



EFFECT OF INCREASING CONCENTRATION OF ACACIA SIEBERIANA GUM ON BOTH MATRIX GRANULES AND TABLET PROPERTIES OF CHLOROQUINE PHOSPHATE AND METRONIDAZOLE TABLETS

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ABSTRACT

The effect of increasing concentrations of a locally sourced *A. sieberiana* gum on the granules and tablet properties of chloroquine and metronidazole tablets was investigated in the gum matrix formulation. Varying concentrations 10-60%w/v of *A. sieberiana* gum composition in the tablet formulation was evaluated. Matrix tablets were formulated via the wet granulation method with 5%w/v maize starch mucilage as binder and at compression pressure of $3.5 \times 10^5 \text{ N/m}^2$. Mean granule size was greater than $500\mu\text{m}$. Flow properties of granules were optimal with average of 4.1g/sec for chloroquine phosphate matrix and 3.5g/sec for metronidazole matrix. Tablets prepared revealed that 50%w/w composition of gum produced the best quality in terms physico mechanical properties base friability, crushing strength and weight variation. Dissolution rate studies revealed T 90% for metronidazole matrix tablet and chloroquine phosphate matrix tablet as 1hr 45min and 50 min respectively. The gum shows better retardant effect with metronidazole than chloroquine phosphate.

Keywords: *Acacia sieberiana* gum, Matrix granules, Matrix tablets

INTRODUCTION

Acacia gum is a hydrophilic polymer. Polymer is becoming more popular in tablet formulation in the area of matrix device. In recent time, pharmaceutical scientists have widened the search for acceptable excipient to the use of both hydrophilic and hydrophobic polymer to formulate a multiple layer matrix tablet whereby the outer layer is made up of hydrophilic polymer and the inner layer, hydrophobic polymer (Mohammad *et al.*, 2005). The

former is intended to release the embedded drug within the first few hours while the latter is formulated to sustain the release for longer period. In view of this, *Acacia sieberiana* gum is chosen as a hydrophilic polymer to investigate its possible use in matrix formulation. Recently, acrylamide was grafted onto acacia gum in different ratios (1:1, 1:3, and 1:5). The grafted copolymer prepared in the ratio 1:5 of acacia gum: acrylamide matrix was found to be

suitable matrix for control release of diltiazem hydrochloride and nifedipine. The drug release continued up to 6 and 14 h respectively, for diltiazem hydrochloride and nifedipine (Udaya, *et al.*, 2004). Shah *et al.*, (2009) employed xanthan and acacia gum in oral sustained release matrix tablets of water-insoluble drug, flurbiprofen. Both polymers were found to have significant effect on the drug release. Acacia gum is therefore gaining recognition in matrix formulation. In view of this; *A. sieberiana* is chosen to investigate its retardant effect. The method of wet granulation is considered for this research as granules tend to have a uniform distribution of all the ingredients in the formulation. The size and shape of the granules may also influence the tableting behaviour (Reipma *et al.*, 1993).

The aim of this research is to study the effect of increasing acacia gum concentration on physical properties of both granules and tablets using two drugs representing highly soluble and poorly soluble drugs and also to evaluate the extent of its retardant effect on drug release.

MATERIALS AND METHODS

Materials

Acacia sieberiana gum was obtained from Jigawa State Ministry of Agriculture and Forestry Dutse, crystalline α -lactose monohydrate B.P., (Veghel, Netherland), chloroquine phosphate B.P., metronidazole B.P. (Liaoyuama Pharm. China) and *Acacia senegal* (sigma, Germany).

METHODS

Purification of gum

The method of Karawya *et al.*, (1971) was adopted.

Particle separation

The U.S.P. (2003) standard method of sieve analysis was used. The set of sieves used were: 500, 250, 150, 125 and 90 μ m arranged in that order on an electric shaker, while 100g of the gum powder was placed on the 500 μ m sieve size. The sieves were shaken for 15 min. After which the portions retained on each sieve was collected. The portion retained on 90 μ m sieve represent >90 and 125 μ m particle size fraction etc.

