ORIGINAL ARTICLE

STUDIES ON THE COMPRESSIBILITY OF WAX MATRIX GRANULES OF ACETAMINOPHEN AND THEIR ADMIXTURES WITH VARIOUS TABLETING BASES

M.U. UHUMWANGHO* AND R.S. OKOR
Department of Pharmaceutics, University of Benin, Benin City, Nigeria

ABSTRACT
Matrix granules of acetaminophen have been formed by a melt granulation process whereby the acetaminophen powder was triturated with the melted wax - goat wax, glyceryl monostearate or carnuba wax. The compressibility of the matrix granules and their admixture, with diluent granules (lactose, α-cellulose or microcrystalline cellulose) was investigated. The granules were compressed to tablets at a constant load (30 arbitrary units on the load scale) of a manesty single punch machine. Resulting tablets were evaluated for tensile strength (T) and disintegration times (DT). Granule flow was determined by measuring their angle of repose when allowed to fall freely on a level surface. Matrix granules prepared by melt granulation with goat wax or glyceryl monostearate were too sticky and therefore did not flow at all. They were also poorly compressible (T values = 0.20MN/m^2). Inclusion of the diluent remarkably improved granule flow property and compressibility. The T values of the tablets (measure of compressibility) increased from about 0.24 to 0.65 MN/m^2 during increase in diluent (lactose) content from 20 to 80 %w/w. Microcrystalline cellulose and α-cellulose were more effective than lactose in promoting compressibility of the granules. By contrast the matrix granules formed with carnuba wax were free flowing (angle of repose, 18.6^0). Addition of the diluent further improved flowability slightly. The matrix granules (without a diluent) were readily compressible (T value, 1.79MN/m^2). Addition of the diluent (80%w/w) reduced T values (MN/m^2) slightly to 1.32 (lactose), 1.48 (α-cellulose) and 1.74 (microcrystalline cellulose). Tablets of the matrix granules only, disintegrated rapidly within 3minutes. DT was further reduced to ≤30s by addition of any of the diluents. The indication is that the inclusion of the diluents studied can be used to improve the compressibility of the otherwise poorly compressible matrix granules. Based on the flowability, compressibility, and disintegration data, carnuba wax proved most promising in the melt granulation of the test drug for sustained release applications.

Keywords: Matrix granules, compressibility, tensile strength, diluents, tablets, disintegration times.

**Corresponding author:* M.U. Uhumwangho, E-mails: mike2003u@yahoo.com

INTRODUCTION

Waxes are made up of a wide range of compounds such as glycerides, fatty acids, fatty alcohols and their esters. They are widely used as drug release retardants in the design of sustained release tablets, suspensions, beads, implants, and microcapsules. Carnuba wax, Bees-wax, ceresine, Microcrystalline wax, Precirol ATO5, and Gelucire 64/02 have been frequently explored for this application (Sariaya and Bolton 1990, Adeyeye and Price, 1991; Bodmeier *et al*., 1992, Remaman *et al*, 1992, Adeyeye and Price, 1994; Li *et al*., 2001). Floating systems which will improve retention of the lipid matrix in the gastric fluid were recently investigated (Kumar *et al*., 2003). The wax (glycerol monooleate) was found useful as the matrix-former in such formulations. Drug particles can be dispersed finely in a wax matrix by a process of melt granulation whereby the drug powder is triturated with the melted wax, followed by screening (Uhumwangho and Okor 2006), hence the term "wax matrix granules". Arising from the lipid nature of waxes, drug release from such wax matrix systems is usually retarded. An earlier study (Liu *et al*., 2001) showed that the extent of retardation can be varied by selection of type and content of wax in the matrix particles. Particles of different release profiles can be formulated in a multi-unit dosage form, either as capsules or tablets with the objective of optimizing drug release and to make the dose regimentation more convenient to the patient. Such a dosage form consists of particles of differing release profiles in one dose. In the case of multi-unit dose tablets, there is invariably the need to include a suitable diluent to prevent direct contact between the matrix particles and hence minimize their deformation during compression. Another urgent reason to include a diluent is to improve flow of the otherwise sticky matrix granules. A suitable diluent should therefore be readily compressible to form hard tablets which also disintegrate rapidly to yield the matrix drug particles intact (i.e. without alteration of their individual release properties prior to compression). The ultimate goal of the study is to develop multi-unit dose tablets consisting of these matrix granules of different release profiles in one dose. In the preliminary aspect of the study we investigated how the choice of type and content of the diluent may influence the compressibility of the matrix particles. Tablet tensile strength was taken as a measure of compressibility. Since rapid disintegration of the tablet to the primary particles is a basic requirement, tablet disintegration times were also measured.

