JOPHAS

Journal of
Pharmaceutical and
Allied Sciences

EFFECT OF FORMULATION METHODS ON THE MECHANICAL AND RELEASE PROPERTIES OF PARACETAMOL TABLETS

AJALA, T. O.[1], AREMU, O. I.[1*], SEGUN, P. A.[1], AND AYORINDE, J. O.[2]

[1]DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY, FACULTY OF PHARMACY, OLABISI ONABANJO UNIVERSITY, SAGAMU, NIGERIA.
[2]DEPARTMENT OF PHARMACEUTICS AND INDUSTRIAL PHARMACY, FACULTY OF PHARMACY, UNIVERSITY OF IBADAN, IBADAN, NIGERIA.

*Corresponding author: E-mail: solabankyahoo.com; Tel: 08033259890

Abstract
This work compared the compressional, mechanical and drug release properties of paracetamol tablets produced through direct compression with those obtained from wet granulation. Compressional properties were analyzed using density measurements, angle of repose, Carr's index and Hausner's ratio. The mechanical properties of the tablets were assessed using the crushing strength (CS), friability(F) and crushing strength-friability ratio (CSFR) of the tablets, while drug release properties were assessed using disintegration time and dissolution profile. The granules possessed better flow properties than the powder mixtures for direct compression. Paracetamol tablets prepared by wet granulation were harder than those prepared by direct compression as shown by the CS. The evaluation of the release properties showed that the amount of paracetamol released at any given time was higher for tablets prepared by direct compression than those prepared by wet granulation. Thus, wet granulation with carefully selected drug excipients may be a better method over direct compression in paracetamol tablets formulation.

Keywords: Paracetamol tablets, direct compression, wet granulation, mechanical properties, drug release properties

INTRODUCTION

Pharmaceutical tablets may be manufactured through three different methods. These include direct compression, dry granulation and wet granulation. Current usage of the term "direct compression" is the process by which tablets are compressed directly from the powder blends of active ingredient/s and suitable excipients. Dry granulation and wet granulation involve processes in which powdered particles are made to possess cohesive qualities, aggregate or adhere to form regular larger sized multi-particulate entities called granules. Granulation of drug particles is usually carried out to impart cohesiveness to the tablet formulation and to improve on the flow characteristics of the individual particles in order to improve the inherent poor compression properties and to prevent segregation of the constituents which may arise primarily from differences in size or density (1). Direct compression as a procedure of tablet production has great advantages because the drug, even with addition of certain

additives, is compressed without previous granulation. While in most cases the advantages of this procedure are economy, production of tablets containing drugs sensitive to moisture and heat, it is also a selective method either for high or low dosage preparations (2). It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. The use of directly compressible adjuvants may yield satisfactory tablets for such materials (3). These directly compressible adjuvants are most often based on sugar, cellulose or inorganic salts. Many researches have been performed with dispersed dextrose (Emdex), aggregates of mechanically disintegrated α-cellulose (Elcema G 250), microcrystalline cellulose (Avicel)® and dicalcium phosphate dehydrate (Emcompress)® (4). Different directly compressible adjuvants have different effectiveness in the formulation of tablets through direct compression.

Paracetamol powder, a potent analgesic agent, with apparent poor flow properties as indicated in its inability to flow through a 13 mm diameter glass funnel was compressed directly by the careful selection of previously examined directly compressible adjuvants. Previously examined wet binders were also used in the wet granulation of paracetamol powder.

This study was undertaken to explore the effectiveness of various directly compressible excipients in paracetamol tablets formulation and also to compare the mechanical and the drug release properties of such drugs with those tablets formulated through wet granulation.

MATERIALS AND METHODS

Materials

The materials used include Paracetamol B.P (BDH Chemicals Ltd, Poole England), Corn Starch B.P (BDH Chemicals Ltd, Poole England), Pregelatinized Starch (BDH Chemicals Ltd, Poole England), Emcompress® (Mendell Co Ltd, Surrey, UK), Avicel® PH- 102 (FPC Biopolymer, USA), acetone (Hopkin and Williams, Chadwell, Health, Essex, UK), lactose (BDH Chemicals Ltd, Poole England), magnesium stearate (Hopkin and Williams, Chadwell, Health, Essex, UK), gelatin (BDH Chemicals Ltd, Poole England), potassium dihydrogen phosphate (Kermel, USA), disodium hydrogen phosphate (Kermel, USA) and Deionized water (May & Baker Nig. Plc).

Preparation of powder mixtures for direct compression

Sixty gram batches consisting of paracetamol powder and Avicel® or Emcompress® or Pregelatinized Starch in a ratio of 1:5 drug: excipient were thoroughly mixed and stored in airtight containers.

Preparation of paracetamol granules

Batches (100 g each) of the basic formulation comprising of paracetamol powder (500 mg), lactose (10%) and corn starch (5%) were dry mixed for about 5 minutes in a Kenwood planetary mixer. The mixture was then moistened with appropriate amount of 4% concentration of binder solution (acacia, gelatin or corn starch). The wet masses were granulated by passing them manually through a 1,400 μm mesh size sieve and dried in hot air oven for 18 hours at 60^0C, and then re-sieved through a No. 16 mesh size (1,000 μm). Sieve analysis was done. The granule sizes between 500-1000 μm were collected for the preparation of the tablets. The granule properties such as density measurements, angle of repose, Carr's index and Hausner's ratio were determined through standard methods. Storage was done in airtight containers.

Preparation of paracetamol tablets

Tablets of final weight, 600 mg were prepared from the powder mixture while tablets of final weight 575 mg were prepared from the granules. Granules of particle sizes ranging from 500- 1000 μm were used. The tablets were made by compressing the materials for thirty seconds with the predetermined loads of 0.25, 0.5, 0.75, 1.0, and 1.25 metric tons using a Carver Hydraulic Hand Press (Model C, Carver Inc, Menomonee Falls, WI, USA). Before each compression, the die (10.5 mm diameter) and the flat-faced punches were lubricated with a 10% w/w dispersion of magnesium stearate in acetone. After ejection, the tablets were stored over silica gel for 24 hours to allow hardening and elastic recovery.