Wet Granulation

Preparation of Starch paste (mucilage): Five grams (5g) of maize starch was weighed and 25ml of distilled water was added in a 250ml beaker. The mixture was stirred until a uniform suspension was formed. Seventy millilitres (70ml) of water was placed in a separate 250ml beaker and heated on hot plate until it boiled. The starch suspension was then added to the hot water and stirred vigorously with a glass rod until a translucent gel was formed and the weight made up to 100g with hot distilled water.

Preparation of granules

Table 1 illustrates the formula and the percentage composition of the granules. The wet granulation processes were carried out for the batches 1 to 6 comprising 60, 50, 40, 30, 20 and 10% w/w gum respectively. The model drugs for the two granulations are chloroquine phosphate and metronidazole. For batch 1, 20g of the chloroquine, was weighed and 30g of fine powder of gum (<90 μ m), both were mixed in an Erweka twin Z-blade mixer for 5 min.

The mixture was transferred into a mortar and the starch mucilage added little at a time while mixing with a pestle until a uniform semi-solid wetted mass (matrix) was obtained which easily balls in hand. The total mixing time was 3 min. these processes were repeated for batches 2 to 6, with lactose added to the mixture of chloroquine

phosphate and gum in amount indicated in Table 1. The whole procedure was repeated for metronidazole. For each batch of granulation, 10ml of the starch mucilage was expended. The amount of starch used was calculated (see Table 1). The resultant moist powder was passed through a 1500 μ m mesh.

Drying of granules

The granules were dried in a Gallenkamp hot air oven. The drying was carried out at 40^oc until a constant weight was obtained. The granules were passed through a 1000 μ m mesh and stored in desiccator at room temperature.

Evaluation of Granules

Size distribution: The following sets of sieves were arranged vertically in the following orders: 500, 250, 150, 125, and 90 μ m. The granules were subjected to size analysis. The sieves were arranged on an electric shaker, and 100g of the granules was placed on the 500 μ m sieve size. The sieves were shaken for 15 min, after which the sieves were dismantled the weight of powder retained by individual sieve was determined and the percentage calculated. The size distribution of the gum matrix granules was then established.

Microscopic Examination of Granules

Some granules were placed on a clean slide and examined under an electric microscope with magnification of x 40 and eye piece, 3.4.

Determination of Flow Rate and Angle of Repose

Angle of repose was determined by the method of Jones and Pilpel (1966).

$$\theta = \tan^{-1} (h/r) \dots\dots\dots (1)$$

The flow rates were determined with the aid of Erweka flowability tester (model GDT, Germany).

Bulk Density and Tapped Density

Bulk and tapped densities were determined by the method of Kumer and Kothan (1999). Sixty gram (60g) of the granules was weighed and transferred into a 100 ml measuring cylinder. The volume (V) was recorded as the bulk volume. The total weight of the powder and cylinder was noted. The bottom of the cylinder was raised about 10cm above the slab and made to fall on the platform continuously for 100 taps. The volume (V_t) of the granules was recorded.

Bulk volume is represented by 'V', while tapped volume is V_t.

$$\text{Bulk density (D}_s\text{)} = \text{Mass/ V} \dots\dots\dots (2)$$

$$\text{Tapped density (D}_t\text{)} = \text{Mass/ V}_t \dots\dots\dots (3)$$

Carr's Index

The ability of the granules to undergo volume reduction (densification) was derived from the following equation.

$$\text{CI (\%)} = 100 (V - V_t) / V = 100 (D_B - D_T) / D_B \dots\dots (4)$$

Compaction of granules

The granules produced were used to formulate chloroquine phosphate and metronidazole gum matrix tablets. The tablets were compacted in a single punch machine (Erweka, AR 400, Germany) at 505mg using 12 mm diameter flat faced punch using various granules containing different gum concentration. Both the die and punches were lubricated with magnesium stearate. The tablets were compressed using 4KN compression force for both drugs.

