PHARMACEUTICAL TABLET MAKING: IS IT AN ART OR SCIENCE?

DEDICATION

This lecture is dedicated to:

First and foremost, to God Almighty, who has given me good health by His grace and mercy. To God be the honour and glory forever and ever, Amen.

To my parents, my father, late Mr. Nathaniel Esezobo Oise and my mother, late Mrs. Edomiete Esezobo Oise, both of blessed memory.

To my wife Aremere and our children Aidolegbe, Ishialose, Oahre and Idaehor whose cooperation, love and encouragement made it possible for me to get this far in my Academic Career.

ACKNOWLEDGEMENT

My sincere gratitude goes to late Professor John E. Carless, who was the Head of Department, Department of Pharmaceutics and Pharmaceutical Technology, Kings' College, University of London. He encouraged me to read for a PhD. Degree. In a similar manner, I will also like to express my profound and heartfelt gratitude to late Professor Neiton Pilpel (of blessed memory) who was my supervisor and showed me the path to success in academics. May their gentle souls rest in perfect peace, Amen.

I also wish to thank the Midwest/Bendel State (now Edo and Delta States) of Nigeria for the scholarship I enjoyed from the late Dr. S.O. Ogbemudia's led military government. I am eternally grateful to him and I wish his soul an eternal rest.

I also thank I.C.I. Ltd. Pharmaceutical Division, Macclesfiled, Cheshire, U.K. for their financial support and gifts of apparatus and chemicals during my postgraduate (PhD) studies. I am also particularly grateful to Professor David Ganderton who was at the time the Director of Research and Development at I.C.I.

I am also grateful to the British Council for the award of a research fellowship and to the University of Benin for granting of a study leave which enabled me to carry out further research work at Kings' College, University of London in 1985.

INTRODUCTION

Mr. Vice-Chancellor, Sir, before I start this lecture I crave your indulgence to permit me to explain briefly what is meant by the term "Pharmaceutics" and how Pharmaceutics fits into the overall scheme of pharmaceutical science.

WHAT IS PHARMACEUTICS?

The word pharmaceutics is used in pharmacy and pharmaceutical science to include all the steps to which a drug is subjected towards the end of its development (i.e. it is the stages that follows its discovery or synthesis, its isolation and purification and testing for advantageous pharmacological effects and the absence of serious toxicological problems). Defined in its simplest form; pharmaceutics convert a drug into a medicine. Therefore, pharmaceutics is concerned with the scientific and technological aspects of the design and manufacture of dosage forms.

Pharmaceutics also includes the following:

1. An understanding of the basic physical chemistry necessary for the efficient design of dosage form – (physical pharnaceutics).
2. The design and formulation of medicine – (dosage form design).
3. The manufacture of these medicines on both a small scale (compounding) and a large scale (pharmaceutical technology) (Aulton, 2002).

WHAT ARE MEDICINES?

Medicines are drug delivery systems. That is, they are a means of delivering drugs to the body in a safe, efficient, reproducible and convenient manner.

It must be emphasized that medicines are rarely drugs alone, but they require addictives to make them into dosage forms and this in turn introduces the concept of formulation. Drugs are formulated into 3 main dosage forms. We have:

1. **Liquid dosage forms**: e.g. solutions, suspensions (mixtures) and emulsions.
   These are for oral administration and external application.
2. **Semi-solid dosage forms**: e.g. ointments, pastes, creams, jellies, suppositories and pessaries. Some of these are for external application while others are for insertion into body cavities.
3. **Solid dosage forms**: e.g. powders or granules, capsules and tablets. These are for oral administration. The oral route is the most common way of administration of drugs, and among the oral dosage forms, **tablets** of various different types are the most common (York, 2002).

THE TABLET: A DOMINANT DOSAGE FORM IN DRUG ADMINISTRATION.

The main features of tablets which have led to their dominant position as a dosage form in practical therapeutics are their convenience and ease of administration, the precision with which their drug content can be controlled and their general durability and stability towards physical and chemical degradation.

Basically, tablets must satisfy two essentially opposing requirements. Firstly, the forces between their constituent particles must be sufficiently strong to give the tablet strength and cohesiveness so that they will be able to withstand mechanical shock or abrasion from outside sources, from the time of manufacture to the time they are handled by a patient. Secondly, these binding forces must undergo fundamental modification in the presence of digestive fluids in the body so that the tablet can break down into fine particles and release the active principle into the patient's systemic circulations.

It rarely happens that the particles of the active principle or drug possess the necessary properties to meet these two conflicting mechanical requirements. Greater or lesser quantities of excipients are therefore needed to produce tablets which, in addition to containing the correct dose of the drug, also meet manufacturing specification in regard to uniformity, weight, hardness, friability and rates of disintegration and dissolution (Gunsel et al., 1970).

COMPOSITION OF TABLET FORMULATIONS AND METHOD OF PREPARATION OF TABLETS

Pharmaceutical tablets may contain up to half a dozen ingredients. Besides the active drug, there is a **diluent** (usually a pharmaceutically inert material) to provide bulk; **a binding agent**, to facilitate compression and impart the structural strength during the processing, packing and handling of tablets; **a disintegrant** to break up the tablet when it is wetted; **a lubricant** to prevent it sticking to the punches and dies of the tableting machine and **a glidant** to make the powders flow freely during the tableting process.

In order to blend these ingredients together in the correct proportions to form free-flowing materials which can be fed into the machines and compressed at a high speed, the formulation is granulated. The granulation process overcomes problems of dustiness, improves the uniformity of the feed rate to the machines and hence the uniformity of the tablets and ensures that their composition is not significantly altered from that of the original formulation as a result of segregation and demixing of the components.

Granulation is carried out either by **dry method** (slugging) which involves simple compression of the ingredients or by a **wet method** in which a granulating agent is used to cement the individual particles together. Of the two, wet granulation is the most widely used in the pharmaceutical industry (Pilpel, 1969).

THE ART OF TABLET MAKING

In spite of the antiquity of tableting process and their widespread use in the pharmaceutical industry, the formulation of tablets is still generally carried out in an empirical manner. Tablet formulators on receiving a new drug to tablet, tend to select the ingredients on the basis of cost and on the basis of their personal likes and dislikes rather than on considerations of proven technical merit. As a result, tablets containing the sme dose of the same active ingredient often have widely varying formulae. A good example of the arbitrary choice of ingredients concerns the selection of binding agents and their methods of application. There has

been a tendency to use only one or two types of binding agents e.g. gelatin, polyvinylpyrrolidone (PVP), without fully investigating the effects produced, for example, by altering their grade, concentration in a formulation and method of application e.g. whether applied in the dry state or in solution or in suspension.

Relatively little systemic work has been done on the combined effects of moisture and binding agents on the mechanical properties of the starting ingredients and of the granules into which they formed as the first stage in a tableting process.

A SCIENTIFIC APPROACH IN TABLET MAKING

In an attempt to adopt a scientific approach to the selection of binding agents and other excipients in tablet formulation, one of the main purpose of my early research work was to study the fundamental mechanical and failure properties of a typical tablet formulation and of the individual components of the formulation.

The objective was firstly, to see if any correlations could be established between the fundamental properties of the ingredients and those of the tablets prepared from them. Secondly, to see how changes in the formulation would affect the mechanical properties of the mixed ingredients and of the tablets.

For this purpose an oxytetracycline tablet formulation was selected. Two pieces of equipment were used to measure the mechanical and failure properties of the drug and the other ingredients used in the tablets. These were the Warren Spring Split-plate tensile tester (Ashton et al., 1964) and the Annular Shear Cell (Carr and Walker, 1968).