Evaluation of paracetamol granules and paracetamol powder blend

Bulk and tapped densities

Thirty grams (30 g) of the granules were carefully poured through a short stemmed glass funnel into a 100 ml graduated cylinder. The volume occupied by the granules was read and the bulk density calculated in gm/ml. The cylinder containing the granules was tapped fifty times from a height of 2 cm and the tapped density calculated in gm/ml (5).

Percentage compressibility (Carr's index) and Hausner's ratio

The percentage compressibility (CI) was calculated from the difference between the tapped (Dt) and the bulk densities (Bt) divided by the tapped density and the ratio expressed as a percentage (6). The Hausner's ratio (HR) is the ratio of the tapped to the bulk density.

$$CI = \frac{Dt - Bt}{Dt} \times 100$$

$$HR = \frac{Dt}{Bt}$$

Angle of repose

This was determined by allowing 20 g of the granules made using different excipients to flow freely through a funnel from a particular height so as to form a conical heap on the horizontal surface. As the heap was formed, the particles slipped and rolled over each other until the mutual friction between the particles just balances the gravitational force. The angle which the heap formed with the horizontal surface is the angle of repose and it was determined by the formula.

$$\tan \theta = \frac{h}{r}$$

Evaluation of paracetamol tablets

Weight uniformity

Twenty (20) tablets were weighed individually on the Mettler electric balance (P163 Mettler instrument AG) from which the mean was calculated and the percentage deviations and standard error of the mean (SEM) determined.

Thickness

The thickness of ten tablets each selected at random from the formulated batches was determined using a vernier calliper and the mean of these readings was taken as the mean tablet thickness. The SEM and the percentage deviation were also determined.

Crushing strength and friability tests

The load (N) required to diametrically break each tablet (crushing strength, CS) was determined at room temperature using a Tablet Hardness Tester (DBK Instruments- Mumbai India). The friability (F) of the tablets were determined using a friabilator (DBK Instruments- England) operated at 25 revolutions per minute for 4 minutes.

Disintegration test

The disintegration times (DT) of the

tablets were determined in distilled water at 37±0.5^{0}C using an Erweka disintegration testing apparatus (Model: Copley ZT2, Erweka Apparatebau GMBH, Heusenstamm, Germany).

Dissolution test

The dissolution profiles of the tablets were determined at 37±0.5 ^{0}C in 900 mls of phosphate buffer solution pH 5.8 using a Dissolution Test Apparatus (DA-6D, Veego Scientific Devices Mumbia, India) with the basket rotated at 50 rpm for 30 minutes. Five (5) milliliter samples were withdrawn and replaced with fresh medium at fixed time intervals. Each withdrawn sample was filtered. One milliliter of the filtrate was poured into a 50 ml round bottom flask and the filtrate made up to 50 ml with the blank buffer. The amount of drug released was determined spectrophotometrically at 249 nm.Determinations were done in quadruplicates. The percentageof drug released at each given time was calculated.

Statistical Analysis

Statistical analysis was carried out using ANOVA test to compare the differences in the effect of methods on the tablet parameters. Data is expressed as mean ±standard error of the mean. The confidence interval was set at 95% and p-values less or equal to 0.05 were considered significant.

RESULTS

The bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose of granules and powder blends prepared by wet granulation and direct compression methods are shown in Table 1.The bulk densities were higher in granules than in the powder blends. The value was highest (0.476) in granules prepared with corn starch as binder. The values of Carr's index (*b*) were higher for the powder blends than for the granules. The ranking of *b* is Acacia<gelatin<corn starch<pregelatinized starch<dicalcium phosphate<Avicel. Also, the value of Hausner's ratio (HR) in the powder blends is greater than in the granules. The ranking of HR values is Avicel<Di-calcium-phosphate<pre-gelatinized starch<gelatin<corn starch <Acacia. Furthermore, the angle of repose was not determinable among powder blends but ranked as follows for the granule formulations: cornstarch<Acacia<gelatin. Tables 2 and 3 show the crushing strength (N), friability (%), CSFR, disintegration time and CSFR-DT of paracetamol tablets produced through wet granulation and direct compression methods. There was a general decrease in the thickness as the compression pressure increased. It was observed that for all the tablets, increase in compression pressure led to a decrease in friability and an increase in crushing strength. The friability of the tablets formulated with the different binders was in the following increasing order: Starch < Gelatin < Acacia < Avicel® < Emcompress® < Pregelatinized Starch, while the order was reversed for the crushing strength. The ranking of disintegration and dissolution times exhibited by tablets prepared by direct compression was Avicel® > Emcompress®>pregelatinized starch, while the ranking for tablets prepared by wet granulation was corn starch >gelatin >acacia.

JOPHAS

Journal of Pharmaceutical and Allied Sciences

Table 1: **Bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose of granules and powder blends prepared by wet granulation and direct compression methods respectively.**

Direct compression					
Diluent	**Bulk density (g/ml)**	**Tapped density (g/ml)**	**Carr's Index**	**Hausner's ratio**	**Angle of repose**
Avicel®PH 102	0.384	0.588	34.69	1.69	-
Dicalcium phosphate	0.400	0.555	27.93	1.39	-
Pregelatinized starch	0.416	0.555	25.1	1.33	-
Wet granulation					
Binder	**Bulk density (g/ml)**	**Tapped density (g/ml)**	**Carr's Index**	**Hausner's ratio**	**Angle of repose**
Gelatin	0.45	0.5	10	1.25	19.32^0
Corn starch	0.476	0.555	14.23	1.17	10.59^0
Acacia	0.400	0.435	8.05	1.09	17.83^0

Table 2: Crushing strength (N), friability (%), CSFR, disintegration time, CSFR-DT of paracetamol tablets produced through direct compression method.

