THE TABLETING AND COMPRESSIONAL CHARACTERISTICS OF VARIOUS ACETYLSALICYLIC ACID TABLET FORMULATIONS PRODUCED BY DIRECT COMPRESSIONAL METHOD

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ABSTRACT

In this study four different formulations of acetylsalicylic acid tablets were investigated, by evaluating the compressional characteristics and tableting properties of these formulations using Heckel and Kawakita equation method. All the formulations investigated complied with British pharmacopeia 2010 tests for weight uniformity, tablet's crushing strength, friability and tablet disintegration test. The ranking order for friability test is AF4< AF3 < AF2< AF1 this ranking was however reverse for tablet crushing test, AF4> AF3 >AF2>AF1 .An inverse proportionality was observed between the various values obtained for tablet crushing strength and tablet friability. The ranking for the mean yield pressure (Py) as obtained from Heckel plots was AF4>AF1 > AF3 > AF2.. This translate to the fact that formulation AF2 the fastest onset of plastic deformation. However from kawakita plots the Pkb values can be ranked as follows, AF1< AF4 <AF2 <AF3. This also translate to the fact that formulation AF1 shows the highest degree of total plastic deformation. Formulation AF2 even though shows the fastest on set of plastic deformation , the total plastic deformation is however low when compared to other formulations. Formulation AF1 can therefore be adopted for large scale production of acetylsalicylic acid tablet production since tablet formulation with highest plastic deformation creates more contact points for interparticulate bonding , and therefore minimize the problem of lamination and capping, most especially on high speed tableting machine. (Alebiowu, et al 2002)

Keywords; Acetylsalicylic acid, compressional properties, and tableting properties, direct compression.

INTRODUCTION

Investigation and evaluation of acetylsalicylic acid tablets can not be over emphasized due to the fact that acetylsalicylic acid is hydroliable and poorly compressible as such both the method of production and the choice of pharmaceutical excipients for acetylsalicylic tablet formulation must be critically assessed.

A lot of effort had been devoted to the development of pharmaceutical tableting excipients from locally available materials, among which are; Microcrystalline cellulose from rice husk, (Okhmafe, *et al* 1992) ethylcellulose from wood shaving (Oyeniyi *et al* 2011) .Direct compression is a method of tablet production that is efficient, and cost saving. It is specifically useful for thermolabile and hydrolabile substances.

Powder compaction study is a process widely used in many pharmaceutical industries to evaluate the optimal conditions to which pharmaceutical powders and pharmaceutical granules can be subjected.

The aim of this study is to critically assess the tableting and compressional characteristics of four different formulations of acetylsalicylic acid tablets produced by direct compression method using both the Heckel and the Kawakita equations.

Heckel and kawakita equations have been used over time to assess the compression characteristics of pharmaceutical powders and granules. (Heckel 1961), and (Kawakita *et al* (1971). The compression of powder/ granules into tablet can generally be divided into three

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(3) distinct stages

a. **Die filling**, in which the blend or powder mixes are delivered into the die cavity.

b. **Compaction**, in which the powder/ granules are compressed inside the die cavity by the two punches; and

c. **Ejection**, the compact is ejected from the die. (Heckel, 1961 and Kawakita, *et al* 1971)

The powder behaviour during the above 3 stages will determine the properties of the final compact. Therefore understanding the compressional behaviours of powders during each stage is very important and has attracted significant attention over the past several decades. (Shivanand *et al* 1992).

Heckel related the relative density (D) of a powder bed during compression to the applied compaction load (*P*).

Mathematically Heckel relationship is expression as;

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

In which A is the intercept of the linear region of the heckel plot on the y axis

K = Constant = gradient of linear portion of the plot

$P_y = 1/K$ = reciprocal of gradient (indication of the onset of plastic deformation).

from the intercept, the relative density D_a can be obtained as follows;

$$D_a = 1- e^{-A} \quad (2)$$

D_o which is the relative density of the powder bed when applied pressure is zero. This describes the initial rearrangement of the powder during the die filling.