FUNDAMENTAL MECHANICAL AND FAILURE PROPERTIES OF A TYPICAL OXYTETRACYCLINE TABLET FORMULATION

The fundamental mechanical and failure properties of a fine powder in quantitative terms are expressed as measures of shearing and tensile properties after consolidating it in a shear cell apparatus (Carr and Walker, 1968) or a tensile tester (Ashton et al., 1964). The results of the shear tests are plotted in the form of yield loci. From these, values of the cohesion and angle of internal friction of the powder can be obtained which provide information about flow and failure properties (Ashton et al., 1965; Williams and Birks, 1967).

We measured the shearing and tensile properties of a typical oxytetracycline tablet formulation which consisted of 90.2% (w/w) oxytetracycline dihydrate, 7.2% (w/w) Avicel (PH101), 2.6% (w/w) alginic acid plus an appropriate quantity of an aqueous gelatin solution to act as binding agent (Esezobo and Pilpel, 1974).

Measurements were made on the individual ingredients then on the formulation without gelatin binding agent and on the formulation plus the binding agent after wet granulation. The granules were dried and milled back to approximately the same particle size as the original mixture. This was necessary to enable the shearing and tensile tests to be performed (Eaves and Jones, 1971) and to ensure that complicating effects caused by differences of particle size (Cheng, 1968; Kocova and Pilpel, 1971 – 1972; Eaves and Jones, 1971) are eliminated.

The result showed that the tensile strength of oxytetracycline is different from that of avicel or alginic acid after allowance has been made for the small but unavoidable differences in their particle size distribution and

moisture contents. Addition of about 7% (w/w) avicel and about 3% (w/w) alginic acid produced a noticeable increase in the tensile strength of the drug at any packing fraction (see Fig. 1). The addition of the excipients reduces the coefficient of reassertion of oxytetracycline and thus prevents spontaneous fracture of compacts prepared from it. This might be due to mechanical interlocking of the addictive particles caused by their fibrous nature and irregular shapes.

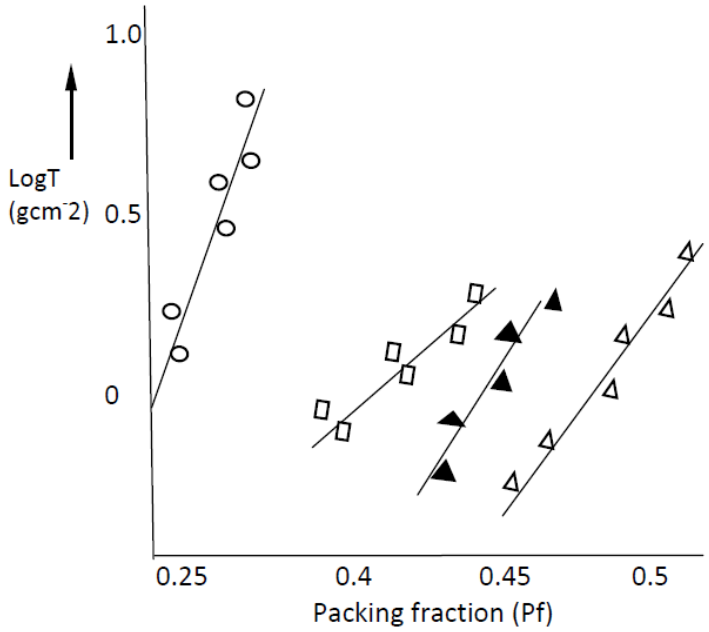
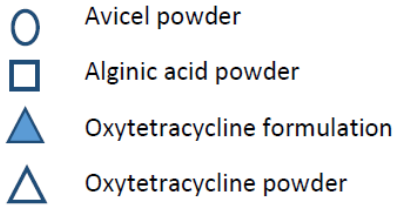


Fig. 1 Log tensile strength vs packing fraction for loosely packed beds of excipients and oxytetracycline formulation



The shearing test results showed that the cohesion and angle of internal friction of the milled granules both increase with increase in the concentration of the binding agent, at moisture levels between 2-4% (w/w). The general conclusion is that there is a considerable increase in the mechanical strength and a decrease in the flowability of the formulation as the concentration of binding agent in it is raised.

The result also showed that as the concentration of gelatin at any moisture level between 0 and 25% (w/w) was increased, the tensile strength of the formulation increased. Within the moisture levels investigated, we found that the tensile strength and cohesive force of the milled granules is a function of the quantity of gelatin present in the formulation (Esezobo and Pilpel, 1974).

The interesting point to be made here is that before this work was carried out, the shearing and tensile tests were used primarily for idealized powders in which only one material was present in a relatively narrow range of sizes and shapes. However, in the present work we have applied the same test procedures and

methods of analyzing the results to real powder systems containing a range of ingredients over a range of sizes and particle shapes.

COMPACTS AND TABLETS PREPARED WITH HAND OPERATED HYDRAULIC PRESS

➢ EVALUATION OF 5g COMPACTS AND 600mg TABLETS

In a further study carried out, we compressed the excipients, the formulated powder and mixed sizes of the oxytetracycline granules containing the same ingredients as before plus appropriate amounts of gelatin and moisture. The milled granules were formed into 5g flat-faced compacts and 600mg deep convex tablets respectively, with a hand operated hydraulic press and the tensile strengths of these were measured using the diametral compression test (Fell and Newton, 1970; Esezobo and Pilpel, 1977a).

For the flat-faced specimen, the tensile strength, T, is

$$T = \frac{2P}{\pi Dt}$$

where, P is the applied stress in mN

D is the compact/tablet diameter in cm,

t is the compact/tablet thickness cm and for the deep biconvex tablets.

$$T = \frac{2P}{\pi(0.28 + 1.03(1 - 0.402))}$$

(Little and Mitchel, 1963; Esezobo, 1975)

The results showed that at any packing fraction, the avicel compacts have the highest tensile strength, followed by those of alginic acid, the oxytetracycline formulation and the pure oxytetracycline dehydrate. The pattern is the same as that obtained on relatively loosely packed beds of these materials using a tensile tester (Esezobo and Pilpel, 1974) (see Figs. 1 and 2).

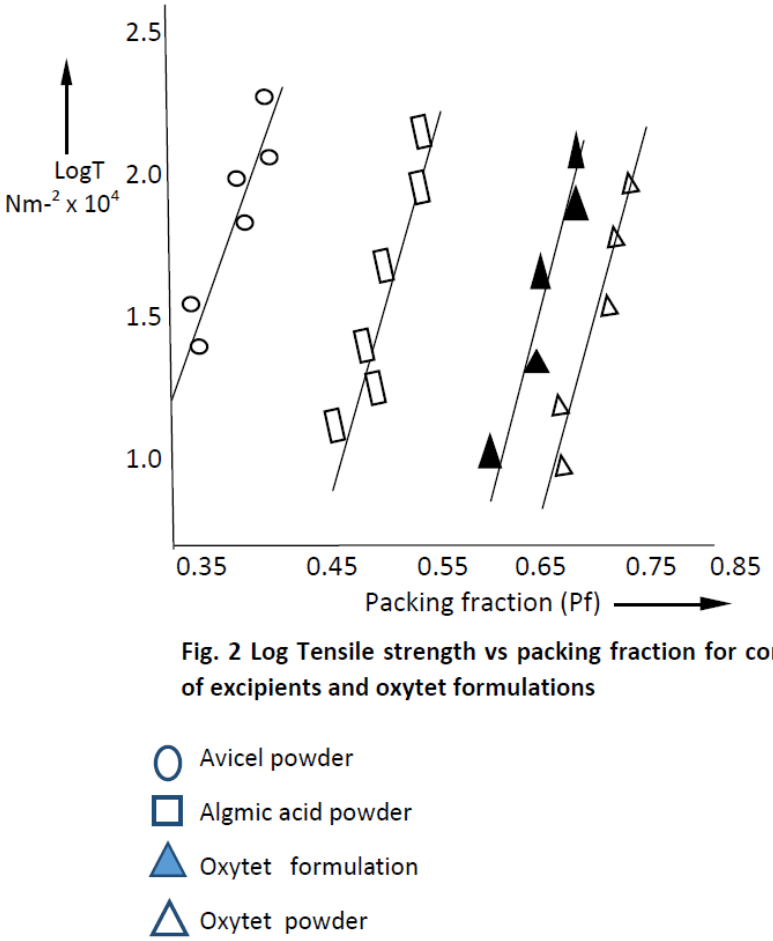


Fig. 2 Log Tensile strength vs packing fraction for compacts of excipients and oxytet formulations

It was also observed that when compression pressures greater than 70 MNm^{-2} were used for preparing compacts, those made from oxytetracycline alone tended to cap or laminate but those made from the formulation did not. Thus, the excipients, avicel, in particular and alginic acid to a lesser extent appear to counteract the elastic recovery of pure oxytetracycline after compression,and thus reduce its tendency to capping and lamination. This explains, in part, their incorporation in the formulation and it is clear that by altering the amounts and proportions of these two excipients, one should to some extent, be able to control the strengths of the compacts (or tablets).