Compression Pressure (Metric tones)		**Direct Compression**				
	Diluent	**Crushing strength(N)**	**Friability (%)**	**CSFR**	**Disintegration time**	**CSFR-DT**
0.25	Avicel	18.7± 0.893	2.8	6.67	0.88	7.57
0.50		27.8± 0.811	2.6	10.69	0.92	11.6
0.75		40.1 ±0.546	2.5	16.04	1.03	15.57
1.0		50.1 ±0.376	2.3	21.78	1.12	19.44
1.25		60.32±0.57	1.8	33.51	1.33	25.19
0.25	Emcompress®	12.8 ± 0.179	3.9	3.28	0.83	3.95
0.50		21.1 ± 0.235	3.4	6.21	0.88	7.05
0.75		29.9 ± 0.239	2.9	10.31	0.95	10.85
1.0		33.2 ± 0.290	2.7	12.3	1.02	12.05
1.25		39.1 ± 0.163	2.2	17.77	1.08	16.45
0.25	Pregelatinized starch	10.1 ± 0.275	4.3	2.35	0.75	3.13
0.50		14.5 ± 0.357	4.1	3.54	0.83	4.26
0.75		18.4 ± 0.275	3.5	5.26	0.87	6.04
1.0		23.8 ± 0.360	3.4	7.00	0.92	7.61
1.25		30.8 ± 0.406	2.9	10.62	1.05	10.11

Compression Pressure (Metric tones)		Wet Granulation				
	Binder	Crushing strength(N)	Friability (%)	CSFR	Disintegration time	CSFR-DT
0.25	Gelatin	45.4± 0.543	2.5	18.16	0.91	19.95
0.50		56.2± 0.595	1.7	33.05	1.2	27.54
0.75		76.6± 0.494	1.2	63.38	1.4	45.27
1.0		102.1±0.571	0.8	127.62	1.55	82.33
1.25		109 ±0.459	0.4	272.5	1.63	167.17
0.25	Corn starch	69.24±1.155	0.84	106.2	1.55	68.51
0.50		89.1 ± 2.012	0.81	147.1	2.06	71.4
0.75		110.9±1.320	0.42	335.5	2.37	141.56
1.0		126.7±0.951	0.26	602.7	3.02	199.6
1.25		134.2±1.774	0.2	1105	3.37	327.89
0.25	Acacia	58.9± 0.880	2.9	20.31	0.66	30.77
0.50		68.1± 0.528	2.0	34.05	0.95	35.84
0.75		86.3± 0.723	1.4	61.64	1.2	51.37
1.0		90.8 ±0.661	1.2	75.66	1.42	53.28
1.25		99.4± 0.242	0.8	124.25	1.83	67.89

Table 3: **Crushing strength (N), friability (%), CSFR, disintegration time, CSFR-DT of paracetamol tablets produced through wet granulation method.**

Table 4: The thickness (mm) of paracetamol tablets prepared by wet granulation and direct compression methods at different pressures

Compression Pressure (metric tones)	Excipients					
	Gelatin	Acacia	Corn Starch	Avicel	Dicalcium Phosphate	Pregelatinized Starch
0.25	6.67 ±0.017	6.38 ±0.019	6.15± 0.007	6.72± 0.017	6.6 ± 0.009	6.51 ± 0.014
0.5	6.26± 0.017	6.26± 0.015	6.03± 0.013	6.32± 0.017	6.53 ± 0.004	6.44 ± 0.016
0.75	6.17± 0.008	6.05± 0.014	5.98± 0.005	6.29± 0.004	6.44 ± 0.009	6.38 ± 0.017
1.0	6.04± 0.012	5.84± 0.018	5.88± 0.008	6.14± 0.029	6.32 ± 0.009	6.26 ± 0.015
1.25	5.99± 0.008	5.78± 0.026	5.71± 0.010	6.02± 0.043	6.2 ± 0.007	6.22 ± 0.019

Expressed as Mean ± SEM; n = 5, $p<0.05$

Table 5: Weight Uniformity of paracetamol tablets prepared by wet granulation and direct compression at varying compression pressures

Compression Pressure (metric tones)	Excipients					
	Gelatin	Acacia	Corn Starch	Avicel	Dicalcium Phosphate	Pregelatinized Starch
0.25	0.5757±0.0072	0.57525±0.00520	0.57285±0.00137	0.597±0.00106	0.598±0.0015	0.598±0.0006
0.5	0.5733±0.00001	0.5714±0.0007	0.5734±0.0013	0.59775±0.0095	0.597±0.0014	0.5974±0.0009
0.75	0.5677±0.0028	0.5665±0.0033	0.5729±0.0008	0.5981±0.0011	0.598±0.0015	0.59695±0.0008
1.0	0.5715±0.0006	0.57695±0.0029	0.5715±0.0006	0.59775±0.00099	0.597±0.0011	0.59675±0.0008
1.25	0.5697±0.0020	0.5723±0.0009	0.57165±0.0004	0.5994±0.0009	0.596±0.0011	0.5997±0.0009