MATERIALS AND METHODS

Materials

Goat wax (mp 58-60^{0}C) was extracted by heat expression from the adipose tissues in the peritoneum of a sacrificed he-goat (*Capra hircus*). The wax before now has no commercial value and hence is normally a reject. Details of the extraction method and purification have been described elsewhere (Okor, 1988). It is whitish in colour and consists mainly of triglycerides and cholesterol. The odorous fraction can be removed by heating under reflux at a high temperature (95^{0}C) for 1h. Carnuba wax (Halewood chemicals Ltd, England) is a fine waxy solid with melting point of 82-88^{0}C, yellowish in colour. Glyceryl monosterate (GMS, MGS-F 75, white to yellow beads, mp 62-64°C, HLB = 1.5, lot no. 2054) was kindly supplied by Nikko Chemical Co Ltd (Tokyo, Japan). Maize starch (BDH, Chemical, Poole, UK) was used as binder and as disintegrant (5%w/w). Magnesium stearate (Pharmaceutical grade BP) was used as lubricant at concentration of 0.5%w/w. Acetaminophen powder (BDH, Chemicals, Poole, UK) was the test drug. Lactose powder (Pharmaceutical grade BP), microcrystalline cellulose (FMC Corporation, Philadelphia, PA) and α-cellulose a fibrous powder obtained by alkali digestion process (Okhamafe *et al*., 1991; 1992) were the test diluents in the tablet formulations.

Methods

Melt granulation technique: The wax material (20g) was melted in a stainless steel container in a water bath at temperature higher than the melting point of the wax material (i.e. 90^{0}C). A sample of the acetaminophen powder (80g) was then added to the melted wax and mixed well with a glass rod, then allowed to cool to room temperature (range 26-30^{0}C). The mass was pressed through a sieve of mesh 10 (aperture size; 710μm). Granules of the diluents were produced by a wet granulation technique using starch mucilage (20%w/v) as binder. The wet mass was dried on a tray in a hot air oven (Kottermann, Germany) at 50^{0}C for 2hours. The granules produced by melt granulation technique were then admixed with granules of the diluents in different proportions as shown in table 1. The diluents were also granulated to prevent size separation during compression.

Table 1: Composition of matrix granule of acetaminophen and their admixtures with the diluent granules

Wax/Drug (1:4) matrix granules (g)	Diluent (g)	Proportion of diluent (%)
100	0	0
80	20	20
60	40	40
50	50	50
40	60	60
20	80	80

Note: The amount of drug in each admixture was therefore 80%w/w of the matrix granules.

Flow property of granules: The flowability of the granules was determined by measuring the angle of repose formed when a sample of the granules (40g) was allowed to fall

