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Original Article

COMPRESSIONAL PROPERTIES OF METRONIDAZOLE TABLET FORMULATIONS CONTAINING ALOE VERA AS BINDING AGENT

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ABSTRACT

The purpose of the present work was to determine the compressional characteristics of metronidazole tablet containing Aloe vera as a binding agent. Metronidazole tablet formulations were prepared using Aloe vera mucilage as a binder at different concentrations (1-5%w/w) and this was compared with formulations containing polyvinyl pyrrolidone (PVP) as a standard. The tablet properties were assessed using friability, crushing strength and disintegration time while compressional characteristics were analysed using density measurements, Heckel and Kawakita equations. The tablet properties conformed to the Pharmacopoeia standards. Tablets formulated with PVP were generally stronger than tablets made from Aloe Vera. All the batches passed the friability tests and the percentage friability decreased with increase in binder concentration. Formulations containing Aloe Vera disintegrated faster than those containing PVP. Tablets containing Aloe Vera exhibited a faster onset of plastic deformation during compression as indicated by the low $P_y$values and a lower degree of total plastic deformation. Results suggest that Aloe Vera could be a useful binding agent in pharmaceutical formulations.

Keywords: Aloe vera, Binding agent, Compressional characteristics, Tablets.

INTRODUCTION

Binding agents are used to impart the structural strength required during the processing, handling and packing of tablets, as well as to improve the free flowing quality of the granules [1]. Gums from natural sources have been used as binders in tablet formulations. Such gums include *Terminalia randii* gum [2], *Khaya* gum [3], *Magnifera indica* gum [4]. Natural gums are being used because they are economical, readily available. Non-toxic and they are biodegradable.

Aloe Vera belongs to the Aloe genus of herbaceous, shrubby evergreen perennial xerophytic succulents of the family *Liliaceae.* The leaves are thick and fleshy, green to grey-green, with some varieties showing white flecks on the upper and lower stem surfaces from centuries Aloe Vera has been used for healing cuts and bruises. Total skin care and curing topical sores of the diabetic patient is the main use of Aloe Vera. From literature, Aloe vera mucilage has been investigated as a binder in tablet formulation [5] but no work has been done on the compressional characteristics.

In this present work, the compressional characteristics of Aloe vera mucilage in metronidazole tablet formulations in comparison with polyvinyl pyrrolidone (Mol. Wt 58,000) will be studied using density measurements, Heckel and Kawakita equations [6,7]. The Heckel equation is widely used for relating the relative density, D, of a powder bed during compression to the applied pressure, P. It is written as

$$\text{Ln } 1/(1-\text{D}) = \text{kP} + \text{A} \ldots\ldots\ldots (1)$$

Plotting the value of ln [1/ (1-D)] against applied pressure P, yields a linear graph having slope, K and intercept, A. The reciprocal of K yields a material dependent constant known as mean yield pressure [8,9]. From the value of A, the relative density, D_A, can be calculated using the following equation[10]:

$$\text{D}_\text{A} = 1 - \text{e}^{-\text{A}} \ldots\ldots\ldots\ldots (2)$$

The relative density of the powder bed at the point when the applied pressure equals zero, D_O, is used to describe the initial rearrangement phase of densification as a result of the die filling. The relative density of the powder at low pressures D_B, describes that phase of rearrangement of particles during initial stages of compression and it is the difference between D_A and D_O.

$$\text{D}_\text{B} = \text{D}_\text{A} - \text{D}_\text{O} \ldots\ldots\ldots\ldots (3)$$

The Kawakita equation was developed to study powder compression using the degree of volume reduction (C) under pressure and is expressed as:

$$\text{C} = (\text{V}_\text{O} - \text{V}_\text{p})/\text{V}_0 = \text{abP}/(1+\text{bP}) \ldots\ldots\ldots (4)$$

In practice, this equation can be simplified to give

$$\text{P}/\text{C} = \text{P}/\text{a} + 1/\text{ab}. \ldots\ldots\ldots\ldots (5)$$

V_O is the initial volume of the powder bed and V_P is the powder volume after compression. The constant **a** is equal to the minimum porosity of the bed prior to compression while **b** is related to the plasticity of the material. The reciprocal of **b** yields a pressure term, $_{PK,}$ which is the pressure, required to reduce the powder bed by 50% [11, 12, 13]. Both the Heckel and Kawakita plots have their limitations and are believed to exhibit linearity at high and low pressures respectively [14]. Therefore, the use of these two equations would provide more accurate information about the effects of Aloe vera gum binder on the compressional characteristics of metronidazole formulation.

Metronidazole on its own has poor compressibility and its directly compressed products tend to cap and laminate. It is therefore essential to incorporate certain excipients to modify its compressibility, which justifies the selection in this study.