Evaluation of Tablets

Weight variation Limit Test

The weights of 10 tablets were determined individually and collectively on a Metler balance (Denver, XP – 300, U.S.A). The mean weight, percentage (%) deviation from the mean and standard deviation were calculated.

Thickness of Tablets

The thickness of the tablets was measured with the aid of micrometer screw gauge. Five tablets were selected randomly and the thickness for each was measured and the mean value determined.

Hardness of tablets

The hardness of the tablets was determined as the crushing strength with the aid of a mansanto Hardness tester.

Friability

The friability test was performed for the tablets formulated in a friabilator (Erweka, TA 3R). The weight of 10 tablets was determined on a Metler balance (Denver, XP – 300, U.S.A). The tablets were placed in the friability and set to rotate at 25 r.p.m for 5min after which the tablets were de-dusted gently and their weight determined. The difference was calculated and the percentage loss in weight and hence the value of the friability was calculated.

Radial Tensile Strength

Tensile strength of tablets was calculated according to fell and Newton equation (Fell and Newton, 1970).

$$T_s = 2 C_s / \pi DH \text{-----} (5)$$

Where T_s (MPa) or (N/M²) is the tensile strength; C_s is the crushing strength; D is the diameter of the tablet (m) and H, the thickness of the tablet (m).

In-Vitro Drug Release Studies

Drug release from various tablets was determined using the paddle method of the U.S.P XXIII dissolution apparatus (model AT7 CH 4008, Sotax, Basel, Switzerland). The tests were conducted in 900ml 0.1N HCl medium maintained at $37 \pm 0.5^\circ\text{C}$ at a paddle rotation speed of 100 rpm. Ten millilitres (10 ml) of the sample were taken at regular intervals and analysed for chloroquine phosphate in one experiment and metronidazole in another experiment. A 10ml of filtered fresh dissolution medium was added to make up the volume after each sample withdrawal.

The drug concentrations in the samples were analysed using a UV spectrophotometer (160 A, Shimader, Japan) at 342nm for chloroquine phosphate and 277nm for metronidazole.

RESULTS

Microscopic examination of the granules revealed irregular shape, non-porous granules, irrespective of the gum concentrations.

Granule size analysis

The chloroquine phosphate matrix granules were characterized by higher percentage of >500 μm granules, ranging from 56% to 75% for the batches 1 to 6; followed by >250 – 500 μm granules, ranging from 10% to 20% for the same set of batches (fig. 1-5). The other granules sizes made up the remaining percentage. Similar results were obtained for the metronidazole matrix granules. The granule size of >500 μm ranged from 65 % to 87.9 % for the batches 1 to 6, followed by >250 – 500 μm , constituting from 1.5% to 12% for batches 1 to 6 (fig. 1-5). The granules of chloroquine phosphate matrix for both *A. sieberiana* and *S. senegalensis* showed increase in bigger

granules with decrease in concentration of the gum, while that of metronidazole showed slight reduction in bigger granules with decrease in concentration of the gum. The granules were irregular in shape and locked non-porous, and the means granule size is greater than 500 μm for all the batches or both chloroquine phosphate and metronidazole matrices.

Characteristics of granules

The results of the characteristics of the chloroquine phosphate matrix granules and

metronidazole matrix granules are as shown in Table 2. The table shows that the metronidazole granules had lower angle of repose than the chloroquine phosphate granules as an expression of better flow for the former than the latter. The compressibility index value for the metronidazole matrix is a little higher than that of chloroquine phosphate matrix. This result reflects higher densification index for the former than the later.

Table 1: Composition of matrix tablets of chloroquine phosphate and metronidazole, each weighing 505mg

	Batches					
	1	2	3	4	5	6
Drug (g)	20	20	20	20	20	20
Gum (g)	30	25	20	15	10	5
Lactose (g)	0	5	10	15	20	25
Starch[(5%w/v) binder]	0.50	0.50	0.50	0.50	0.50	0.50
Total (g)	50.50	50.50	50.50	50.50	50.50	50.5

The total weight was given for 100 tablets.