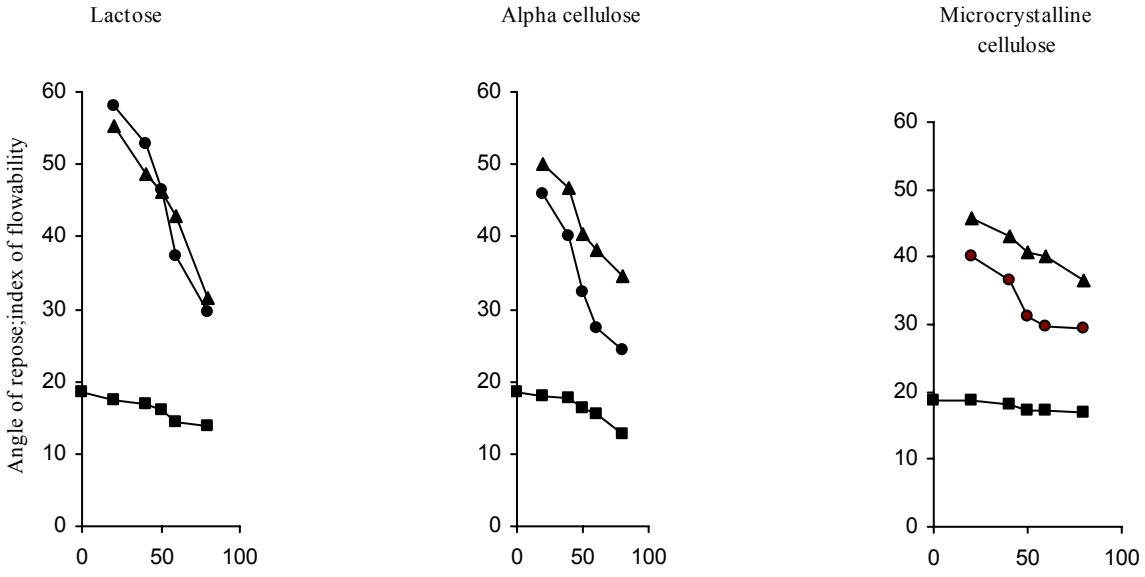

Fig. 1: Effect of diluent type and concentration on the flowability of the matrix granules prepared with goat wax (●), carnuba wax (■), glyceryl monostearate (▲).