Employing the theory of tensile strength, proposed by Cheng (1968) we found that increases in both moisture and gelatin contents of compacts and tablets increased the range of the attractive forces that operate between the granules. In addition, by studying the effects of moisture and gelatin on the compressional behaviour of the granules,it was possible to classify them into different types. Thus, we found that all the formulated oxytetracycline granules behaved as Type B materials.

Type B material is usually obtained from different particle size fractions of the powders. (With Type B materials, there are initial curved regions followed by parallel straight lines indicating that the particles are fragmenting at an early stage of the compaction process) (York and Pilpel, 1973). These granules had essentially the same particle size distributions (slight differences being due to their different gelatin contents), and thus, the Type B behaviour must be due to the combined effects of moisture and binding agent and not in these systems to differences in particle size.

A further analysis of the results in terms of the equations of Cheng (1968) and of Heckel (1961) it was found that fragmentation of the oxytetracycline granules takes place between packing fraction of 0.745 and 0.835 depending on the amount of gelatin present in the formulation (see Table 1).

Table 1: The calculated packing fractions of points where the curved and linear portions meet in the Heckel plots and points at which breaks occurred in the graphs employing the Cheng equation.

Gelatin content	Values of packing fraction (P_f) at which brakes occurred in graphs using:	
	HECKEL EQUATION	CHENG EQUATION
0	0.815	0.835
2.50	0.798	0.818
3.75	0.801	0.834
5.00	0.780	0.825
6.25	0.767	0.791
7.50	0.745	0.767

It is seen that the values in columns 2 and 3 compare satisfactorily over the whole range of gelatin content.

➢ EVALUATION OF 300mg TABLETS

Commercial oxytetracycline tablets normally contain 250mg of the drug and have packing fraction in excess of 0.75. We therefore considered it desirable to see to what extent the changes produced by moisture and gelatin on the mechanical properties of rather loosely packed powder beds and of 5g compacts (made from milled granules) would be reflected in the properties of 300mg deep convex tablets prepared from un-milled granules of the same formulations.

We prepared the tablets from the formulated granules as before, in a hand press. The tensile strengths of the tablets were measured, as stated previously, by the diametral compression test (Fell amd Newton, 1970), the disintegration times of the tablets by the standard BP (1973) method and their dissolution times by the Levy and Hayes (1960) beaker method (Esezobo and Pilpel, 1976).

The result showed that increasing the gelatin content in all cases caused an increase in tensile strength of the tablets. At a particular packing fraction, as the moisture increased, initially, the tensile strength of the tablets increased with moisture content but at concentrations above 3 – 4% (w/w) they started to decrease. The maximum tensile strength occurred when the tablets contained between 2.5 and 4.5% (w/w) of moisture and this was found to depend on the gelatin content (see Fig. 3).

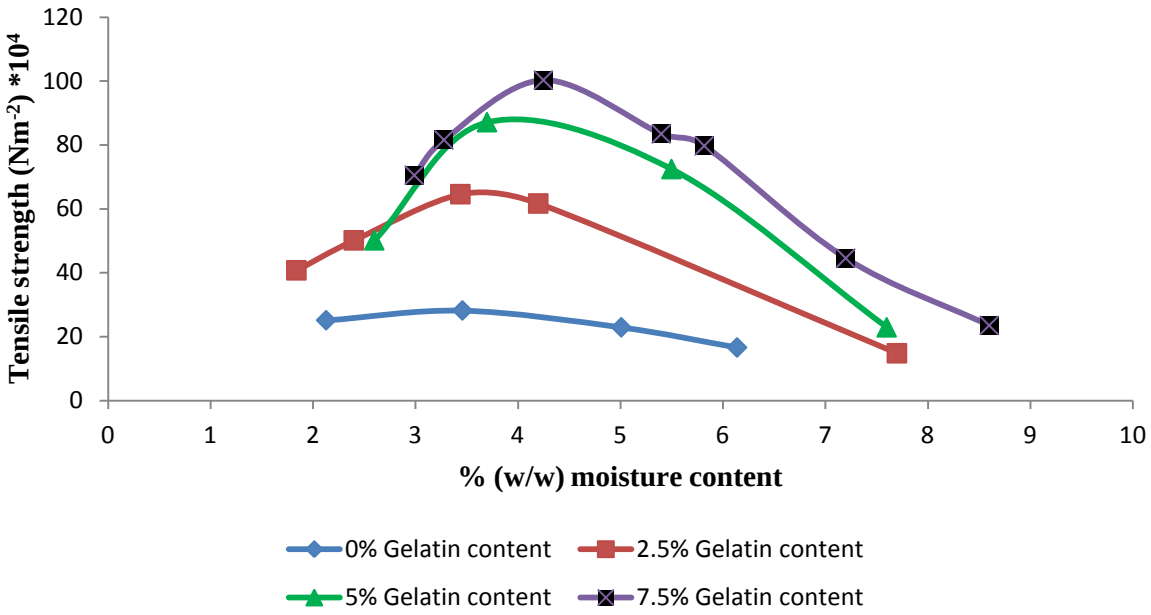


Fig. 1: Effect of moisture and gelatin contents on the tensile strengths of 5g (2.54 diameter) flat-faced compacts made from unmilled granules at P_f = 0.70.

The properties of the tablets was also found to depend on their packing fraction and the results showed that as the packing fraction was increased there was initially a decrease in both the disintegration and dissolution times and attained a minimum value when the packing fraction was between 0.77 and 0.82. But when the packing fraction was increased further (i.e. beyond 0.82) the disintegration and dissolution values increased (see Fig. 4) (Esezobo and Pilpel, 1976). The minima observed in the disintegration and dissolution times of the tablets, corresponded to the range of packing fraction at which fragmentation of the oxytetracycline granules was found to occur (see Table 1).