Fig.1: Drug release from matrices of metronidazole (metr-matr), chloroquine phosphate (chlor-matr), while chlor-matr –R' denote matrix of *A. senegalensis*.

Table 2: Effect of gum concentration on granule properties of chloroquine phosphate and metronidazole matrices.

Batch	Purified gum % w/w	Flow rate g/sec (n=3)	Angle of repose (n=3) degree	Bulk density g/cm ³	Tapped density g/cm ³	Carr's index %
1	60	(a) 4.194	29.8	0.699	0.839	16.7
		4.20	28.0 ^R	0.690 ^R	0.826 ^R	19.7 ^R
		b) 3.28	24.0	0.656	0.820	20.0
2	50	(a) 4.08	29.5	0.636	0.781	18.6
		4.13 ^R	28.5 ^R	0.650 ^R	0.758 ^R	16.6
		(b) 3.63	22.6	0.630	0.844	25.4
3	40	(a) 4.49	29.2	0.641	0.816	21.5

		4.36	28.8 ^R	0.563 ^R	0.752 ^R	15.0 ^R
		(b) 3.66	23.4	0.600	0.819	19.4
4	30	(a) 3.99	29.2	0.655	0.814	19.4
		4.06 ^R	29.0 ^R	0.652 ^R	0.762 ^R	16.9 ^R
		(b) 3.69	24.0	0.673	0.816	22.2
5	20	(a) 4.04	24.4	0.766	0.831	7.8
		4.02 ^R	26.5	0.754 ^R	0.831 ^R	10.2 ^R
		(b) 3.70	26.6	0.651	0.816	20.2
6	10	(a) 3.76	27.3	0.700	0.770	9.1
		3.97 ^R	28.0 ^R	0.710	0.754	6.2 ^R
		(b) 3.24	24.8	0.466	0.514	9.3

Values designated by 'a' and 'b' represent values for chloroquine phosphate and metronidazole matrix tablets respectively. While values with the superscript "R" denote values for the *A. senegalensis* chloroquine phosphate matrix tablets.

Drug release from the matrices

The percentage (%) drug release with time from matrix tablets containing 60% gum is illustrated in Fig. 6. The T_{90%} for metronidazole matrix tablet was found to be 1hr 45min, while the values for chloroquine

matrix tablets of *A. sieberiana* and *A. senegalensis* were found to be 50 min and 60 min respectively. Drug release from the matrix containing insoluble drug was found to be slower than that of soluble drug.

Table 3: Effect of gum concentration on tablet properties of chloroquine phosphate and metronidazole both compacted at 4KN. Weight of each tablet was 505mg.

Batch	Gum content (%w/w)	Average tablet thickness (cm) n=5	Average crushing strength (N) n=5	Radial tensile strength $\times 10^5$ N/m ²	Friability (%)	Mean weight $\pm$ SD (mg)
1	60	(a) 0.418	125	15.2	0.65	504.5 $\pm$ 1.0
		0.415 ^R	125 ^R	15.9	0.50 ^R	504.6 $\pm$ 1.6 ^R
		(b) 0.414	135	17.3	0.00	504.3 $\pm$ 1.3
2	50	(a) 0.414	150	19.4	0.64	504.6 $\pm$ 2.5
		0.410 ^R	152 ^R	19.7 ^R	0.64 ^R	504.3 $\pm$ 2.8 ^R
		(b) 0.408	145	18.9	0.65	503.7 $\pm$ 2.3
3	40	(a) 0.405	145	19.0	0.65	503.9 $\pm$ 0.5
		0.404 ^R	145 ^R	19.1	0.50 ^R	503.5 $\pm$ 0.8 ^R
		(b) 0.407	130	17.0	0.65	503.7 $\pm$ 1.6