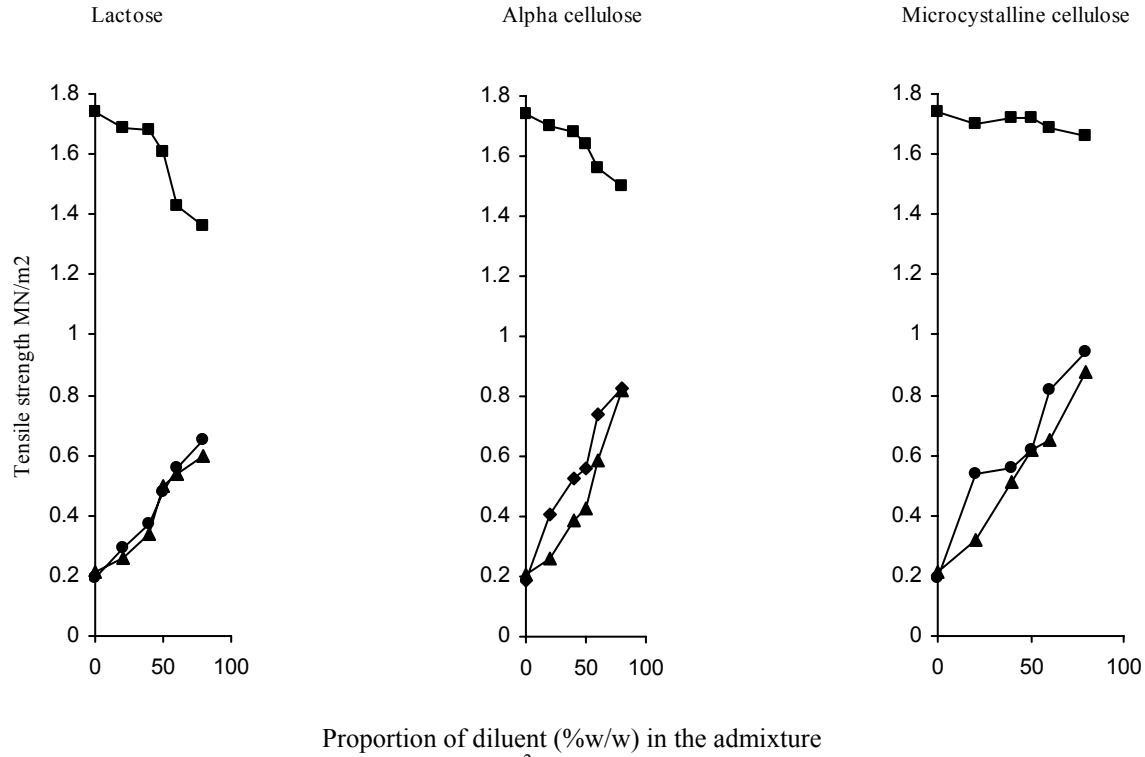

Fig 2: Effect of diluent type on tensile strength (MN/m^2) of acetaminophen tablets when admixed with granules of goat wax (●), carnuba wax (■), glyceryl monostearate (▲).

freely from the stem of a funnel to a horizontal bench surface (Richards, 1972). The radius (r) and the height (H) of the powder heap was then determined. The angle of repose (θ) was calculated using the expression:

$\theta = \arctan H/r$ (1)

Tableting: The granules or their admixtures with the different diluents were compressed using a single punch tableting machine (Manesty Type F_3, Liver Poole, England) at constant load (30 arbitrary units on the load scale) to form flat faced tablets of diameter 12.5mm, thickness, 3.36mm,

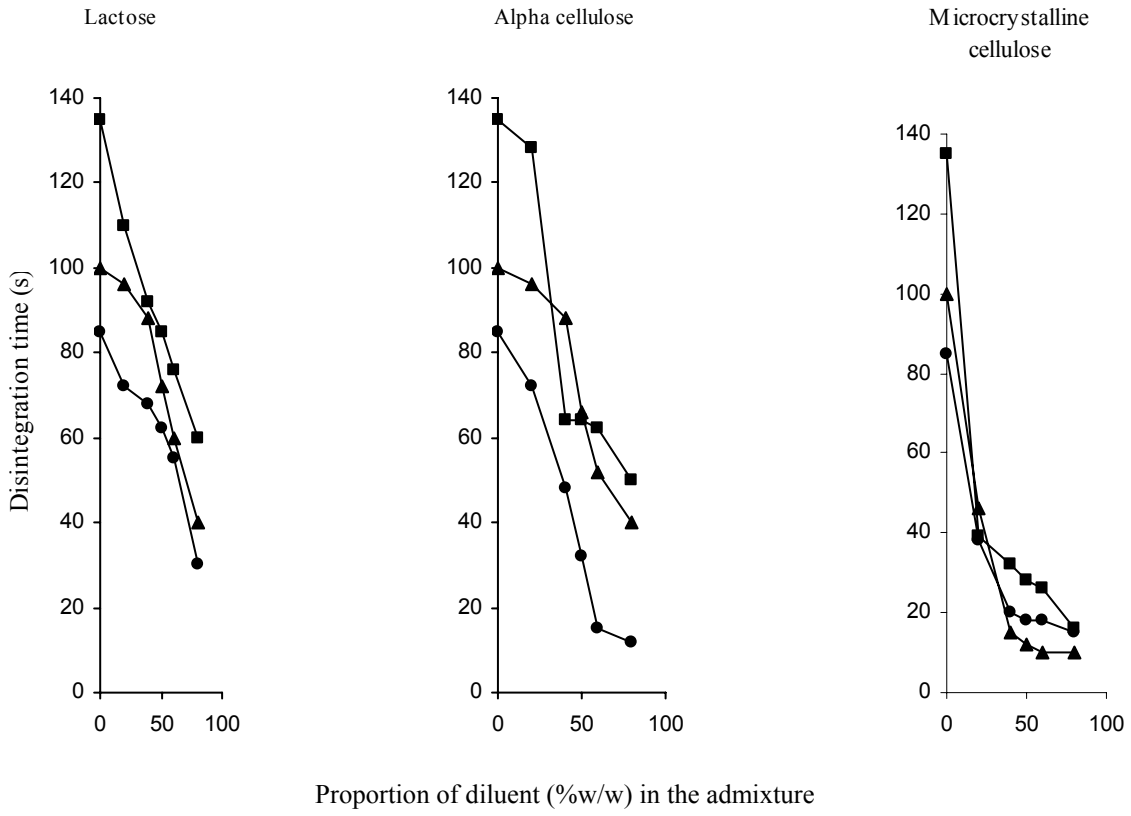

Fig. 3: Effect of diluent on the disintegration time (s) on acetaminophen tablets, goat wax (●), carnuba wax (■), glyceryl monostearate (▲).