Mathematical, D_o = bulk density/ particle density.

By simple calculation the relative density of powder at low pressure (D_b) can be obtained;

$$D_b = D_a – D_0 \quad (3)$$

Kawakita however relates applied pressure to the degree of powder bed volume reduction (C).

The degree of volume reduction (C) upon application of pressure to a powder bed was first expressed by Kawakita and the mathematical equation

$$C = (V_o - V_p)/ V_o = abP / (1+ bP) \quad (4)$$

Therefore, $P/C = P/a + 1/ab$

Where V_0 = Initial bulk volume

V_p = bulk volume upon application of pressure a is a constant which is an indication of minimum porosity b is an indication of plasticity of the material the reciprocal of b give the PK_b value an indication of the total plastic deformation of powder, and by definition it is the pressure required to reduce the powder bed by 50%. (Shivanand *et al* 1992) and (Lin *et al* 1995)

MATERIALS

The materials used were Acetylsalicylic acid BP (Sigma Chemicals), Corn starch BP (BDH chemical limited. Poole UK), Acid modified starch (ABU Zaria), Pregelatinized starch (ABU Zaria) and microcrystalline cellulose from Saw dust(ABU Zaria).

METHODOLOGY

PREPARATION OF ACID MODIFIED STARCH.

Method according to the Buwalda and Willemina (1997) was adopted.

36% W/V corn starch BP slurry was prepared. 45g of the slurry was measured and poured into stainless steel vessel maintained at 50^0 . 28ml of 6N HCl was added drop wise while stirring for 18h. The stainless steel vessel was removed after 18 h, cooled and filtered. The filtrate was washed with deionised water and re-suspended in 250ml of water. The pH was adjusted to pH 6 with 1N sodium hydroxide solution. The product was filtered and washed with deionised water and 800ml of ethanol to eliminate all the chloride ions. The acid modified starch obtained was then dried in Gallenkamp hot air oven (Philips Harris limited England) at 40^0C for 48 h. The percentage yield was determined

Dried acid modified starch was milled and sieved, fraction retained on 150µm sieve was used for further studies.

PRODUCTION OF PREGELATINIZED CORN STARCH (BPC, 1979)

The pregelatinized corn starch was prepared using method describe in the British Pharmaceutical Codex 1973. Aqueous slurry of the starch was made with 100g of corn starch powder suspended in 100ml of deionised water.

This was heated to 55^0C for ten minutes while continuously stirred. The resultant paste was dried in a hot air oven (Gallenkamp) at 60^0C for 48h. The dried mass was sized reduced and sized sieve. The weight retained on 150µm sieve was collected and used for further studies.

PRODUCTION OF MICROCRYSTALLINE CELLULOSE FROM SAWDUST (SDMCC)

Sawdust alpha cellulose used was obtained from the department of Pharmaceutics, Ahmadu Bello University, Zaria, Nigeria. Sawdust microcrystalline cellulose was however prepared using 500ml concentrated hydrochloric acid boiled for 15min

100g of alpha cellulose was weighed and transferred to 1L beaker containing 500ml boiled concentrated HCL, this was stirred continuously for 15 min., after which the slurry was filtered and residue washed and neutralized with ammonia solution. (Okhmafe, *et al* 1992

DETERMINATION OF THE FLOW PROPERTIES OF THE FORMULATIONS.

The various formulations of acetylsalicylic acid were prepared according to table 1, the bulk and tapped densities of the powder were determined using standard procedure, Carr's indices and Hausner's ratios were calculated and presented in table 2.

DETERMINATION OF PARTICLE DENSITY.

The particle densities for the various formulations prepared according to table 1 were determined by pycnometer method using xylene as the displacement fluid. A 50ml pycnometer bottle was weighted (W), this was filled with xylene, and re weighted (W_1). The difference between (W) and (W_1), was taken as (W_2). One gram quantity of the sample was weighed and labelled (W_3), which was carefully transferred into the xylene filled pycometer, after which the bottle was re-weighed (W_4) , the particle density (p_t) was calculated from the equation below;

$$p_t = (W_2{}^x W_3) \div (W_3 - W_4 + W_2 + W)$$

the same procedure was repeated for all other formulations.