4	30	(a) 0.402	140	18.5	0.66	503.2 ±1.5
		0.400	145 ^R	19.2	0.60 ^R	504.5±1.2 ^R
		(b) 0.402	120	15.8	1.25	504.7±1.7
5	20	(a) 0.402	130	17.0	0.65	501.0 ±0.2
		0.401 ^R	133 ^R	17.6	0.70	503.2±0.8 ^R
		(b) 0.410	100	12.9	1.28	503.7±2.3
6	10	(a) 0.405	128	16.0	0.71	501.0 ±0.2
		0.403	130 ^R	17.1	0.70 ^R	502.5±1.8 ^R
		(b) 0.481	70	7.7	1.31	502.0±1.0

Values designated by 'a' and 'b' represent values for chloroquine phosphate and metronidazole matrix tablets respectively. While values with the superscript "R" denote values for the *A. senegalensis* chloroquine phosphate matrix tablets.

DISCUSSION AND CONCLUSION

The physico – mechanical properties of the granules are listed in Table 2. The angle of repose of a powder provides an insight into the magnitude of cohesiveness of the powder or granules, i.e., flowability (Carl, *et al*, 1981; Paronen *et al* 1984). The angle of repose value (all under 30°) indicated that all studied granules are freely flowing (Table 2). While angle of repose containing *A. senegalensis* gum for chloroquine formulae are in the range of 28° to 29°, for formulae containing 30 to 60 %, those of metronidazole formulae range from 23° to 26° for the same gum contents. It could be inferred that, metronidazole matrix granules been less cohesive has superior flow property (Standard value is 25°).

Volume reduction is favoured by plastic deformation and or fragmentation of the granules (Train, 1956). Microscopical examination of the granules revealed irregular shape which favoured mechanical interlocking (hooking and twisting) of particles in bond formation during compaction (Fuherer, 1977). The compressibility index values for metronidazole matrices are a little higher

than that of chloroquine matrices indicating a better densification for the latter than the former.

The granules of both soluble and insoluble drug matrix were compacted at 4KN (3.5 x 10⁵ N/m²). It was observed that, the compact radial tensile strength increased with increase in concentration of gum for both chloroquine and metronidazole matrix tablets, with the former drug forming stronger than the later drug with the gum.

Table 3 shows that, compactness of matrix tablets (measured as radial tensile strength) followed a declining trend from higher to lower concentration of gum with an exceptional observation between tablets of batch 1 containing 60% gum without lactose and batch 2 containing 50% gum and 10% lactose. The tablets of former batch have an average tensile strength of 17.3 x 10⁵ N/m², while those of the later batch have an average tensile strength of 18.9 x 10⁵ N/m². The increase in strength for the batch was attributed to the introduction of additional bonds as a result of the presence of lactose. According to: Rumpf, (1962); Nystrom *et al*, (1982); Leuemberger, (1982); Duberg and Nystrom, (1985), the strength of a tablet is a

reflection of total number of bonds present in that tablet. In absence of lactose the mechanical strength of insoluble drug matrix tablets ($17.3 \times 10^5 \text{ N/m}^2$) was found to be higher than of soluble drug matrix tablets ($15.2 \times 10^4 \text{ N/m}^2$) (see batch containing 60% gum). The tablets of metronidazole become more friable as the gum content reduces from 60 % to 10 % as shown by friability results ranging from 0.00 to 1.31 % (Table 3). For chloroquine phosphate tablets, friability results range from 0.64 to 0.70%. All batches of chloroquine matrix tablets passed the test (<1.0%) while batches containing 40% to 60% gum in metronidazole matrix tablets passed the test, hence the effect of varying the percentage of the gum is more pronounced on the mechanical strengths of insoluble drug than on highly soluble drug.

Fig 1 shows the result of drug release from matrices of metronidazole and chloroquine phosphate containing 60% gum. The T90% for metronidazole matrix tablets and chloroquine matrix tablets were found to be 1hr 45min (105 min) and 50min respectively.

Acacia gum, preferably from 40 to 60% concentration can be employed in matrix formulation as drug release retardant.

In conclusion, *Acacia sieberiana* gum can be employed in the formulation of matrices preferably for poorly water-soluble drugs. This research revealed that, the higher the percentage of the gum content, the stronger the compact and less friable. Unmodified form of this gum can be used in multiple layer matrix tablet to convey the initial dose of poorly water soluble drugs.