Expressed as Mean ± SEM; n = 5, $p<0.05$

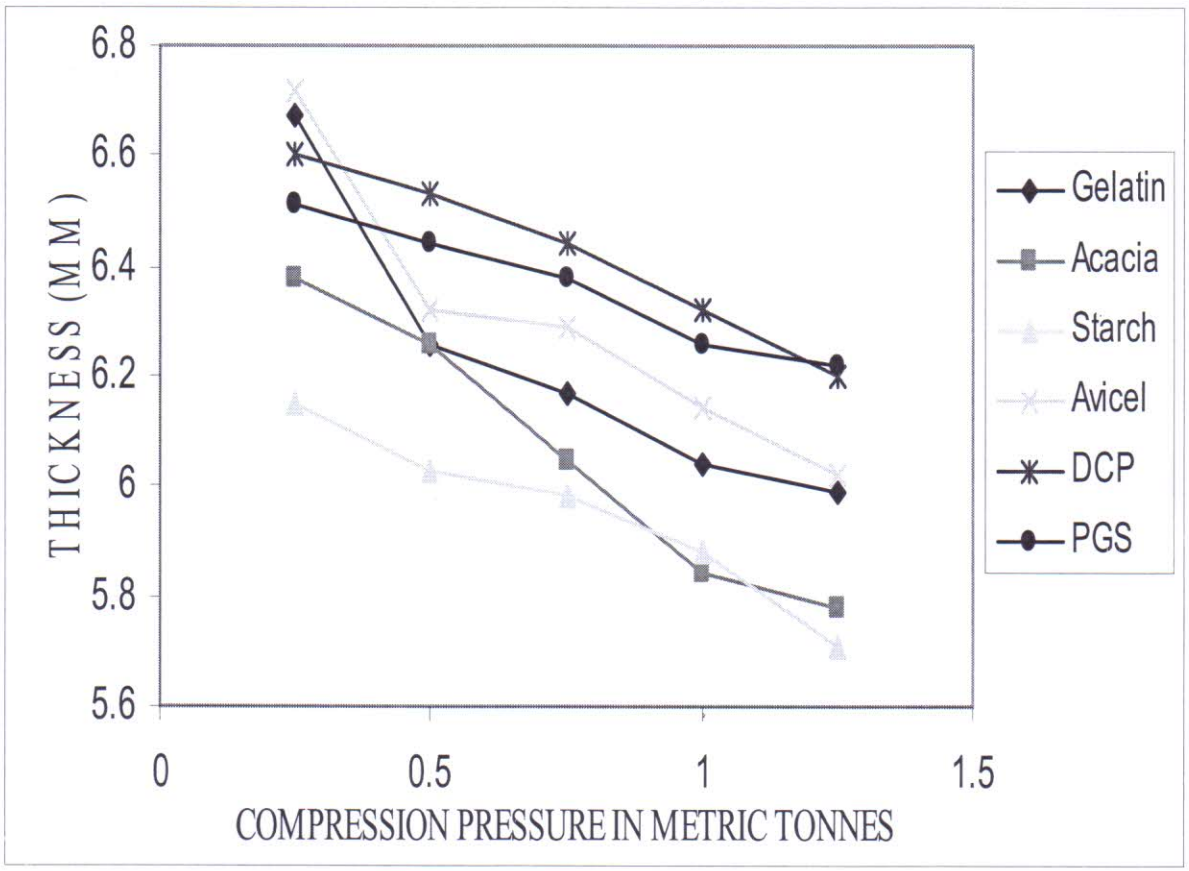

Fig 1: Thickness (mm) vs. Compression Pressure (metric tons) showing the effect of different binders on the thickness of Paracetamol tablets.

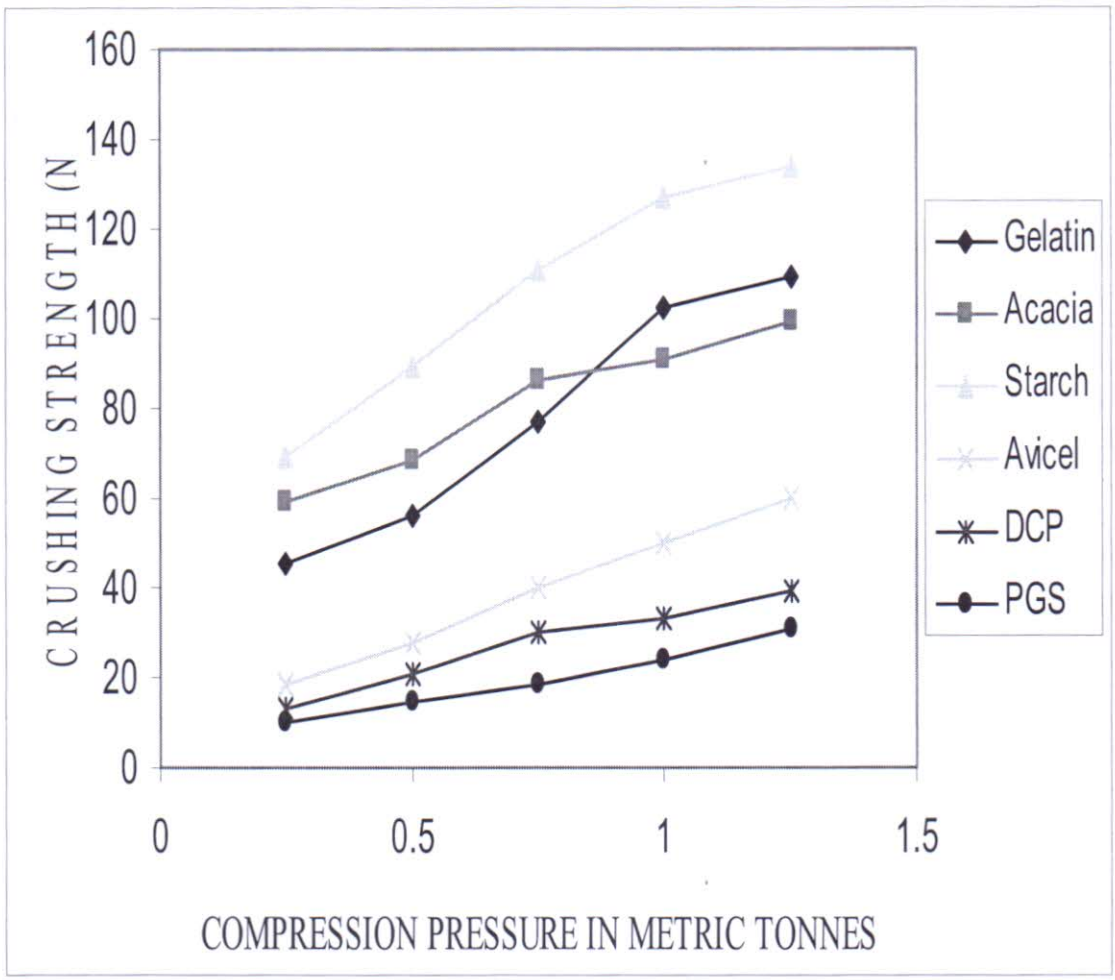

Fig 2: The plot of Crushing Strength (N) vs. Compression Pressure (Metric tons) showing the effect of the binder type on the crushing strength of Paracetamol tablets.