DETERMINATION OF PRE-COMPRESSION DENSITY (D_o)

D_o which is the pre-compression density and is the ratio between the bulk density and particle density

$$D_o = \frac{\text{Bulk density}}{\text{Particle density}}$$

PREPARATION OF COMPACTS

KEYS:

ASA …….Acetylsalicylic Acid

SDMCC……Microcrystalline Cellulose from Sawdust

CS ……..CORN Starch

Table 1 : Tablet Formulations

Material	AF_1(mg)	AF_2(mg)	AF_3 (mg)	AF_4(mg)
ASA	300	300	300	300
SDMCC	80	80	80	91.2
CS	11.2	0	0	0
AMS	0	11.2	0	0
PGS	0	-	11.2	0
TALC	8	8	8	8
Mag.Stearate	0.8	0.8	0.8	0.8
TOTAL (mg)	**400**	**400**	**400**	**400**

AMS…….Acid Modified Starch

PGS……..Pregelatinized Starch

For each batch the required quantities of each ingredient were weighed and mixed in a mortar and pestle for about 30 min.

400mg of admixture powder was compressed for 30 sec with pre-determined forces (28.31,56.62,84.93,113.23,141.54.,169.85 mega Newton per meter square) using hand held hydraulic tableting machine fitted with pressure guard, Model C, Carver inc., Menomonee Falls, WI)

2% dispersion of Magnesium Stearate in a 1:1 ether - ethanol solution was used to lubricate the surfaces of the dies and punches size (10.5mm)

After ejection the compacts were stored over silica in a gel desiccator to allowed elastic recovery and hardening to prevent false low mean yield pressure. Odeku, *et al* 2003.

The tablet metrics were the after determined. The relative density for each formulation (D) was calculated using the equation

$D = W / (V_t \times P_t)$

where V_t = tablet volume

P_t = Particle density

Heckel plots of In (1/ (1-D) versus applied pressure were constructed.

So also, the Kawakita plot of P/C against applied pressure was also constructed

DETERMINATION OF TABLETING PROPERTIES

Using the single punch tableting machine, (Type AR 400, Erweka Gmbh, Germany) fifty tablets per formulation as in table 1 were produced. The various ingredients were weighed as in table1 and these were mixed for about 30min with the aid of mortar and pestle.

400mg of admixture powder was accurately weighed and used to calibrate the tableting machine fitted with 10.5mm dies and punches.

In each formulation tablets produced were stored in a desiccator to allow for elastic recovery.

The following tests were carried out on each formulation according to the British Pharmacopoeia methods.

- Tablets weight uniformity
- Tablets diameter and thickness
- Tablets disintegration time test

Tablet crushing strength and friability were also determined using standard methods

STATISTICAL ANALYSIS

Statistical analysis was carried out to compare the tableting properties of the four formulations of acetylsalicylic acid tablets using the student's t-test as a statistical tool. At 95% confidence interval, $p \leq 0.05$ were considered significant.

RESULTS AND DISCUSSION

DISCUSSION OF RESULTS

All the four formulations of acetylsalicylic acid tablets evaluated in this study shows acceptable tableting properties. The friability values range from 0.46 to about 0.5% ,this is below the limit of 1% . The British Pharmacopoeia 2010 stated that all uncoated tablets must have friability values less than 1%.

The friability of tablets is an indication of the ability of the tablets to withstand normal handling and transportation stress. (Leon *et al* ,2009)

Also, the tablet crushing strength and the disintegration time values of all the four formulations fall with the British Pharmacopoeia 2010 limits.

Specifically, the crushing strength of all tablets are expected to be between 4 and 15 KgF while all uncoated tablets are expected to disintegrate within 15min.

Tablets are not expected to be brittle, but rather they are expected to be hard and strong throughout the shelf life. Interestingly, AF4, a formulation containing SDMCC is the least friable and the strongest among all the four formulation evaluated.