MATERIALS AND METHODS

Materials

Metronidazole BP, Corn Starch B. P., Polyvinyl pyrollidone (molecular weight 58 000; ISP Technologies Inc, Wayne, USA), Lactose B. P. (DVM Veghel, Holland), Magnesium stearate (Loba Chemie Pvt Limited, Mumbai, India). Aloe Vera mucilage was prepared in the laboratory of Olabisi Onabanjo University. All other materials were analytical grades.

Methods

Extraction of aloe vera mucilage

Fresh leaves of *Aloe barbadensis* were harvested and properly identified. The inner mucilage was obtained by cutting open the leaves and excess water was removed through straining and the

resulting slake was washed in acetone. It was then soaked in diethyl ether to precipitate the gum. The gum was spread to allow the evaporation of the diethyl ether and then finally dried for two hours using an oven at 40°C. The dried gum was pulverized and passed through a number 60mesh. (250µm) [5].

Preparation of metronidazole granules

100g batch size of basic formulation containing 60% w/w metronidazole, 30% lactose and 10% corn starch were used. Each ingredient was passed through 250µm sieves before dry mixing for 5 minutes in a planetary mixer. It was then moistened with an appropriate amount of distilled water or PVP and Aloe Vera solution at appropriate concentrations (1-5%). Massing was continued for 5 minutes and the mass was passed through a mesh size 1400µm to produce granules which were dried in hot air oven at 60°C for 2 hours. The dried granules were then dry screened with a sieve mesh 1000µm and the granules obtained were kept in air tight containers for further use. Particle densities of the granules were determined by the pycnometer method using xylene as the displacement fluid.

Determination of precompression density

The bulk density of each formulation at zero pressure (loose density) was determined by pouring the granules at an angle of 45^0 through a funnel into a glass measuring cylinder with an internal diameter of 21 mm and a volume of 50 ml[15]. Determinations were done in triplicate. The relative density of each formulation was obtained from the ratio of its loose density to its particle density

Determination of granule flow rate.

10g of the granules were passed through a cylindrical funnel with a large stem. The funnel was clamped on a retort stand and the time of flow in seconds through the orifice was taken. The flow rate is the ratio weight of the granules to the time taken to pass through the orifice. Determinations were done in triplicate.

Determination of angle of repose

The angle of repose was determined by the fixed funnel method. The granules after being accurately weighed were taken in a funnel and allowed to flow through the funnel under the force of gravity to form a conical heap. The angle of repose was calculated using the following equation

$$\tan\theta = h/r. \ldots\ldots\ldots\ldots (6)$$

Where θ is the angle of repose, h is height of the heap of the powder and r is the radius of the base of the heap formed by the powder

Preparation of tablets

400 mg of metronidazole granules was compressed for 30 seconds into tablets with predetermined loads on a Carver hydraulic press (Model C, Carver Inc. Wisconsin, USA), using a 10.5 mm die and flat faced punches lubricated with a 1 % dispersion of magnesium stearate in acetone prior to compression.

After ejection, the tablets were stored over silica gel for 24 hour to allow for elastic recovery and hardening. The weights (w) and dimensions of the tablets were measured to within ± 1mg and ± 0.01 mm respectively, and their relative density D was calculated using the equation:

$$D = w/v_t\rho_s. \ldots\ldots\ldots\ldots\ldots (7)$$

Where V_t is the volume, cm^3, of the tablet and ρ_s, is the particle density, gcm^{-3}, of the gum powder.

Table 1: Granule properties

Binder	Conc. Of binder (%w/w)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's index (%)	Hausner's Ratio	Particle Density	Angle of repose (◦)	Flow rate (g/sec)	Granule size µm
Control	0%	0.47±0.01	0.50±0.01	5.67±0.06	1.06±0.00	1.524±0.00	30.84±0.06	3.50±0.07	350
PVP	1%	0.44±0.00	0.47±0.01	6.67± 1.15	1.07±0.02	1.439±0.01	30.30±0.14	2.92±0.02	560
	2%	0.48±0.01	0.50±0.01	4.33± 2.08	1.04±0.02	1.467±0.00	30.44±0.14	3.13±0.02	680
	4%	0.49±0.01	0.52±0.02	5.00±4.00	1.05±0.04	1.340±0.01	32.93±0.10	2.94±0.02	720
	5%	0.43±0.01	0.46±0.02	5.33± 3.06	1.06±0.03	1.691±0.00	31.45±0.06	2.94±0.02	800
ALOEVERA	1%	0.46±0.02	0.49±0.01	4.33±3.51	1.07±0.04	1.430±0.00	31.00±0.10	3.02±0.02	690
	2%	0.45±0.01	0.48±0.01	4.33±3.51	1.08±0.04	1.441±0.00	30.54±0.06	2.82±0.03	770
	4%	0.43±0.01	0.47±0.01	6.67±1.15	1.07±0.02	1.420±0.00	30.11±0.09	2.04±0.01	920
	5%	0.41±0.01	0.44±0.01	4.67±1.15	1.05±0.02	1.376±0.00	28.85±0.05	1.53±0.01	990

