts of Africa. The fresh leaves chewed and swallowed are claimed by people of the Middle Belt region of Nigeria to be a cure for peptic ulcer (personal communication). Preliminary pharmacological investigations in our laboratories have confirmed that some extracts of the leaf do possess gastrointestinal effects, the hot water extract (HWE) having the most pronounced effect (6). As part of studies to develop the suitable formulation for this extract, the Heckel equation (3) was used to study the compaction characteristics of the test formulations.

The Heckel equation which is widely used for relating the relative density, D, of a powder bed during compression to the applied pressure, P, has been described as the most informative of several equations describing the events that occur during compact formation because it provides information on the mechanism of powder consideration. The equation is given by;

$$\ln (1/1-D)=KP+A \quad \ldots\ldots 1$$

The slope of the straight line portion of the curve, K, is the reciprocal of the mean yield pressure, P_y, of the material. From the intercept, A, the relative density D_a, can be calculated using the following equation (Humbert-Droz et al[6])

$$Da=1-e^{-A} \quad \ldots\ldots 2$$

D_o which is the relative density of the powder at the point when the applied pressure equals zero is used to describe the initial rearrangement phase of densification as a result of die filling.

The relative density, D_b describes the phase of rearrangement at low pressures and is the difference between D_c and D_o

$$D_b=D_c-D_o \quad \ldots\ldots 3$$

Based on their deformation characteristics as described by the Heckel plots, materials are described (9) either as: (i) type A where a linear relationship is observed at all the applied pressures indicating densification apparently only by plastic deformation, for example NaCl, (ii) type B where there is an initial curved region followed by a linear one, an example of which is lactose, and (iii) type C where there is initial steep linear region which becomes superimposed and flatten out as the applied pressure is increased, for example, fatty acids.

This study is also aimed at investigating the effect of using insoluble diluents on the compaction characteristics of HWE as compared to our observation with lactose, a soluble diluent (6). The insoluble diluents used were heavy magnesium carbonate ($MgCO_3$) and Aerosil (colloidal silicon dioxide) In addition to this the presence of the HWE on the type B deformation characteristics of heavy magnesium carbonate (2)

will be determined.

MATERIALS AND METHODS

Materials: Lactose B.P 200mesh (Lactose Co., New Zealand), maize starch B.P (May and Baker, UK); PVP (Plasdone K-29/32, ISP Technologies Inc., USA), gelatin BP (Hopkins and Williams, UK), sodium alginate (Alginate INd., IK)< heavy magnesium carbonate and magnesium stearate (BDH Chemicals, UK), Aerosil (Degussa, UK) and HWE (prepare from Ficus sur (Morecae) leaves in our laboratory).

PREPARATION OF HWE

The leaves which were collected in Suleja, Niger State, Nigeria, were thoroughly cleaned and dried at 60°C in a hot air oven until brittle to touch and milled to a coarse powder in a hammer mill (Manesty, UK). Hundred grams of the powder were exhaustively extracted with 1 litre of water in a Soxhlet apparatus. The liquids were then filtered, dried, powdered and stored in a dessiccator until needed.

PREPARATION OF GRANULES

The wet granulation method of massing and screening was used. Twenty one batches (40g each) of a basic formulation of HWE (20 g) and either $MgCO_3$ or Aerosil (20 g), which served as the diluent, were mixed in a Multimix MX 32 blender (Braun, Germany) for 5 minutes at a speed equivalent to a machine scale setting of 3. The powder mix was then transferred into a mortar where the binder was added in 3 aliquots of 2 ml each and mixed with a pestle. The binder was either an aqueous solution of PVP, Na alginate, gelatin or starch paste at three concentration levels of 5, 7.5 and 10% w/w. The moistened mass was forced through a 599 un screen and dried at 60°C for 1 h. The dried granules were again passed through the 599um screen to break up agglomerates that might have formed.

DETERMINATION OF PRECOMPRESSION DENSITY

The bulk density of each formulation at zero pressure was determined using the method of Paronen and Juslin (8). The relative density, D_0, of each formulation was obtained from the ratio of its loose density to its particle density.

GRANULES SIZE ANALYSIS

The sieve method was used with 5 sieves of sizes 75, 150, 250, 355 and 500 um arranged in descending order. The weighted amount of granules was placed on the top sieve and shaken on an Endecotts test sieve shaker (Endocotts Ltd., England) for 15 min. The mass of granules retained on each sieve was determined and the percentage cummulative oversize plotted against the sieve size. The mean size of the granules was taken as the 50% cummulative oversize.

PREPARATION AND ANALYSIS OF COMPACTS

Compacts equivalent to 250 mg of HWE were produced by compressing the granules for 1 min with predetermined loads (at various compaction pressures) using a hydraulic hand press (Model C, Carver Inc., USA). Before each compression, the die (10.5 mm diameter) and the flat-faced punches were lubricated with a 1%w/v dispersion of magnesium stearate in ethanol. After ejection, the tablets were stored over silica gel in a dessiccator for 24 hours to allow for elastic recovery and hardening to prevent falsely low yield values (5). The compact masses, and dimensions were determined. Dimensions were determined with a Mitutoyo model IDC-1012EB (Mitutoyo Corporation, Japan) thickness gauge to the nearest 0.01mm. The graphs were plotted and regression analyses carried out with the Graphpad computer software.