and weight 550mg. Immediately prior to compression of the granules, magnesium stearate (1%w/w) and dried maize starch powder (5%w/w) were added.

Evaluation of compressibility (measurement of tablet tensile strength)

Tablet tensile strength (T) is the stress needed to fracture a tablet by diametral compression. It is given by (Fell and Newton 1970):

$$T = 2P/\pi Dt \quad (2)$$

while P is the load that causes tensile failure of a tablet of diameter, D and thickness, t. The fracture loads (Kg) of ten tablets were determined individually with the Monsanto hardness tester, following Brook and Marshal (1968). The mean values of the fracture loads were used to calculate the T values for the various tablets.

Disintegration test (DT): The method described in the British Pharmacopoeia BP (2002) was followed. Six tablets were used in each determination, which was carried out in triplicate and the mean results reported.

RESULTS AND DISCUSSION

Effect of diluents on the flowability of the granules

The matrix granules prepared with goat wax or glyceryl monostearate were very sticky, with no measurable flow. It can be seen (fig. 1) that addition of the diluent granules considerably improved flow as reflected by the sharp decrease in angle of repose. By contrast, the carnuba wax matrix granules exhibited a high degree of flow (angle of repose $=18.6^0$) which was further improved by addition of the diluent granules. The diluent granules were on their own free flowing, angle of repose 20.8^0 (lactose), 38.2^0 (α-cellulose) and 32.4^0 (microcrystalline cellulose). A low angle of repose indicates high flowability. Hence, expectedly, lactose was more effective than α-cellulose or microcrystalline cellulose in improving the flowability of the matrix granules. The need for free flow of granules during compaction is to minimize weight variation of resulting tablets.

Effect of diluents on the tablet tensile strength (T)

T values were taken as measures of compressibility. A high T value indicates high compressibility, usually as a result of plastic deformation and hence, a more extensive interparticulate bonding (Itiola and Pipel, 1991). The T values of the diluent granules were (MN/m^2), 1.25 (lactose), 1.42 (α-cellulose) and 1.48 (microcrystalline), indicating that the latter two diluents were more plastic than lactose.

The matrix granules prepared with goat wax or glyceryl monostearate as matrix former were poorly compressible (T

values = 0.20 MN/m^2). The granules were also sticky and cohesive. Admixing with any of the diluent granules improved compressibility as reflected by the sharp increase in T values of resulting tablets (fig 2) Microcrystalline cellulose and α-cellulose were more effective than lactose in improving the compressibility of the matrix granules.

The matrix granules prepared with carnuba wax were readily compressible (T value, 1.78MN/m^2), attributable to the plastic nature of this wax. Addition of the diluents decreased compressibility as reflected by the slight decrease in T values (fig. 2). Lactose was more effective than α-cellulose or microcrystalline cellulose in decreasing compressibility of these matrix granules. However, sufficiently hard tablets were formed when the admixtures were compressed ($T \geq 1.40 MN/m^2$). This means that diluents can be incorporated without serious impairment to compressibility of the granules. This finding is important because invariably it is desirable to incorporate diluents in multi-unit dose tablets in order to prevent direct contact of the medicated particles during compaction and to promote disintegration to the medicated particles with their individual release profiles intact.

Tablet disintegration times

The tablets made of the matrix granules only, disintegrated rapidly within 3minutes irrespective of the nature of the matrix former used in the melt granulation. Addition of diluent granules further reduced the disintegration time considerably down to ≤30s (fig. 3), attributable to the reduction in wax (hydrophobic) content of the tablets as the proportion of the diluent in the tablets increased. Microcrystalline and α-cellulose were more effective than lactose in decreasing the disintegration times to a few seconds (fig. 3).