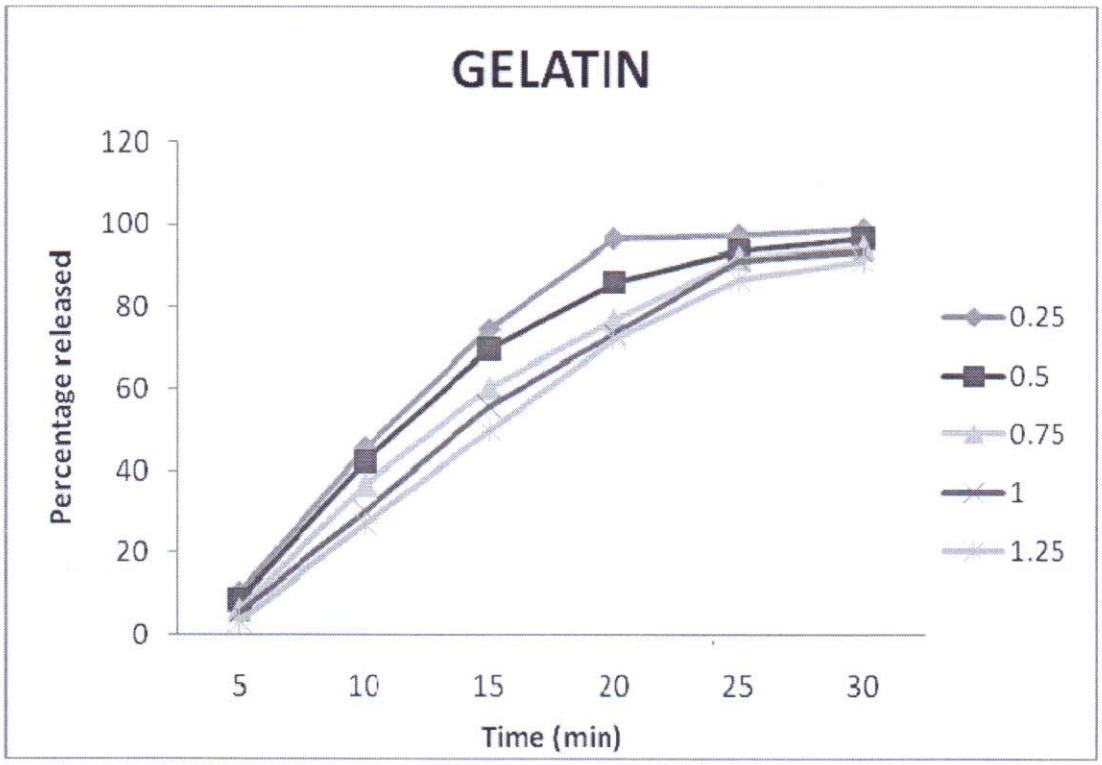

Fig 3. Percentage released vs. time (mins) showing the relationship between the compression pressure and the time taken for the paracetamol tablets compressed with gelatin to be released in solution.

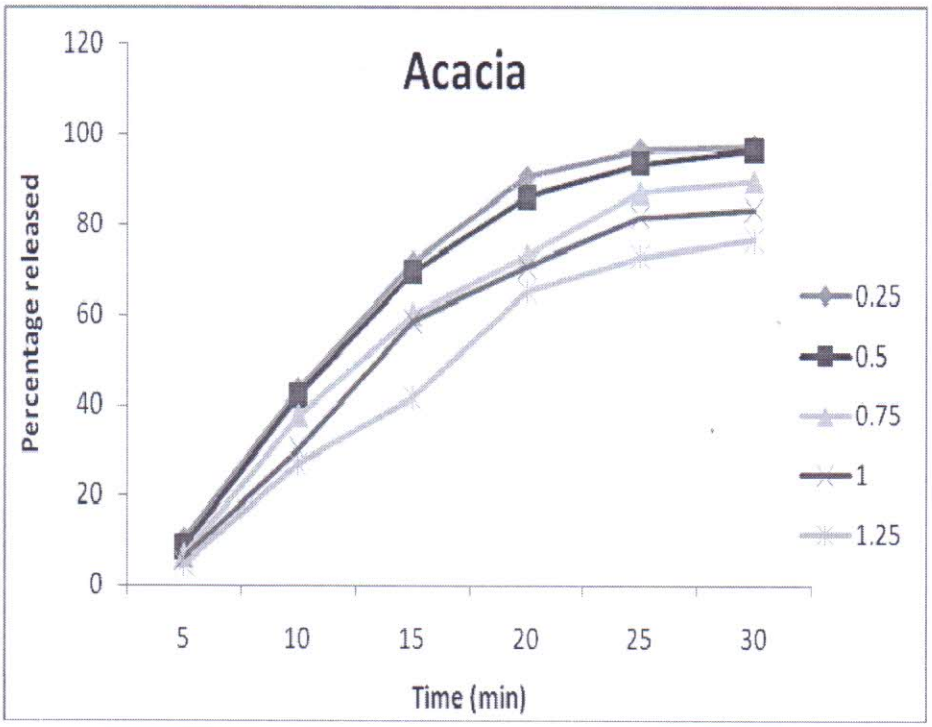

Fig 6: Percentage released vs. time (mins) showing the relationship between the compression pressure and the time taken for the paracetamol tablets compressed with acacia to be released in solution.