Table 2: Tablet Prperties

Binder	Conc. of binders (%w/w)	Crushing strength (N)	Friability (%)	Disintegration (mins)
Control	0%	9.54±6.09	0.85±0.03	0.010± 0.00
PVP	1%	35.94±14.28	0.64±0.01	0.107±0.44
	2%	48.62±6.51	0.59±0.02	0.216±0.02
	4%	137.32±8.03	0.51±0.02	0.247±0.03
ALOEVERA	1%	12.96±4.22	0.77±0.01	0.015±0.00
	2 %	21.82±6.52	0.60±0.00	0.840± 0.46
	4 %	42.18±21.32	0.52±0.05	0.231±0.02
	5%	42.38±7.69	0.40±0.01	0.225±0.02

Table 3: Parameters derived from density measurements and Heckle plot

Binder	Concentration	D_0	Py	D_A	D_B
PVP	1%	0.306	500.0	0.762	0.547
	2%	0.327	200.0	0.737	0.409
	4%	0.366	333.3	0.791	0.425
	5%	0.254	1000.0	0.686	0.432
ALOE	1%	0.322	500.0	0.768	0.446
	2%	0.312	1000.0	0.768	0.455
	4%	0.303	200.0	0.724	0.421
	5%	0.298	166.6	0.744	0.446

Table 4: Parameters obtained from Kawakita plots

Binder	Concentration	*a*	$D_1 (1 - a)$	*b*	P_k
PVP	1%	0.991	0.009	204.08	0.005
	2%	0.990	0.010	71.94	0.014
	4%	0.989	0.011	78.12	0.013
	5%	0.992	0.008	22.42	0.045
ALOEVERA	1%	0.991	0.009	112.36	0.009
	2%	0.991	0.009	67.57	0.015
	4%	0.992	0.008	20.12	0.050
	5%	0.992	0.008	28.01	0.036

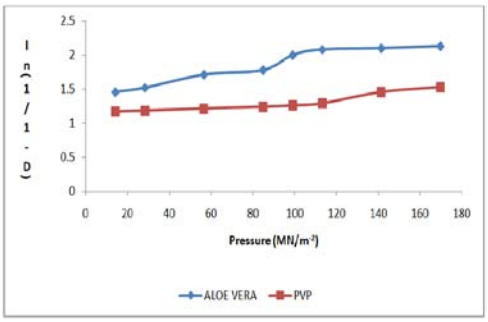

Fig. 1: Heckel plot of metronidazole tablets at 5% w/w concentration

Evaluation of tablet properties

Determination of tablet crushing strength

This was determined by measuring the force required to fracture tablet by diametrical compression on a manual hardness tester. Five tablets were tested from each batch of tablets, which were placed between the anvil and a force generated through the spring was applied by turning the screw. The force was measured in Newtons and the average force was calculated.

Determination of tablet friability

20 tablets from each batch were weighed and subjected to the tumbling action of a friabilator at the rate of 25rpm for 4 minutes. The intact tablets were dusted and re-weighed. The result was expressed as a percentage weight loss by using the formula:

Determination of tablet disintegration time

This was carried out using DBK tablet disintegration test apparatus, DBK instruments, England; containing distilled water as disintegration medium maintained thermostatically at a constant temperature of 37±0.5C. The time taken for five tablets to completely disintegrate was recorded and the mean disintegration time was calculated.

RESULTS AND DISCUSSION

Granule Properties

The result of the granule properties are presented in Table 1. The bulk and tapped densities of the granules of both binders increased with increase in binder concentration. The low densities result when void spaces created by larger powder particles are not filled by smaller particles leading to consolidation of the powder particles [16]. This explains that granules containing Aloe Vera is not as porous as PVP. The lower the Carr's index of a material, the better the flowability and the poorer the compressibility of the material. The compressibility index of granules prepared with both Aloe Vera and PVP was < 15% for all the batches, which indicates good to excellent flow properties [17]. The flow rates were observed to be comparable although there was a decrease in flow rate with increasing binder concentration. This could be as a result of increased bonding and cohesiveness between particles leading to reduction in the flow of granules [18]. Aloe Vera caused a decrease in flow rate of metronidazole granules with increase in concentration compared to PVP, indicating a better flow property than PVP. The results of the physicochemical properties of the various batches of metronidazole tablets are presented in Table 2, all batches showed acceptable uniformity of weight as none had percent deviation in weight > 5% as stipulated by the British Pharmacopoeia [19]. The significance of this test is to ensure that the tablets in each lot are within the appropriate size range.