The order of friability is `AF4<AF3<AF2<AF1. Differences in crushing strength, disintegration time and friability values of tablet formulations were statistically significant at $p \leq 0.05$.

TABLE II

Parameters Derived from Density Measurement and Tableting properties.

Parameters	AF1	AF2	AF3	AF4
Bulk Density (g/cm^3)	0.588	0.606	0.625	0.588
Tapped Density (g/cm^3)	0.769	0.800	0.880	0.800
Carr's index (%)	23.53	24.25	28.97	27.50
Hausner's ratio	1.31	1.32	1.41	1.36
Uniformity of tablet weight (mg)	400±0.05	400±0.04	400±0.04	400±0.07
Uniformity of tablet diameter (mm)	10 ±0.05	10±0.001	10±0.01	10±0.01
Tablet friability (% w/w)	0.53	0.5	0.46	0.40
Tablet crushing strength (KgF)	5.0	5.5	6.0	7.0
Tablet disintegration time (Min)	2.7	0.6	0.9	5.0

TABLE III
Parameters derived from Density Measurements, Heckel and Kawakita plots

Formulations	D_O	P_Y	D_A	D_B	P_K	D_I
AF1	0.227	353.85	0.693	0.466	0.035	0.569
AF2	0.214	117.95	0.7583	0.5443	0.052	0.375
AF3	0.217	128.7	0.7583	0.5413	0.090	0.538
AF4	0.196	382.55	0.7724	0.5764	0.036	0.5625

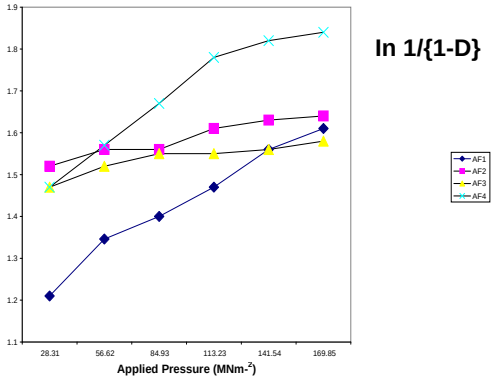
The crushing strength however is in the order of AF4>AF3>AF2>AF1.

SDMCC used in formulation AF4 function as both a diluent, and a dry binder. Formulation AF4 containing only SDMC gave tablets that are less friable and stronger, when compared to those containing acid modified starch and native starch.

Even though all formulations passed the disintegration time test, the values rank in the order of AF1<AF2<AF3<AF4.

Figure I shows the Heckel plots for the acetylsalicylic acid tablets, P_y was obtained from

Figure I Heckel plots for four Acetylsalicylic acid tablet Formulations



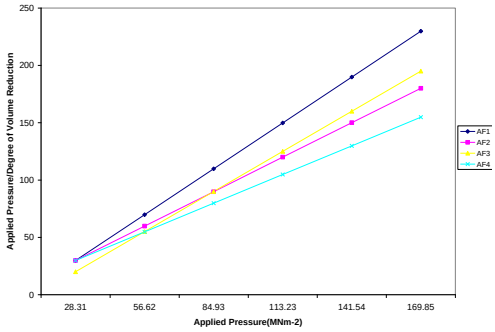
the region of the plots showing correlation of >0.990 for all the formulations.

The intercept was determined by extrapolation of each plot. The values of D_A ,D_B ,D_O and the mean yield pressure where presented in table iii.

D_O values represent the degree of initial packing of the powder in the die ranks in the order of $AF_4<AF_2<Af_3<AF_1$

The D_A values which represent the total degree of packing at zero pressure rank in the order $AF_1<AF_2<AF_3<AF_4$.

Figure II Kawakita plots for acetylsalicylic acid tablet formulations



Formulation AF_4 containing only SDMC gave the highest D_O value.

In general it was observed that formulations containing native cornstarch showed the lowest D_A value, while that highest value is from AF4 formulation containing SDMCC.

The D_B value represents the particle rearrangement stage in compression cycle, and this is a good indication of the extend of particle fragmentation which can also occurs simultaneously with plastic and elastic deformation.