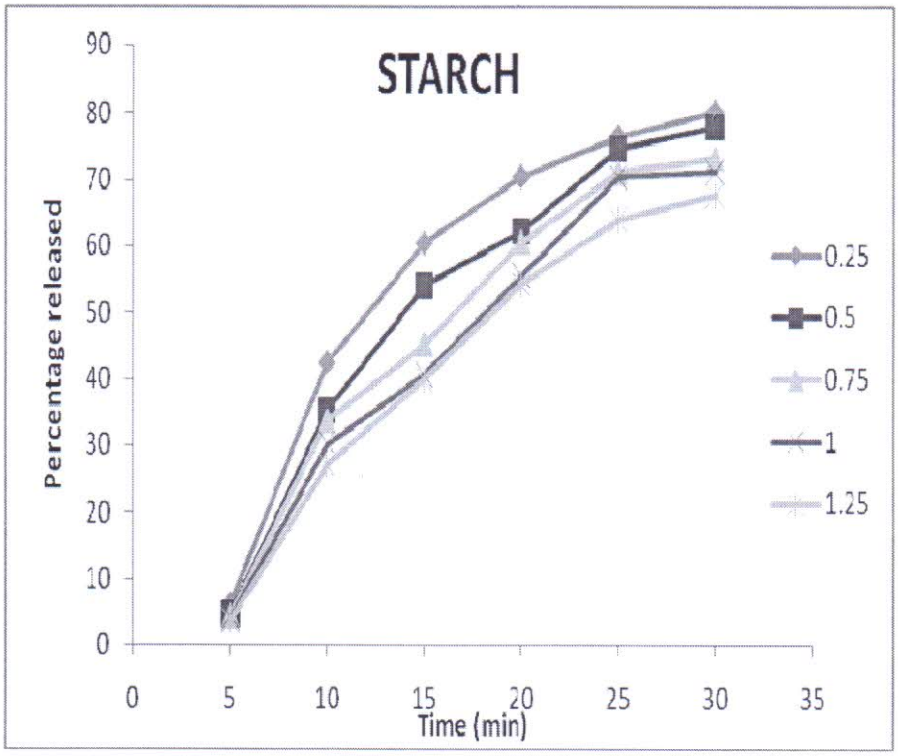

Fig 7: Percentage released vs. time (mins) showing the relationship between the compression pressure and the time taken for the paracetamol tablets compressed with starch to be released in solution.

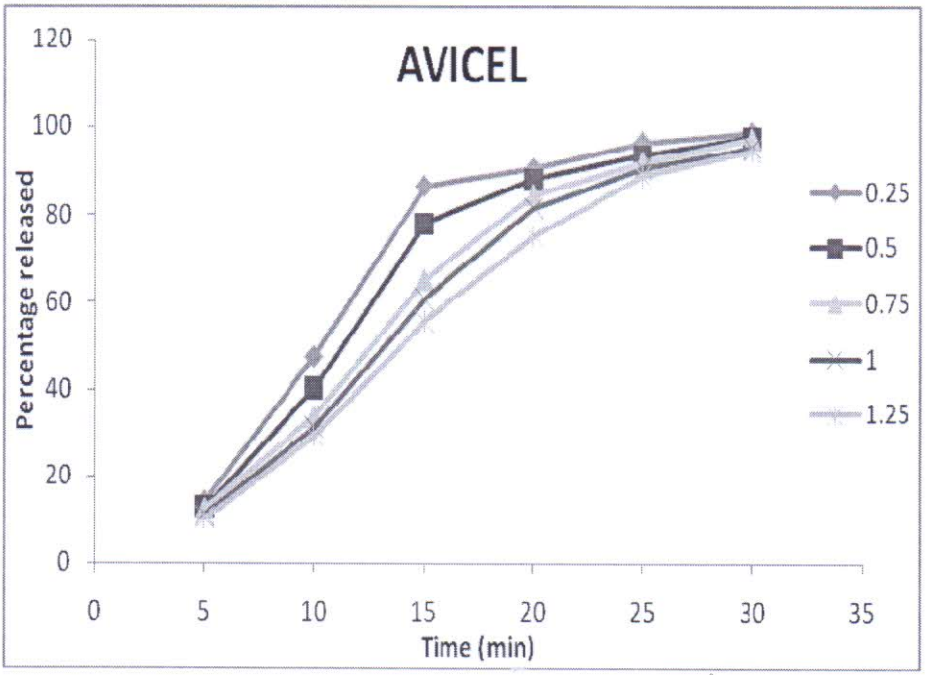

Fig 8: Percentage released vs. time (mins) showing the relationship between the compression pressure and the time taken for the paracetamol tablets compressed with Avicel to be released in solution.

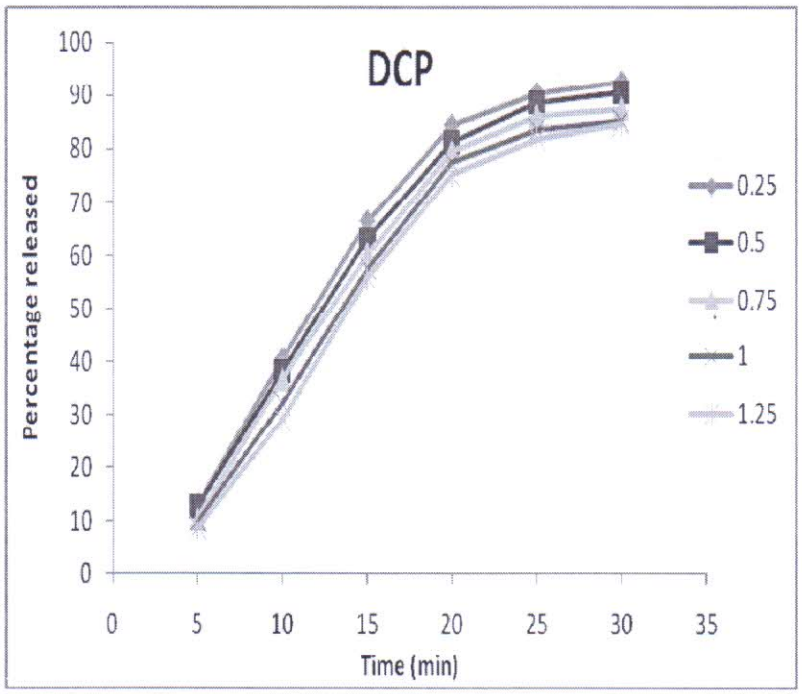

Fig 9: Percentage released vs. time (mins) showing the relationship between the compression pressure and the time taken for the paracetamol tablets compressed with dicalcium phosphate to be released in solution.