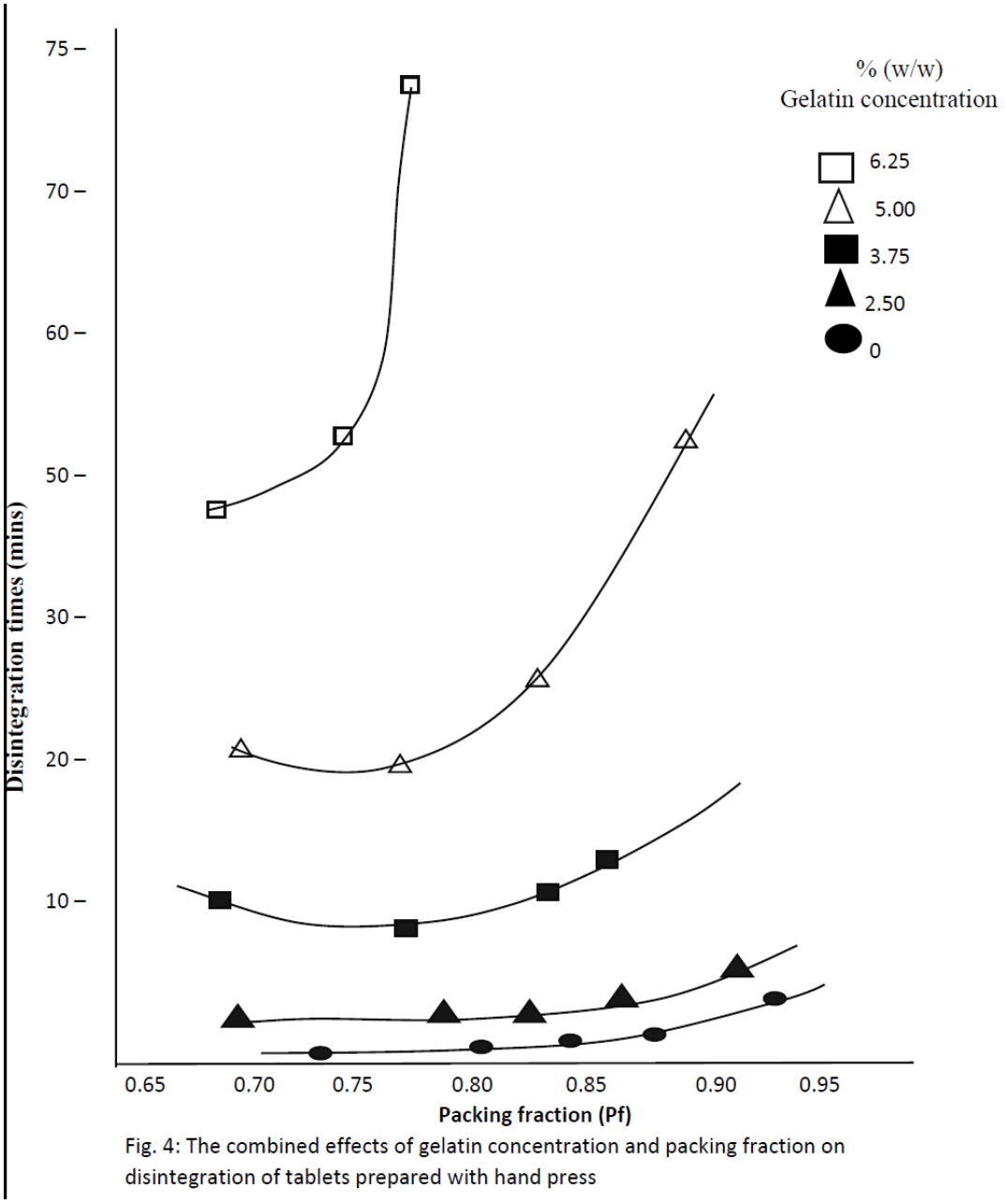


Fig. 4: The combined effects of gelatin concentration and packing fraction on disintegration of tablets prepared with hand press

TABLETS PREPARED WITH HIGH SPEED TABLETING MACHINES

In order to see whether any correlation existed between the properties of tablets made in a hand press and those made in high speed tableting machines, the study was extended further by employing **TWO** types of high speed tablet machines to prepare the tablets. The machines employed were:

1. Single-punch (model F3 manesty machines) and
2. Rotary punch (model D3B manesty machines)

The machines were equipped with flat-faced or deep concave punches. These were used to compress the granules into tablets (Esezobo and Pilpel, 1977b). (The operations and setting on each of the machines and the types of tablets prepared with the nachines are given in Appendix A.)

The results of tablets prepared with the single punch machine showed that increasing the gelatin concentration increased the tensile strengths of the tablets (see Fig. 5). The result was therefore similar to that obtained on loosely packed powdered beds (Esezobo and Pilpel, 1974), on compacts and tablets produced with a hand operated press (Esezobo and Pilpel, 1976, 1977a) and on a particular oxytetratcycline formulation (similar in some respects to the one used in this investigation but with povidone as the binding agent (Chalmers and Elworthy, 1976).

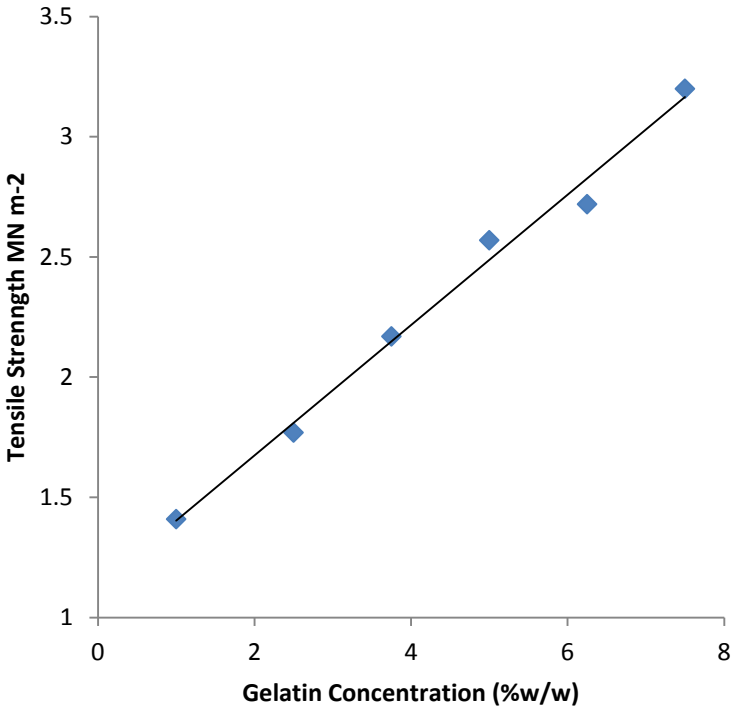


Fig 5: Tensile strength versus gelatin content of flat-faced tablets prepared with a single punch machine. (The range of P_f =0.85 – 0.87 and the range of moisture content was 2.4 – 3.2% (w/w)).

CAPPING PRESSURE OF 300mg BICONVEX TABLETS

It was earlier observed (Esezobo and Pilpel, 1976) that the 300mg deep convex tablets spontaneously capped when subjected to the diametral compression test; presumably because of their very thin edges. (These tablets are known to be subject to capping in production).

However, we found that the higher the gelatin concentration in the formulation, the higher was the packing fraction which the tablets could be compressed before capping occurred (see Table 2). Therefore, to overcome the tendency of the 300mg biconvex tablets to cap during production a reasonably high concentration of gelatin should be incorporated into the formulation.

Table 2: Effect of gelatin concentration on the capping pressure of 300mg deep biconvex tablets using a hand operated hydraulic press

Gelatin concentration (%w/w)	Capping pressure (MNm^{-2})	Packing fraction (P_f)
0	29.8	0.74
2.50	59.5	0.81
3.75	89.3	0.83
5.00	119.1	0.85
6.25	129.4	0.87
7.50	148.9	0.88

ANALYSIS OF THE DISSOLUTION RESULTS OF THE TABLETS

In order to arrive at a better understanding of the mechanisms of dissolution in a typical oxytetracycline tablet formulation, the dissolution results obtained on all the tablets were analyzed employing two methods of analysis. The methods employed were the equations of Wagner (1969) and that produced by Kitazawa et al., (1975).

Analysis of the results showed that the oxytetracycline tablets containing less than 5% (w/w) gelatin content conformed satisfactorily to Wagner's concept of log-normal distribution plot, since linear graphs were obtained for these samples. When more than 5% (w/w) gelatin was present, the graphs became curved and exhibited kinks when linearized by the first order method of plotting (see Fig. 6).