REFERENCES

- Carl, L.F., Colombo, I., Simioni, L., and Bianchini, R., (1981). The effect of compression on the capillary microstructure of tablets. *J. Pharm. Pharmacol.* 35, 129-135.
- Duberg, M., and Nystrom, C. (1982). Evaluation of Method for the estimation of particle fragmentation during compaction. *Acta Pharm. Suec.* 19, 421-436.
- Duberg, M., and Nystrom, C. (1985). Consolidation and bonding properties of some pharmaceutical compounds and their mixtures with Avicel PH 105. *Int. J. Pharm. Tech. Prod. Mfr.* 6, 17-25.
- Fell, J.T., and Newton, J.M. (1970). Determination of tablet strength by diametral compression test. *J. Pharm. Sci.* 59, 688-691.
- Fuhrer, C. (1977). Substance behaviour in direct compression. *Labo-Pharma Probl. Tech.* 25, 759-762.
- Jones, T.M., and Pilpel, N., (1966). The flow properties of granular magnesia. *J. Pharm. Pharmacol.* 1966; 18:81-93.
- Karayya, M.S., Balba, S.L., and Afofi M.S.A., (1971) Investigation of the carbohydrate contents of certain mucilaginous plants. *Planta medica* 20: 14-23.
- Kumer, V., and Kothan, S.H., (1999). Effect of compressional force on the crystallinity of directly compressible cellulose excipients. *Int. J. Pharm.* 177 (2) : 173-182.
- Leuenberger, H., (1982). The compressibility and compactibility of powders systems. *Int. J. Pharm.* 12, 41 -55.

Mohammad, R.S., Mohammad, B.J., Farnaz, M., Fatemeh, G., and Shirzad, A. (2005). Design and Evaluation of 1- and 3- Layer Matrices of Verapamil Hydrochloride for sustaining its release. *AAPS PharmSciTech*; 6 (4) Article 77.

Neumann, B.S., (1967). The flow properties of powders. In Bean, H.S., Bech, A.H., and Carless, J.E., (eds). *Advances in Pharmaceutical Sciences*, Academic Press, London and New York. Vol. 2, 181-221.

Nystrom, C., Mazur, J., and Sjogreen, J. (1982). Studies on direct compression of tablets II. The influence of the particle size of a dry binder on the mechanical strength of tablets. *In. J. Pharm.* 10, 209-218.

Paronen, P., Juslin, M., and Kasanen, K., (1984). Comparison of Xylan and some commercial materials as disintegrants in tablets. Book of proceedings 4th Pharm. Tech. Cont. Vol. 11, April 11th, 1984.

Reipma, K.A., Lerk, C.F, De Boer, A.H., Bolhuis, G.K., and Kussendrager, K.D. (1993). Consolidation and compaction of powder mixtures. *Int. j. Pharm.* 66, 47-52.

Rumpf, H., (1962). The strength of Granules and Agglomerations. In Knepper, W.E. (ed). *Agglomeration. Interscience Publisher, New York*, pp. 379-418.

Shah, S.N.H., Asghar, S., Choudhry, M.A., Akash, M.S.H., Rehman, N., and Baksh, S. (2009). Formulation and evaluation of natural gum-based sustained release matrix tablets of flurbiprofen using response surface methodology. *Drug Dev. Ind. Pharm.* 35(12):1470-1478.

Train, D. (1956). An Investigation into the compaction of powders. *J. Pharm. Pharmacol.* 8, 745-761.

Udaya, S. T., Kumares, S.S., Nadagouda, N.M., and Tejjraj, M.A. Acrylamide – grafted – acacia gum polymer matrix tablets as erosion – controlled drug delivery systems. *J. Appl. Polym. Sci.* 93; 5: 2245-2253

United State Pharmacopoeia XXIII, (2003). Drug Release. United State Pharmacopoeial Convention, Rockville, MD: 729 – 730