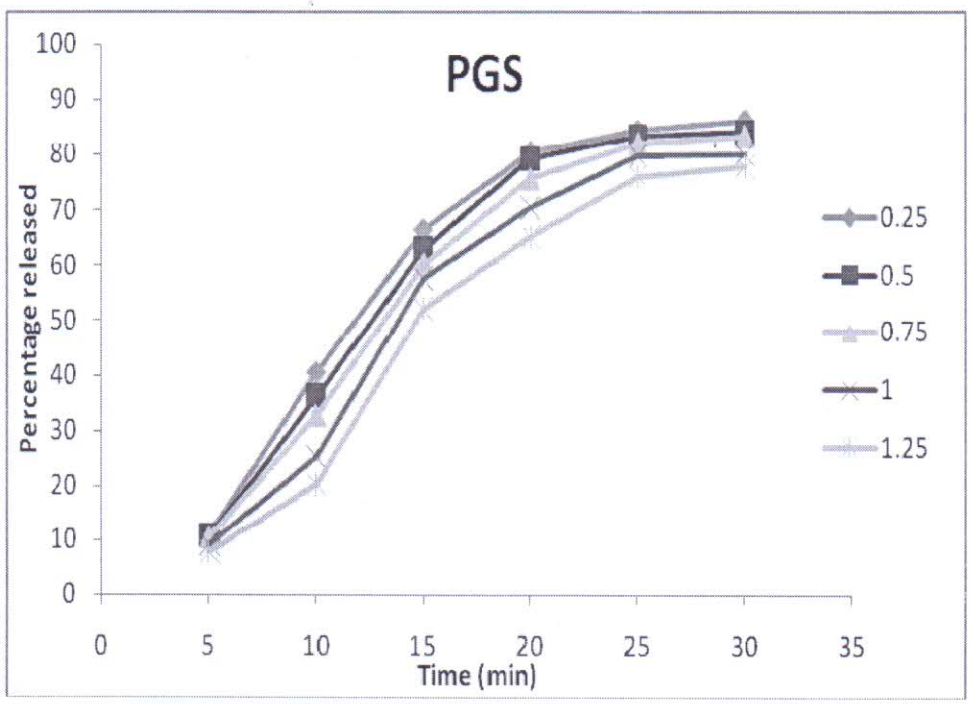

Fig 10: Percentage released vs. time (mins) showing the relationship between the compression pressure and the time taken for the paracetamol tablets compressed with pregelatinized starch to be released in solution

DISCUSSION

Parameters for assessing the flow properties of granules include angle of repose, bulk and tapped densities, Hausner's quotient and Carr's compressibility. The higher bulk densities observed in the granules compared to the powder blends is expected because granulation makes particle become more spherical and this increases the bulk density. Spherical particles pack more closely than irregularly shaped ones. Compressibility of granules is determined so as to assess the ability of the granules to compact and decrease in volume when pressure is applied. This is needed to ensure the suitability of the granules for tabletting in order to produce strong tablets which can withstand pressure (7). When Carr's compressibility is below 15%, the granules have excellent flow properties while cohesive granules have Carr's compressibility above 25% indicating poor flow properties (8, 9). Acceptable Carr's index reveals material compressibility.

Granules with Hausner's ratio below 1.25 have good flow properties and granules with angle of repose below 40° but preferably below 30° exhibit good flow (10), while granules with 50° would flow with difficulty (11). The Carr's index for the granules made with gelatin, starch and acacia were found to be less than 15% which means that the granules have excellent flow properties with acacia having the best property. The Carr's index for the powder blends for direct compression were found to be more than 15% with Avicel having the highest value (34.69%). Also, the Hausner's ratios for the granules were less than 1.25 with acacia having the least value (1.09); this means that the granules have good flow properties. However, the Hausner's ratio for the paracetamol powder blends was more than 1.25 with Avicel having the highest value (1.69); this means that the paracetamol powder blends had poor flow properties. The angle of repose for the granules were lesser than 30° with corn starch exhibiting the least value (10.59°). This indicates that the granules exhibited good flow properties. However, the angle of repose of the paracetamol powder blends could not be determined since the powder did not flow out through the funnel, indicating poor flow properties. It can therefore be inferred that the paracetamol granules produced through wet granulation had a better flow property than the paracetamol powder blends used for direct compression.

The compendial specification for uniformity of weight states that for tablets weighing more than 324 mg, weights of not more than two tablets should deviate from the average weight by more than 5% (12). The paracetamol tablets from the different batches which had different excipeints met the compendial specification. Furthermore, there were statistically significant ($p<0.05$) differences in the uniformity of weight and thickness values of paracetamol tablets prepared by both methods.

The general increase in crushing strength as the compression pressure increased was due to the increase in the number of contact points which led to an increase in the degree of bonding between the particles (13, 14). For the mechanical strength of a tablet to be satisfactory, the minimum requirement is 4 N (14). All the tablets had crushing strengths of more than 4N which means that they all possess adequate hardness. However, the hardness for the tablets produced using the granules (wet granulation) had higher crushing strengths than those produced using paracetamol powder blend (direct compression).

Friability is another mechanical property of a tablet with compendial specification of not more than 1% (12). While crushing strength test is a bulk deformation of the tablet, friability is a surface deformation

which may be enhanced by the morphology of the tablet (16). The rougher the surface of the tablet, the more friable it will be. Ideally, friability should decrease with increase in compression pressure and should increase with decrease in binder concentration (16). Only tablets produced using starch as the binder met the USP specification for tablets. It was also observed that tablets produced through wet granulation had lower friability than those produced through direct compression. If the concentration of the binder in each tablet is increased, a stronger tablet that will be resistant to fracture and abrasion (friability) may be formed.

The mechanical strength of tablets can also be measured by the crushing strength – friability ratio (CSFR). Generally, the higher the CSFR, the stronger the tablet (17). The CSFR of the tablets formed through wet granulation were higher than those formed through direct compression. This suggests that the tablets formed through wet granulation were stronger than those formed through direct compression.

Disintegration is a crucial step in release of drugs from immediate release dosage forms. The rate of disintegration is directly proportional to the rate of dissolution. All the tablets had disintegration time of less than 15 minutes which means that they all met the USP specification. There was a direct relationship between the crushing strength of the tablets and the disintegration time; the higher the crushing strength, the higher the disintegration time. However, tablets produced through direct compression disintegrated faster than those produced through wet granulation. The disintegration time of the tablets was is in the following order: Pregelatinized < Emcompress® < Avicel < Acacia < Gelatin < Starch.

The *CSFR/DT* ratio has been suggested as a better index for measuring tablet quality than the crushing strength-friability ratio (*CSFR*) because in addition to measuring tablet strength (crushing) and weakness (friability), it simultaneously evaluates all negative effects of these parameters on disintegration time (18). In general, higher values of the *CSFR/DT* ratio indicate a better balance between binding and disintegration properties (19). There was increase in CSFR/DT ratio for paracetamol tablets with increasing compression pressure. It was also observed that tablets produced through wet granulation have higher CSFR/DT ratio than those produced through direct compression. Tablets produced using starch as binder had the highest CSFR/DT ratio indicating that there is a better balance between the binding and disintegration properties.