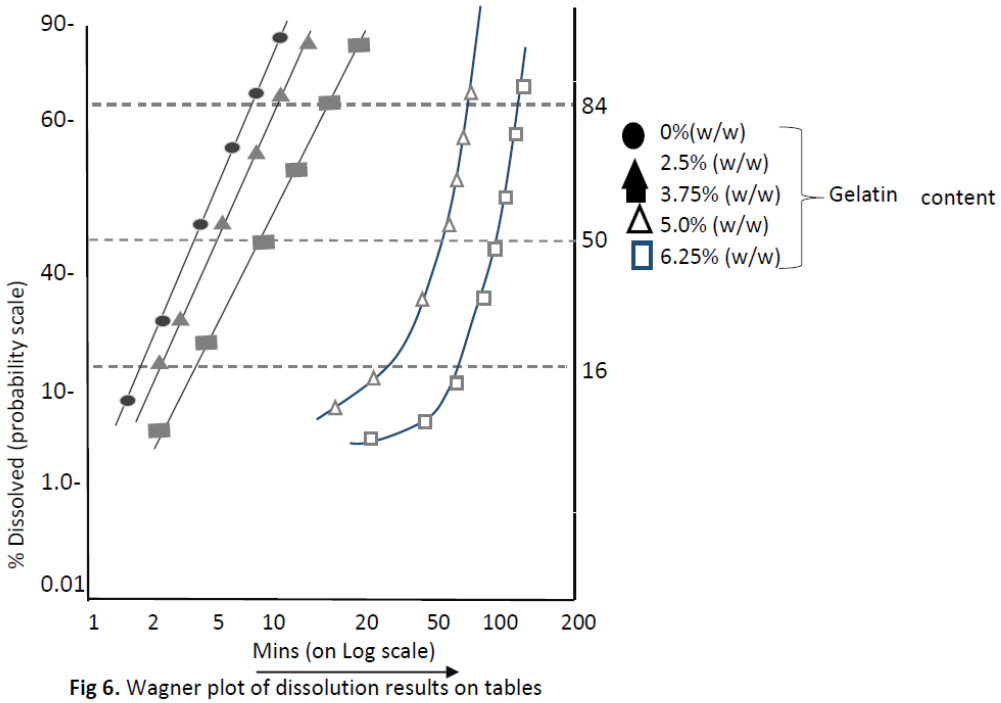


Fig 6. Wagner plot of dissolution results on tables (Pf =0.80) prepared with a single punch machine

Analysis by the Kitazawa et al., (1975) method showed that tablets compressed to a packing fraction of approximately 0.80 and containing less than 5% (w/w) gelatin yielded straight lines, with one dissolution rate constant, k, in each case (see Fig. 7). These tablets broke up rapidly into small particles as soon as they were in contact with the dissolution medium, resulting in a subsequent constant decrease as the granules dissolved. However, for tablets more than 5% (w/w) gelatin, the dissolution rate constants changed from k_1 to k_2 at certain times t_1 at all packing fractions (see Fig. 7).

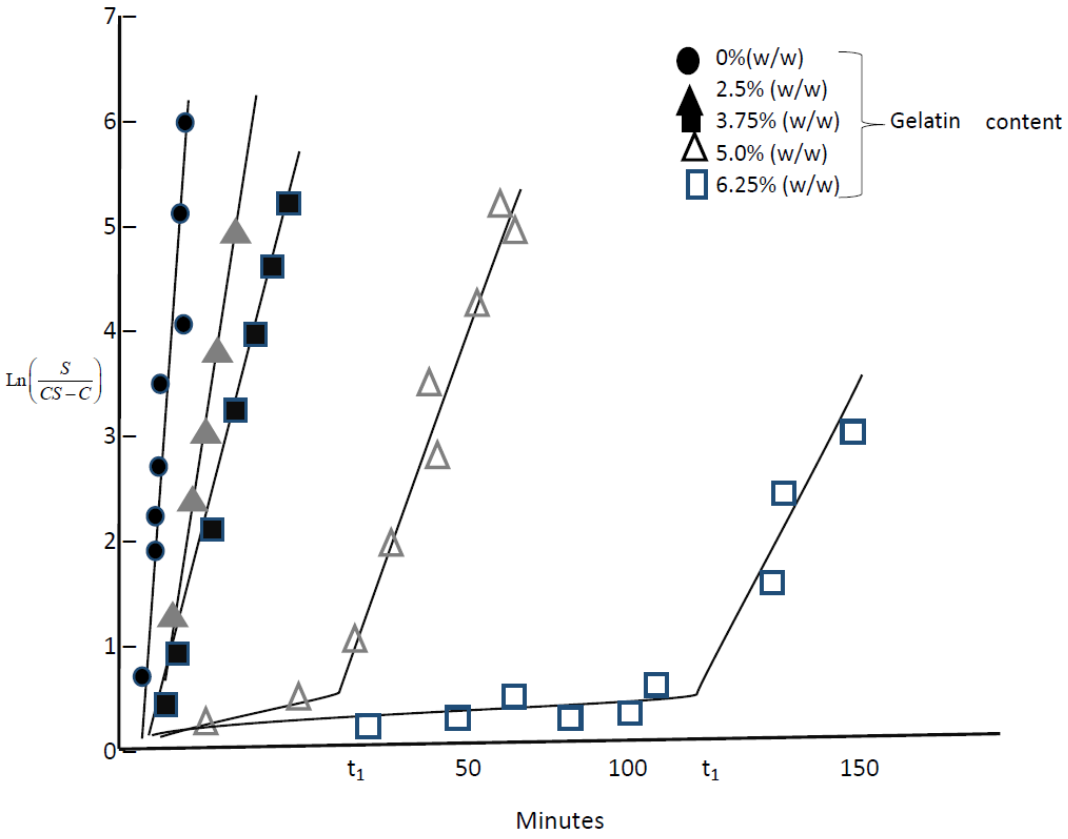


Fig. 7: Effect of gelatin content on the determination of dissolution rate constant using Kitizawa et al, (1975) equation for oxytetracycline tablets prepared with a single punch machine at Pf =0.80

Irrespective of the tableting equipment employed, the values of k for all tablets prepared with the 3 types of machines decreased with increase in their binding agent content (see Fig. 8).

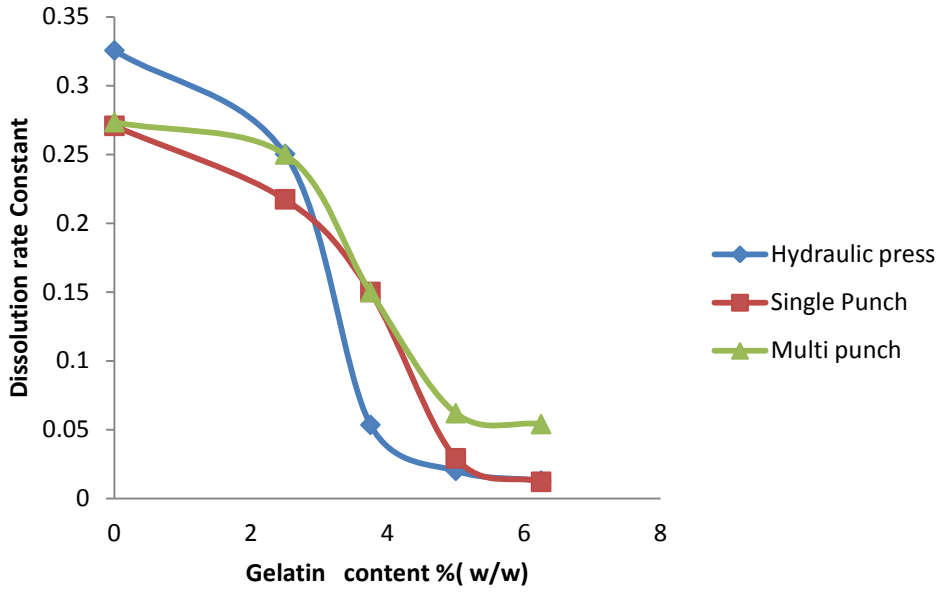


Fig 8: Effect of gelatin content on the k values calculated using Kitazawa et al., (1975) equation for tablets prepared with the 3 types of machines at P_f = 0.80.