The D_B value rank in the order of $AF_1<AF_3<AF_2<AF_4$.

Formulation containing SDMCC exhibited the highest value, while that containing corn starch showed the lowest values. D_B values where actually observed to be higher than that of D_O . This may be due to fact that particle fragmentation and subsequent filling of void spaces between particles occurred extensively at low pressure. Odeku *et al* 2005.

Also the loose packing of large particle at zero pressure tend to yield low D_O values. (Itiola and Pilpel1991)

There is an inverse relationship between the mean yield pressure and the ability of a material to deform plastically when pressure is applied. The P_y values rank in order of AF_4> AF_1> AF_3> AF_2

Interestingly formulation AF4 showed the highest value of mean yield pressure which indicates low onset of plastic deformation while formulation AF_2 that have the lowest mean yield pressure indicate fastest onset of plastic deformation .

This shows that formulation containing acid modified starch plastically deform faster during compression than other formulations.

Figure ii, shows Kawakita plots for the four formulations. The values of constants a and ab were calculated from the intercept and slope respectively.

D_1 values which is a measurement of initial relative density of the formulation when small pressure is applied to the powder bed is obtained from equation below

$D_{1=}$ 1-a

And for all the formulations the value of D_1 is higher than $D_{O.}$ this is in agreement with previous finding of Itiola et al, 1998.

The *P*K values are inverse measurement of total or overall plastic deformation.

Formulation AF1 shows the lowest *P*K value and thus the highest total plastic deformation.

Formulation AF_2, even though show the fastest onset of plastic deformation, the total plastic deformation was highest with formulation AF_1 while particle fragmentation was highest with formulation AF_4.

CONCLUSION

This study provides a useful understanding of the properties of four different formulations acetylsalicylic acid tablet. And from the result obtained aboved, we reasonably came to the conclusion that formulation AF_1 having the highest total plastic deformation is the best formulations among all the formulations of acetylsalicylic acid tablets evaluated, and can be expected to give best optimized products.

REFERENCES

1. Alebiowu, G., and Itiola, O.A. "Compressional Characteristics of Native and Pregelatinized Forms of Sorghum, Plantain, and Corn starches and the Mechanical Properties of their Tablets"
2. Elder, M.G., Deswiet, M., and Robertson, A. Low Dose of Aspirin in Pregnancy. *Lancet* 1998**.1**:410
3. Grotta, J.C., Current medical and Surgical Therapy for Cerebro-Vascular Diseases. *Eng. J. Med.* 1987, **317**:1505-1516[IDIS 236147] *pubmed.* 3317048
4. Heckel, R.W. "Density-Pressure Relationships in Powder Compaction," *T. Metall Soc. AIME* **221**, 671 – 675 (1961a).
5. Heckel, R.W. " An Analysis of Powder Compaction Phenomena" ," *T. Metall Soc. AIME* **221**, 1001 – 1008 (1961).
6. Kawakita, K and Ludde, K.H "Some Considerations On Powder Compression Equations." *Powder Technol*. **4** (2), 61-68 .1970-1971
7. Okhamafe, A.O, Igboechi,A.c., Ubrufitih, C.E., Akinyemi,B.O and Ighalo,M.O . cellulose extracted from Groundnut shell, and Rice husk, (a &b) *Pharmworld J***.**9 (**1**) 11-16
8. Oyeniyi, Y.J ., Ibrahim, M.A., and Oyi, A.R Physicochemical Properties of Ethycellulose derived from Sawdust. *Nigerian Journal of Pharmaceutical Sciences*, Vol. **10**. No.1 Oct.2011
9. Shivanand, P., and Sprockel, O.L. "Compaction Behaviour of Cellulose Polymer" *Powder Technol*. **69** (2), 177-184 (1992)
10. Lin,C., and Chan, T. "Compression Behaviour and Tensile Strenght of HEAT-Treated polyethylene Glycols." Int.J.Pharma.sci. **66** (2), 169-179 (1995)