RESULTS AND DISCUSSION

Heavy magnesium carbonate as diluent

The Heckel plots for the various MgC^{o}_{3} granulates were mainly type B as typified by Fig. 1. All of the $MgC0_3$ granulates with starch as binder had type B plots. The 7.5% (W/W) starch paste granulate whose plot did not correspond on any of the 3 types of materials based on Heckel equation. It would seem that the compaction characteristic of this granulate cannot be explained by the Heckel equation. The result of further analysis showed that the slope of the line was not

significantly different from zero, indicating that a linear fit was unsuitable for the data. It thus confirms the inability of the Heckel equation to explain this result. There was however an initial portion, which was similar to what obtains with fragmentation.

With PVP as binder, all the plots had 2 distinct portions with the 2.5 and 7.5% w/w concentrations giving a virtually flat second portion, which indicates a tendency towards type C behaviour. This is most common for soft ductile materials. It would therefore seem that the HWE had been able to soften the type B heavy MgCO3 to such an extent as to change its compaction behaviour.

Those granulates with Na alginate as binder also had 2 portions with a rise between the last 2 pressures especially for the 2.5 and 5%w/w concentration levels. This is probably as a result of further plastic deformation, with increased pressure due to asperity melting or breakdown in particle structure of the material, which the lower pressures could not achieve.

Gelatin as binder at a concentration level of 10%w/w produced granulates that seem to have type C deformation characteristics indicating a softening of the granulates. The 7.5% granulate however, rose sharply at pressure above 222.93MNM^{-2}, which could have been due to a breakdown of the binder coat around the particles. This results in further fragmentation and the formation of fresh surfaces from which new bonds are formed and also as a result of new particles undergoing further plastic deformation.

The yield point was affected by the binder concentration with the extent being however dependent on the binder type (Table 1). The observed increase in yield point with increased binder concentration is probably because the higher concentrations of binder strengthened the granules thus increasing their resistance to yield. The yield point for starch granulates was found to follow the same order as particle size (Table 1). In the case of PVP granulates, yield point decreased with increased binder concentration. This observation is similar to those of other investigators (1,8). It could have been due to the soft and plastoelastic nature of binders like PVP which results in increased rate of deformation of a mateial. This characteristic would be expected to increase with increased binder concentration. The low yield point obtained for the 7.5w/w PVP (Table 1) granulate supports the earlier assertion that it had a type C behaviour. In the case of alginate granulates, the larger particles had the highest resistance to yield while with gelatin it did not have a relationship to granule size.

D_0, the packing fraction of the granulate which describes the die filling or the density of the powder column in the die at zero pressure, was determined. A high value of D_0 indicates very dense packing. The ranking order for the starch granulates was related to the particle size, decreasing as size increased. This is because larger particles will pack more loosely than smaller ones, since they would allow for large intergranular pores. It was also established (9,11) a relationship between packing fraction in the bulk state and particle size and shape. The other binders produced granulate that did not seem to be significantly affected by binder concentration.

The binder type (Table 1 also affected D_0, an indicator of resistance to particle movement, High D_0 values indicate increased resistance to movement. With starch as binder, it increased with binder concentration and particle size because the larger particles will result in reduced movement within a given space. The results with the other binders followed the same trend.

D_b represents the phase of rearrangement of particles at low pressures and the extent of this depends on the theoretical point of densification at which particle deformation begins. For the starch granulates, it increased with increased granule size while the reverse was the case with gelatin granulates. In the case of PVP and alginate granulates, it was not significantly affected by particle size. On the whole however, the smaller sized particles had the highest values of D_B, possibly because they allow for the almost complete

filling of intergranular voids. Except in a few cases-5% starch paste and 10% gelatin-D_8 values were higher than D_0 values. This indicates that the effect of low pressures was more than that of initial packing of the formulation in the die as a result of die filling showing that fragmentation was extensive in the compaction of these granulates[8].

AEROSIL AS DILUENT

All the granulates gave plots which most closely resembled that for type B materials irrespectve of binder type and concentration (Fig. 2). This is an indication that aerosil as diluent produced granules with similar deformation characteristics as $MgCO_3$.

The yield pressure was affected by the binder concentration (Table 2). It followed the same pattern as the average particle size with alginate and gelatin as binders. In these cases, the largest granules had the highest yield point probably because the increased binder concentration, which resulted in increased granule size, strengthened them against deformation.

The results show that the initial packing of the granules in the die as a result of die filling as represented by D_0 varied with binder concentration with the specific relationship dependent on the binder type (Table 2). While it increased with alginae concentration the reverse was the case with gelatin as binder. On the whole however the smaller the particles the higher the value of D_0. This is an indication that fragmentation was not extensive compared to rearrangement in contributing to the consolidation of the granulates.