EFFECTS OF FORMULATION AND PROCESSING PROCEDURES ON THE MECHANICAL PROPERTIES OF TABLETS

My research interest soon after I completed my postgraduate (PhD) degree programme in King's College, University of London, was to continue further work on the formulation and processing factors that influence the mechanical and physical properties of pharmaceutical tablets.

EFFECT OF TEMPERATURE

The first processing variable we investigated was the effect of temperature on the mechanical properties of pharmaceutical powders/granules. This subject is relevant in pharmacy when formulations contain low melting drugs and exicipients whose melting points could be exceeded during a compression process.

Two tablet formulations were selected for investigation. They were the typical formulation for commercial oxytetracycline tablets used in my previous studies (Esezobo and Pilpel 1974)) and a paracetamol tablet formulation consisting of (%w/w) paracetamol 90 and maize starch 10. The oxytetracycline formulation was granulated with 5% (w/w) gelatin solution while the paracetamol formulation was granulated with 5% (w/w) polyvinylpyrolidone (PVP) solution. The wet granules were dried and then compressed into tablets, in a hand press, at a range of temperatures from -20°C to +120°C. The tensile strengths and disintegration times of the tablets were measured in order to see how these properties depended on the temperatures employed during their preparation.

The result showed that the tensile strengths and disintegration times of the tablets for both drugs increased with increase in the temperature employed during their preparation (Pilpel and Esezobo, 1977).

We also found that the overall effect of temperature produced by friction and by the ambient conditions on the tensile strengths and disintegration times of the tablets resulted in approximately rectilinear graphs when

Log. T and Log. DT were plotted against the reciprocal of the absolute temperature (in K°). The graphs are shown in Fig. 9 for the two types of tablets over the temperature range -20°C to +120°C at a particular packing fraction of 0.85.

Thus, the tensile strengths and disintegration times of the tablets appear to vary in the same way with the ambient temperature as those of sintered metals etc. and obey a form of the Arrhenius equation:

Property = $ke^{\frac{-E_o}{R\theta}}$ ---------- Equation (1)

where property = T or DT or $\frac{SR}{ER}$ ratio

where T = Tensile strength,

DT = Disintegration time and

$\frac{SR}{ER}$ = Plasto-elasticity ratio,

R = 8.3 J/mol,

E_o =Is the activation energy of bonding,

k = is a constant for each material at each packing fraction.

θ = is the temperature (in k).

Values of E_o obtained from the slopes (= $-E_o/2.303R$) of the graphs in Fig. 9 are listed in Table 3A.

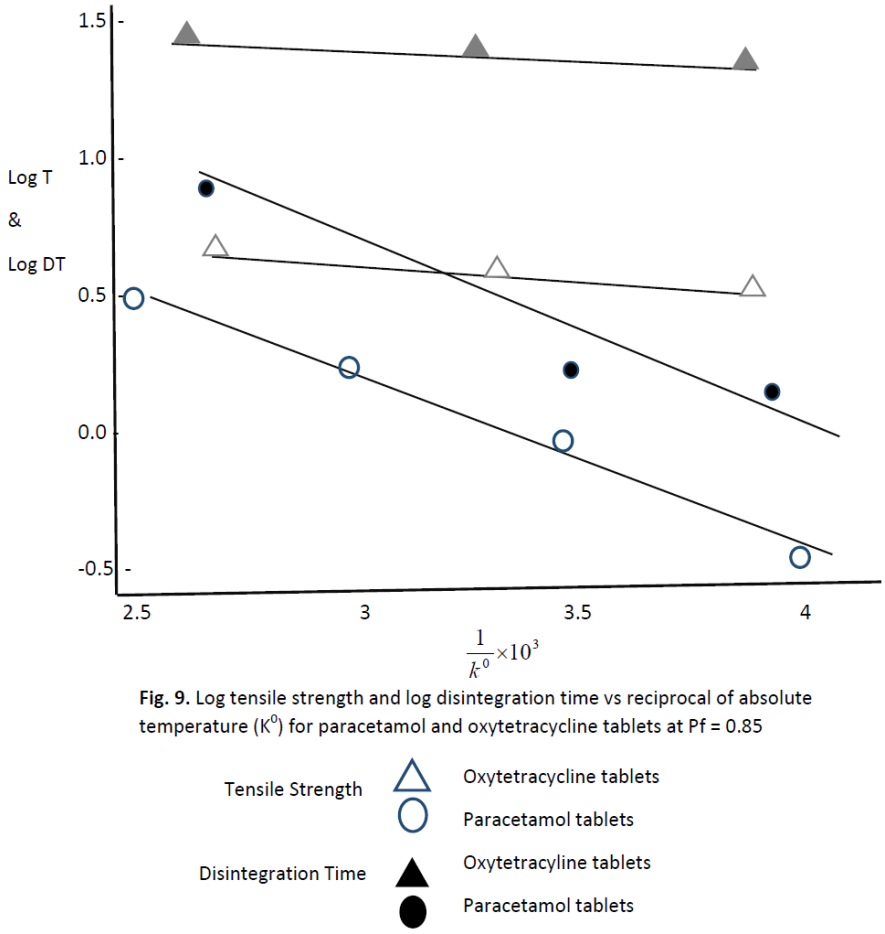


Fig. 9. Log tensile strength and log disintegration time vs reciprocal of absolute temperature (K^0) for paracetamol and oxytetracycline tablets at Pf = 0.85

Table 3A: Calculated Activation Energies E_o (kJ/mol) from measurements of Tensile Strength (T) and Disintegration time (DT)

Materials	E_o (kJ/mol)	
	P_f	T and $\triangle$T
Oxytetracycline formulation	0.85	4.0
Paracetamol formulation	0.85	13.0

Oxytetracycline Tablet Formulation consisted of

Oxytetracycline Dihydrate	90.2% (w/w)	Granulated with 5% gelatin binder solution
Avicel PH101	7.2% (w/w)	
Alginic acid	2.3% (w/w)	

Paracetamol Tablet Formulation consisted of

Paracetamol Powder	90% (w/w)	Granulated with 5% PVP binder solution
Maize Powder	10% (w/w)	

Source: (Pilpel and Esezobo, 1977).

[I will like to inform the audience that at the time this work was published, it appeared to be the first report of pharmaceutical materials being tabletted at temperatures below zero degrees. Furthermore, the result of this work appears in chapter 4 of the pharmaceutics textbook titled "Solid Pharmaceutics" Mechanical Properties and Rate Phenomena, authored by Jens Thuro Carstensen of the Center for Health Sciences, School of Pharmacy, University of Wisconsin, Madison, Wisconsin, Published by Academic Press in 1980.]

PLASTO-ELASTICITY OF POWDERS

In 1985, I was fortunate to receive the British Council Fellowship award to carry out research work at King's College, University of London. To be able to utilize the award, the University of Benin generously granted me study leave for which I am indeed very grateful.

On my arrival at King's College (i.e. at the laboratory where I carried out my postgraduate studies), I met a new equipment: **The Dartec 100kN M2501**, universal testing machine (Dartec Ltd.) which had just been acquired by the college. The machine measures the compression characteristics of pharmaceutical powders and granules.

TEMPERATURE EFECTS ON PLASTO-ELASTICITY OF POWDERS

As a follow up to our earlier work on the effects of temperature on the mechanical properties of tablets, the Dartec machine was employed to measure the plasto-elasticity (ER/SR) ratio (i.e. stress-relaxation, SR, during compression and Elastic recovery, ER, after compression) of 4 directly compressible excipients, a pure drug and a paracetamol tablet formulation at temperatures between -10°C to +65°C and of the tensile strengths of the tablets produced (Esezobo and Pilpel, 1986). (The list of materials are given in Table 3B).

Table 3B: Caculated Activation Energies E_o (kJ/mol) from measurements of Tensile Strength (T) and plastoelasticity (SR/ER) ratio.