CONCLUSIONS

The study has shown that all three diluents investigated are capable of improving the compressibility of the matrix granules of acetaminophen prepared by melt granulation with either goat wax or glyceryl monostearate. Although the carnuba wax matrix granules (without a diluent) were readily compressible, the inclusion of a diluent is still considered necessary to prevent direct contact between the matrix granules during tableting and hence promote rapid disintegration of the tablets to their primary particles (i.e. the matrix granules). These finding may be exploited in the design of multiunit dose tablets.

REFERENCES

Adeyeye CM and Price JC (1991). Development and evaluation of sustained release ibuprofen-wax microspheres. I. Effect of formulation variables on physical characteristics. *Pharm. Res.,* **8**: 1377-1383.

Adeyeye CM and Price JC (1994). Development and evaluation of sustained release ibuprofen-wax microspheres. II. *In vitro* dissolution studies. *Pharm. Res.,* **11**: 575-579.

Bodmeier R, Wang J and Bhagwatwar H (1992). Process and formulation variables in the preparation of wax microparticles by melt dispersion technique for water insoluble drugs. *J. Microcapsulation,* **9**: 89-98.

British Pharmacopoeia (2002). Her Majest's Stationery Office, London A_{237} monograph on disintegration times of coated tablets.

Brook DB and Marshall K (1968). Crushing Strength of compressed tablets 1. Comparison of testers. *J. Pharm. Sci*., **57**: 481-484.

Fell JT and Newton JM (1970). Determination of tablet strength by diametral compression test. *J. Pharm. Sci.,* **59**: 688-691.

Itiola AO and Pipel N (1991). Formulation effects on the Mechanical properties of Metronidazole tablets. *J. Pharm. Pharmacol.,* **43**: 145-147.

Kumar MK, Shah MH, Ketkar A, Mahadik KR and Paradkar A. (2004). Effect of drug solubility and different excipients on floating behaviour and release from glyceryl monooleate matrices. *Int.J.Pharm.,***272**(1-2):151-60.

Liu J, Zhang F and McGinity JW (2001). Propertties of lipophilic matrix tablets containing phenylpropanoll-amine hydrochloride prepared by hot-melt extrusion. *Eur. J. Pharm. Biopharm.,* **52**: 181-190.

Okhamafe AO, Igboechi AC and Obaseki TO (1991). Cellulose extracted from groundnut shell and rice husk 1; Preliminary Physicochemical Characterization. *Pharm. World J.,* **8**(4): 120-123.

Okhamafe AO, Igboechi AC, Ubrufih CE, Akinyemi BO and Ighalo MO (1992). Cellulose Extracted from Groundnut Shell and Rice Husk 2: Disintegrant Properties. *Pharm. W. J*., **9**(1): 11-16.

Okor RS (1988). Mechanism of drug release from a new ointment base consisting of goat fat and palm kernel oil. *Nig. J. Pharm.,* **19**(2): 62-64.

Remaman C, Bretal M, Nunez A and Bila Jato JL (1992). Accelerated stability of sustained release tablets prepared with Gelucire. *Int. J. Pharm.,* **80**: 151 -154.

Richards JH (1972). Powder flow and compaction. *In*: Carter SJ (ed). Tutorial Pharmacy. Pitman Medical Publishing Co Ltd., London, 6th ed., pp.211-233.

Sariaya D and Bolton D (1990). The use of percirol to prepare sustained release tablets of theophylline and quinidine gluconate. *Drug Dev. Ind. Pharm.,* **16**: 1963-1969.

Uhumwangho MU and Okor RS (2006). Modification of drug release from acetaminophen granules by melt granulation technique – consideration of release kinetics. *Pak. J. Pharm. Sci.,* **19**(1): 22-27.

Received: 21-03-2006 – Accepted: 03-05-2006