While D_0 increased with increased PVP concentration, it increased with particle size for alginate granulates while it increased with increased gelatin concentration. Inspite of this inconsistency between binders, there was obviously some relationship with size, even though this was probably affected by other particle properties, such as shape and surfaces properties. While D_b was observed to have decreased with increased PVP concentration and decreased particle size, there was no consistent relationship in the case of other binders.

CONCLUSION

Even though no reports were obtained as to the deformation characteristics of aerosil, visual observation would give the impression that it was a softer material than $MgCO_3$. However, it was genrally observed that granulates from both diluents used have similar type B characteristics an indication of their ability to form strong compacts mainly fragmentation. The extent of fragmentation was however higher with $MgCO_3$ Aerosil.

The HWE seemed to have been able to change the compaction behaviour of $MgCO_3$ by softening to give type C behaviour in one case - 7.5%w/w PVP. The results also indicate that compared to the observations with lactose as diluent (7) the solubility of the diluent used in the formulation of HWE tablets did not affect its compaction characteristics. The results obtained are a clear indication that HWE granules with aerosil as diluent would be expected to give hard and strong compacts since they would have essentially type B deformation.

Table 1: Granule size and Heckel constants for formulations with $MgCO_3$ as diluent

Binder type	Conc.(%)	Granule size (um)	P_y	D_o	D_o	D_B
Starch paste	5	95	125	0.42	0.28	0.14
	7.5	160	143	0.51	0.23	0.28
	10	170	-	-	-	-
PVP	5	80	167	0.64	0.29	0.35
	7.5	85	200	0.63	0.31	0.32
	10	90	111	0.67	0.29	0.38
Na-alginate	5	130	125	0.71	0.27	0.44
	7.5	240	167	0.68	0.27	0.41
	10	250	125	0.71	0.26	0.34
Gelatin	5	90	143	0.66	0.32	0.34
	7.5	95	200	0.62	0.31	0.31
	10	140	83	0.49	0.33	0.16

Table 2: Granule size and Heckel constants for formulations with Aerosil as diluent

Binder type	Conc.(%)	Granule size (um)	P_y	D_o	D_o	D_B
PVP	5	200	100	0.61	0.39	0.22
	7.5	165	250	0.59	0.34	0.25
	10	90	83	0.54	0.39	0.15
Na-alginate	5	260	250	0.51	0.34	0.17
	7.5	275	200	0.66	0.43	0.23
	10	195	143	0.61	0.45	0.16
Gelatin	5	180	167	0.53	0.32	0.21
	7.5	200	333	0.53	0.31	0.22
	10	220	500	0.42	0.25	0.17

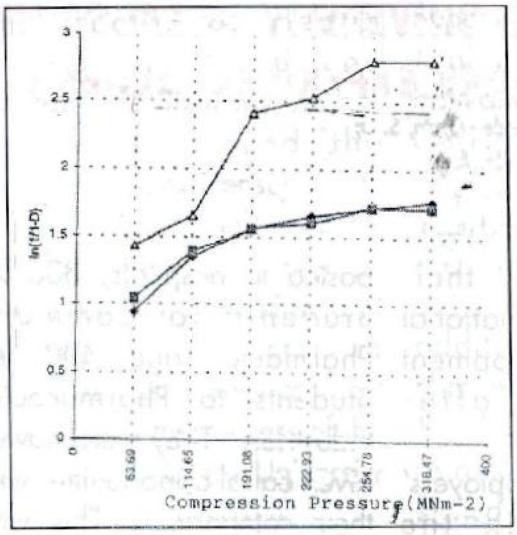
TITLES OF FIGURES

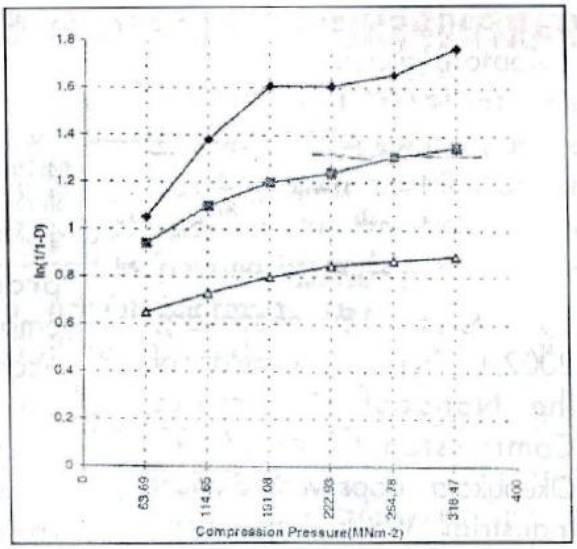
Fig. 1. Heckel plots of $MgCO_3$/Starch Compacts.

Fig. 2. Heckel Plots of Aerosil/Gelatin Compacts.

Keys for Figs 1 and 2

- 5% starch paste or gelatin as binder
- 7.5% starch paste or gelatin as binder
- 10% starch paste or gelatin as binder





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