Materials	E_o (kJ/mol)		
	P_f	T	SR/ER
Avicel	0.95	-	6.0
Sta-R_x	0.91	10.1	17.7
Emcompress	0.70	3.6	4.5
Spray dried lactose	0.90	5.8	5.4
Chloroquine phosphate	0.85	1.4	6.3
Paracetamol formulation +5% w/w PVP	0.85	2.7	8.1
Paracetamol formulation + 5% w/w Gelatin	0.85	3.0	7.3

Source: (Esezobo and Pilpel, 1986).

The results showed that at a fixed packing fraction, the tensile strength (T) and the stress relaxation (SR) of all the materials increased, the ER tended to decrease and the ratio ER/SR decreased as the compression temperature was raised. These results confirm the choice of SR as a measure of plasticity (which increases with temperature) of ER as a measure of elasticity (which decreases with temperature and generally support the theory of asperitic melting at high pressures (York and Pilpel, 1972); Britten and Pilpel, 1978; Malamataris and Pilpel, 1981).

Plots of Log T and Log (SR/ER) respectively versus the reciprocal of absolute temperature produced similar graphs as in Fig. 9. In both cases, good straight lines were obtained for all the materials investigated showing once again that the Arrhenius equation (eqn. 1) was obeyed. Values of the activation energies, E_o, were obtained as in the previous case and these are listed in Table 3B. The E_o values derived from SR/ER tended to be between 1.5 and 4.5 times higher than those derived from tensile strength. All the E_o values obtained and listed in Tables 3A and B were of the magnitude expected for interaction between particles to be occurring by physical rather than by chemical processes.

The implication of these results is that the increases that occur in the tensile strength of pharmaceutical powders/granules when they are heated during compression might be usefully applied to the process of tabletting. To test the idea, some additional experiments were performed using a paracetamol tablet formulation consisting of paracetamol powder 85% (w/w) and microcrystalline cellulose (Avicel PH101) 15% (w/w). granules were prepared by the wet granulation method. After drying, the granules were formed into tablets in a single punch Manesty machine operated at 70 strokes/min.

We observed that when the granueles were pre-heated to 70°C before feeding into the machine there was approximately 50% reduction in the incidence of lamination and breakage. This finding suggests that moderate heating might prove beneficial also in other cases. If so, it should not be difficult to adapt a conventional single punch machine to operate at temperate up to about 100°C (Pilpel et al., 1991).

Another implication of these results is that except for the possibility of retarding the decomposition of thermally unstable drugs and perhaps increasing the flowability of cohesive granulations (Britten and Pilpel, 1977) little benefit is likely to result from carrying out tableting operations at temperatures below ambient.

EFFECTS COATED POWDERS ON PLASTO-ELASTICITY

Pharmaceutical powders for the production of capsules or tablets are often coated with relatively small amounts of excipients. The coating may act as a binding agent, lubricant, a wetting agent or promote sustained release of the drug.

We carried out a study (Ejiofor et al., 1986) on the changes produced in the tensile strength, T, Brittle Fracture Index, BFI, and elasto-plasticity, ER/SR ratios of **sodium salicylate** and **calcium carbonate** tablets by coating the particles with increasing amounts of **polysorbates** and **silicones** before subjecting them to compression.

[Sodium salicylate was chosen as representative of low density, directly compressible materials and calcium carbonate as representative of high density, poorly compressible materials. Both are insoluble and apparently unaffected chemically by the coating materials used. The silicones were selected as representative of hydrophobic coatings frequently used as lubricants and the polysorbates (Tweens) as hydrophilic coatings].

The results obtained from this work showed that silicones and polysorbates produced systematic decreases in the tensile strength and systematic increases in the ER/SR and BFI values. Linear relationships were found to exist between ER/SR and BFI and between Log. T and ER/SR, some of these are plotted in Figs. 10 and 11. The concentrations of coatings corresponded to layers, a few molecules thick, and reduced the tensile strengths of the tablets by masking the London and van der Waals forces between the particles.

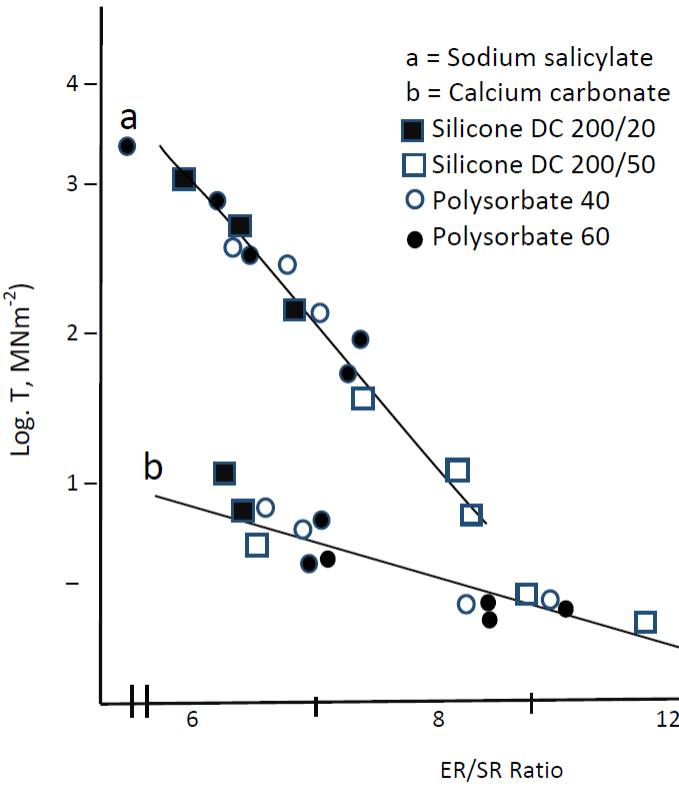


Fig. 10. Variation of tensile strength, T, and plasto-elasticity ratio ER/SR

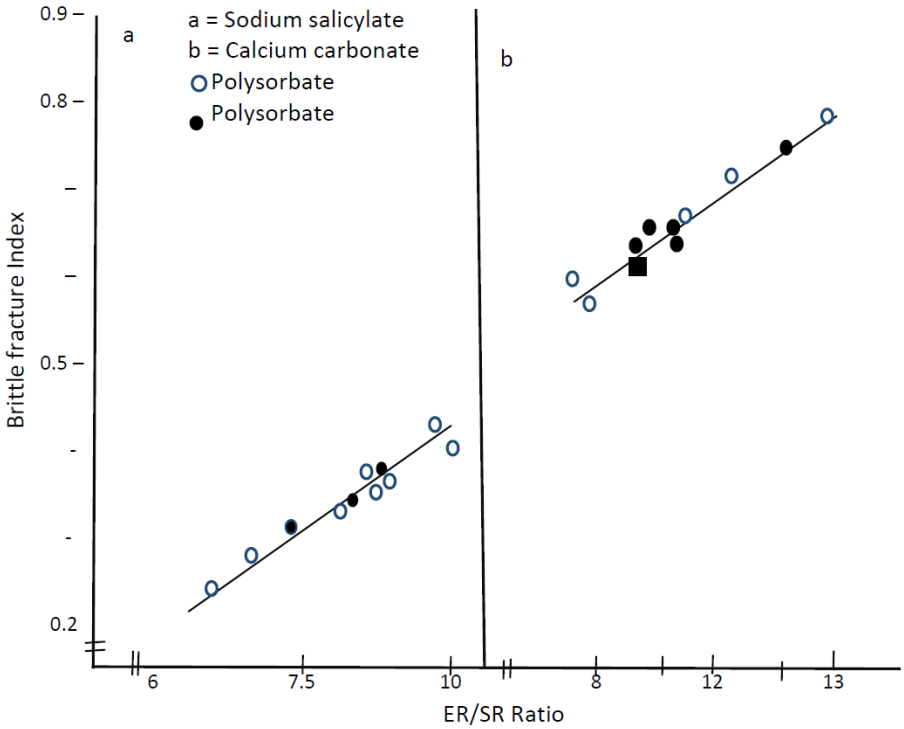


Fig. 11 Variation of Brittle Fracture Index (BFI) with ER/SR ratio

It was also found that for all particulate systems investigated here, SR tended to be high when ER/SR was low and vice versa. Samples for which the ratio ER/SR was less than 9 had sufficiently high tensile strengths (i.e. $1MNm^{-2}$ or above) to hold together as tablets, but when ER/SR is greater than 9, the tablets tended to cap or laminate.