The dissolution rate of a drug is directly related to the surface area exposed to the dissolution media. In order to increase the dissolution rate for a given amount of drug, the effective surface area has to be increased. The surface area of the individual particles themselves changes during the compaction process. Initially, an increase in surface area is noted owing to fracture as compression forces increase. Eventually, the surfaces are decreased by bonding and consolidation of particles as compression forces increase (20). Since drug absorption depends on having the drug substance in the dissolved state, suitable dissolution characteristics is an important property of a satisfactory tablet. The USP states that the quantity of drug released should not be less than 85% of the labeled amount of paracetamol in 30 minutes. It was observed that for all the tablets, the percentage of paracetamol released reduced as the compression pressure increased. It was also observed that all the tablets passed the dissolution test apart from those produced using corn starch and pregelatinized starch which failed to release 85% of the paracetamol within 30 minutes. This could be due to the high bond strength and lower swelling capacity of starch which could be responsible for the increase in dissolution time. Underwood and Cadwallder (20)

suggested that tablets containing starch with large particles have a smaller starch particle ratio (less starch separating individual drug particles), so that aggregates of the drug may form and thus, will take a longer time for the drug to be released.

Conclusion

The method of preparation of paracetamol tablets needs to be carefully selected to ensure the production of tablets with adequate bond strength to withstand the rigours of handling and at the same time release the active compound for biological action. Due to the poor flow and compressional properties of paracetamol tablets, a wet binder may be needed to produce tablets with desirable properties. Paracetamol produced through wet granulation had higher CSFR-DT than those prepared through direct compression. This indicates a better balance between the binding and disintegration properties of paracetamol tablets produced through wet granulation than those produced through direct compression. Hence, wet granulation with carefully selected drug excipients may be a better method over direct compression in paracetamol tablets formulation.

REFERENCES

1. Rudnic EM, Schwartz JD. Oral solid dosage forms. In: Gennaro A, Remington R ed. the Science and Practice of Pharmacy, vol 1, 20th ed. Lippincott Williams and Milkini Inc. Philadelphia,2010 pp. 858-893.
2. Senjkovic R., Becirevic M., and Usmiani I. Effect of fillers on the Properties and Acetyksakicykic Acid Tablets Prepared by Direct Compression. Pharm. 1992, Ind. 54, Nr. 6.
3. Shangraw, R. F., Wallace, J. W., and Bowers, F. M. Morphology and Functionality in Tablet Excipients for Direct Compression, Pharm.Technol. 1987, 11: 136- 143.
4. Vromans, H., Bolhuis, G. K., Lerk, C.F., Kussendrager, K.D., Bosch, H., Acta Pharm.1986, Sci. 23,231.
5. Stanley-Wood, N.G. and M. S. Shubair. The influence of binder concentration on the bond formation of parmaceutical granules. J. Pharm. Pharmacol. 1987, 31: 429.
6. Schwartz, J.B., E.T. Martin and E.J. Deliner. Intragranular starch: Comparison of starch U.S.P and modified corn starch. J. Pharm. Sci. 1975, 64: 328-332.
7. Mohammadi MS, Harnby N. Bulk density modelling as a means of typifying the microstructure and flow characteristics of cohesive powders. Powder Technol. 1997, 92(1): 1-8.
8. Endale A, Gebre-Mariam T, Schmidt P. Granulation by Roller Compaction and Enteric Coated Tablet Formulation of the Extract of the Seeds of Glinus Lotoides Loaded on Aeroperl® 300 Pharma. AAPS Pharm. Sci. Tech. 2008, 9(1): 31-38.
9. Bacher C, Olsen PM, Bertelsen P, Sonnergaard JM; Compressibility and compactibility of granules produced by wet and dry granulation. Intern. J. Pharm. 2008, 358(1-2):69-74.
10. Reddy K, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil: Formulation and in vitro evaluation. AAPS Pharm. Sci. Tech. 2003, 4(4): 480-488.
11. Reus-Medina M, Lanz M, Kumar V, Leuenberger H. Comparative evaluation of the powder properties and compression behaviour of a new cellulose-based direct compression excipient and Avicel PH-102. J. Pharm. Pharmac. 2004, 56(8): 951-956.
12. US Pharmacopeia National Formulary USP 23/NF 18 (1995). UnitedStates Pharmacopeial Convention. Inc., Rockville,
13. Luangtanan-Anan M.D and Fell J.T. Bonding mechanisms in tabletting, Int. J. Pharm.1990, 6, 197–202.
14. Bi Y.X., Sunada H, Yonezawa Y, Danjo K. Evaluation of Rapidly Disintegrating Tablets Prepared by a Direct Compression Method. Drug development and industrial pharmacy, 1999, 25(5):571-581
15. Allen L.V, Popovich N.G, Ansel H.C. Ansel's pharmaceutical dosage forms and drug delivery systems" 8th Edition edn, Lippincott Williams and Wilkins,2004, Philadelphia. pp. 236.
16. Riippi M, Antikainen O, Niskanen T, Yliruusi J. The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets. Euro. J. Pharmac. Biopharmaceutics, 1998, 46(3): 339-345.

17. Odeku O.A, Itiola O.A. Evaluation of the effects of Khaya gum on the mechanical and release properties of Paracetamol tablets. Drug Dev. Ind. Pharm 2003; 29 (3): 311-320.
18. Upadrashta.P. R, N. O. Nuessle. Chitosan as a tablet binder, Drug Dev. Ind. Pharm. 18, 1992, 1701–1708.
19. Gbenga Alebiowu, Oludele Adelanwa Itiola. Effects of starches on the mechanical properties of paracetamol tablet formulations. II. Sorghum and plantain starches as disintegrants. Acta Pharm. 53,2003.
20. Higuchi T. Bonding and consolidation of powder particles: J Pharm. Sci.1963, 52, 1145.