Crushing strength and friability

The mechanical properties of the tablets are indicators of the ability of the tablets to withstand the rigors involved in manufacture, transportation, dispensing and usage. Two important parameters used to quantify the mechanical properties of tablets are crushing strength and friability. The crushing strength of the tablet increased as the concentration of binder increased. Binders promote plastic deformation of particles and thereby increase the area of contact for inter-particulate bonding [20], subsequently leading to the formation of more solid bonds in the tablet. The crushing strength of the tablets is measured because tablets need sufficient mechanical resistance to withstand stresses and strains of transportation and storage. It is an essential criterion in the determination of the ability of the tablets to resist chipping, abrasion or breakage under conditions of storage, transportation and handling before storage. Crushing strength was observed to be higher with PVP at all the concentrations employed compared to those formulations containing Aloe Vera. This indicates that tablets made from PVP had stronger bonds than those produced with Aloe Vera. Another tablet property related to crushing strength is friability, which is designed to evaluate the ability of the tablet to withstand abrasion during packaging, handling and shipping. For compressed tablets, percentage loss in weight of ≤1% is acceptable [19]. From the results, all the batches passed the friability tests. The percentage friability however decreased with increase in binder concentration. Formulations with PVP had lower friability valuesand this correlates with the result of the crushing strength.

Disintegration time

The disintegration time increased with increase in increase in binder concentration for both binder formulations. Formulations with PVP had a higher disintegration time compared with that of Aloe Vera. This can be attributed to the high crushing strength exhibited by tablet formulations with PVP.

Compression characteristics

The compressional characteristics of the binders were evaluated using the Heckel and Kawakita plots. Each of the plots is known to have its limitations. Heckel plots exhibits linearity at high pressures while Kawakita exhibits linearity at low pressures [14, 21]

Heckel plots for the formulation at 5% w/w concentration are shown in Fig 1, while values obtained from the Heckel plot are presented in Table 3. D_0 value represents the degree of initial packing in the die as a result of die filling. Formulations containing PVP binder had the highest D_0 values; formulations containing Aloe Vera had the lowest. This result indicates that formulations containing PVP exhibited the higher degree of packing in the die. The Db value represents the particle rearrangement phase in the early compression stages and tends to indicate the extent of particle or granule fragmentation, although fragmentation can occur concurrently with plastic and elastic deformation of constituent

particles. Values D_B were also observed to be higher than the values of D_i which have been described as the packed initial relative density of the formulations. Thus representing the closest possible packing of the formulations before fragmentation. These two parameters are influenced by the particle size and size distribution, particle shape, and surface properties such as electrostatic charge which influence the particle-particle attraction [17].

A faster degree of plastic deformation is reflected by a low P_y value in a general sense. The mean yield pressure, P_y, is inversely related to the formulations ability to deform plastically under pressure. The $P_y$values decreased with an increase in the binder concentrations. Formulations containing PVP generally exhibited higher P_y values than those containing Aloe Vera. This result indicates that formulations containing Aloe Vera as a binder exhibited faster onset of plastic deformation during compression.

The Kawakita plots of the tablets are presented in Fig.2. A linear relationship was obtained at all compression pressures with a linear correlation coefficient of 0.999 for both binders. The values obtained from the Kawakita plots are presented in Table 4. Values of *a* and *ab* were obtained from the slope and intercept of the plots, respectively. Values of $1 - a$ yield the initial relative density of the binders (D_I) while $P_k$values were obtained from the reciprocal of *b.* The D_I values, which is a measurement of the packed initial relative density of the binders generally decreased as the concentration of binders increased.

The value of P_k provides an inverse measurement of plastic deformation during the compression process. It has been established that the lower the $P_k$value, the more the total plastic deformation occurs during compression [21, 15] which leads to more contact points thus leading to high crushing strength. Formulations containing PVP gave lower P_k values and higher crushing strength.

Although formulations containing Aloe Vera exhibited a faster onset of plastic deformation during compression as indicated by the low $P_y$values, they also exhibited the lowest degree of plastic deformation during the compression process. On the other hand, formulations containing PVP exhibited a slower onset of plastic deformation but a higher amount of plastic deformation during compression. Thus, Aloe Vera will be more useful than PVP in a high-speed tablet machine.

CONCLUSION

The result of the study proves that Aloe Vera produces granules with better flow properties than PVP and exhibits lower degree of total plastic deformation during the compression. Therefore Aloe Vera would be more useful for minimizing the problems of lamination and capping especially on high-speed tableting machines. In addition, the mucilage of Aloe Vera can be used as a pharmaceutical excipient in the formulation and manufacture of pharmaceutical tablets because of its good physicochemical and compressional characteristics.

CONFLICT OF INTERESTS

Declared None

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