T and ER/SR are thought to be indicators of the strengths of bond formed between the particles; BFI is thought to be residual elastic stress in a tablet. If this exceeds the strengths of the bonds then the tablet will fracture when it is ejected from the die, this apparently occurs when the BFI value rises above ca 0.7 (Pilpel et al., 1992).

BINDING AGENT ON PLASTO-ELASTICITY

Although we showed (Pilpel et al. 1992) that binding agents increase the tensile strengths of metronidazole tablets by reducing the inter-particle separation, γ, and increasing the value of α, where,

γ = the mean separation between particles

α = a quantity which depends on the hardness, brittle fracture and toughness of the material

However, Fig. 12 shows how ER/SR and BFI both decreased as increasing amounts of binding agents were added to metronidazole powders (Pilpel et al., 1992).

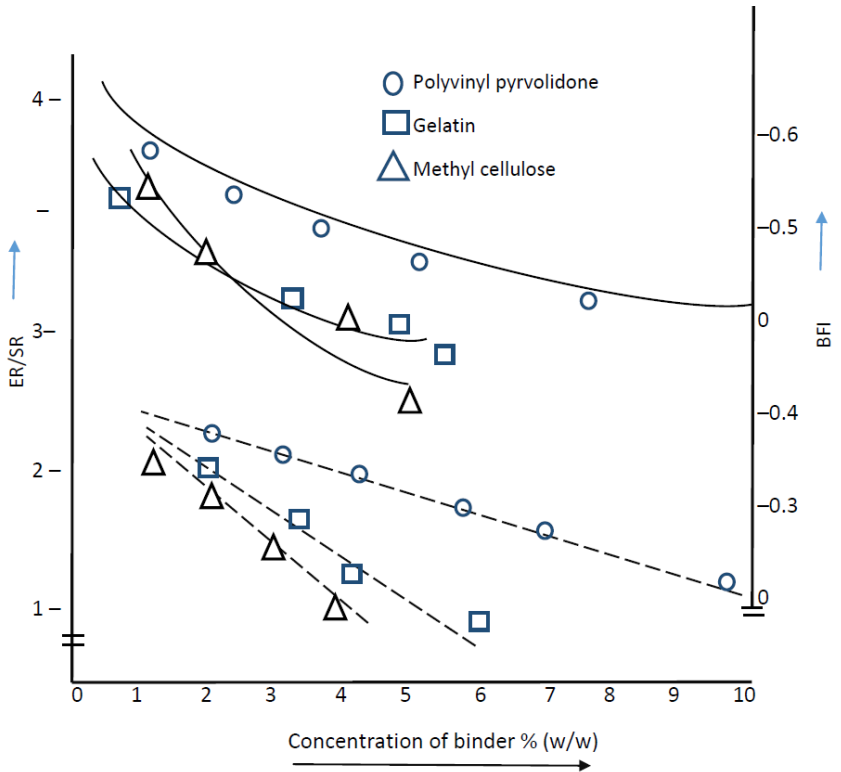


Fig 12. ER/SR and BFI for metronidazole tablets at Pf=0.90 vs concentration of binding agents(——) ER/SR; (-----) BFI

PARTICLE SIZE ON PLASTO-ELASTICITY

The effect of particle size on the tensile strengths, T, of several powders when tabletted at packing fraction = 0.85 showed that for all the tablets, T, decreased substantially with increasing particle size. In contrast to T, the ratio ER/SR did not change systematically with increasing particle size. We showed (Esezobo and Pilpel, 1987) that for dicalcium phosphate it decreases, for starch it increases and that for lactose and microcrystalline cellulose, it remains approximately constant for particles in the size range of about 30 to 100 μm. This is presumably due to their different mechanisms of consolidation (Pilpel et al., 1992).

APPLICATIONS OF PLASTO-ELASTICITY

The data we have obtained so far seem to suggest that T, ER/SR and BFI are all measures of the plasto-elastic properties of powders. They might thus be used to follow the systematic changes as their composition is altered by incorporation of addictives.

APPLICATION OF FACTORIALLY DESIGNED EXPERIMENTS IN ASSESSING THE FORMULATION AND PROCESSING VARIABLES AFFECTING THE PROPERTIES OF TABLETS

The evaluation of the separate and combined effects of formulation and process variables on the properties of tablets are carried out with the objectives of optimizing the production and therapeutic performance of various tablet formulations. It is hoped that this type of analysis will prove useful in the future development of commercial tablets.

EVALUATION OF TAPIOCA AS A TABLET EXCIPIENT

WHAT IS TAPIOCA?

Tapioca is the dried fibrous remnant material obtained from cassava (Manihot Utillisima) - a starchy tuber/root. The material appears as white to buffy cream cake known locally as kpo-kpo garri in the Niger Delta region of the country where it is consumed extensively as food. Although its use in pharmaceutical tablet formulations has not been widely reported, it is used in the preparation of baby foods.

Being largely a **fibrous** material and also from a **starchy** source, it was considered reasonable to assume that it may have some **bulking, binding,** and/or **disintegrant** properties when included in tablet formulations. This is because preliminary work showed that it has the ability of absorbing water, swelling and also forming a mucilaginous mass in the presence of water.

We evaluated the binding effects of tapioca on the physical properties of paracetamol tablets (Zubair et al., 1988). Its binding effects were compared with tablets made with two well known binders (i.e. gelatin and polyvinypyloridone (PVP)).

A factorially designed scheme was used to analyse the separate and combined effects of compression pressure/packing fraction (P), nature of the binder (N) and concentration of the binder (C) on the tensile strength, disintegration and dissolution ($t_{50\%}$) times of paracetamol tablets (Zubair et al., 1988).

The results obtained showed that in general the compression pressure (P) had the greatest effect on the tensile strength, disintegration and dissolution ($t_{50\%}$) times, followed by concentration (C) then the nature (N) of the binder (i.e. the ranking of the effects is P > C > N).

For the variables in combination, the ranking effects on:

(a) Tensile Strength

For PVP/Gelatin formulations are: P&N > N&C > P&C

For PVP/Tapioca formulations are: P&C = N&C > P&N

(b) Disintegration times and dissolution ($t_{50\%}$) times

For PVP/Gelatin formulations are:

P&C > P&N = N&C – disintegration time and

P&N > P&C > N&C – dissolution ($t_{50\%}$) times.

For PVP/Tapioca formulations are:

P&N > N&C = P&C – both disintegration and dissolution (($t_{50\%}$) times.

The results showed that tapioca acts as a binding agent when added, in the form of a solution, to a paracetamol tablet formulation. However, it is a much weaker binder than either PVP or gelatin.

MEASUREMENT OF CONTACT ANGLE OF WATER ON THE SURFACES OF TABLETS

Measurement of the wetability of tablet surfaces was another technique we employed in evaluating the binding effects of tapioca (Esezobo et al., 1989).

The wetability of paracetamol tablets made with tapioca and tablets made with the other two binders (i.e. gelatin and PVP) was estimated by measuring the contact angle, θ, of water on the surfaces of the tablets and hence their Adhesion Tension (AT).

The result showed that the disintegration and the dissolution ($t_{50\%}$) times increased with binder concentration and the values of the cosine of contact angle ($\cos\theta$) and Adhesion Tension (AT) of water on the tablets decreased with binder concentration (see Fig. 13).

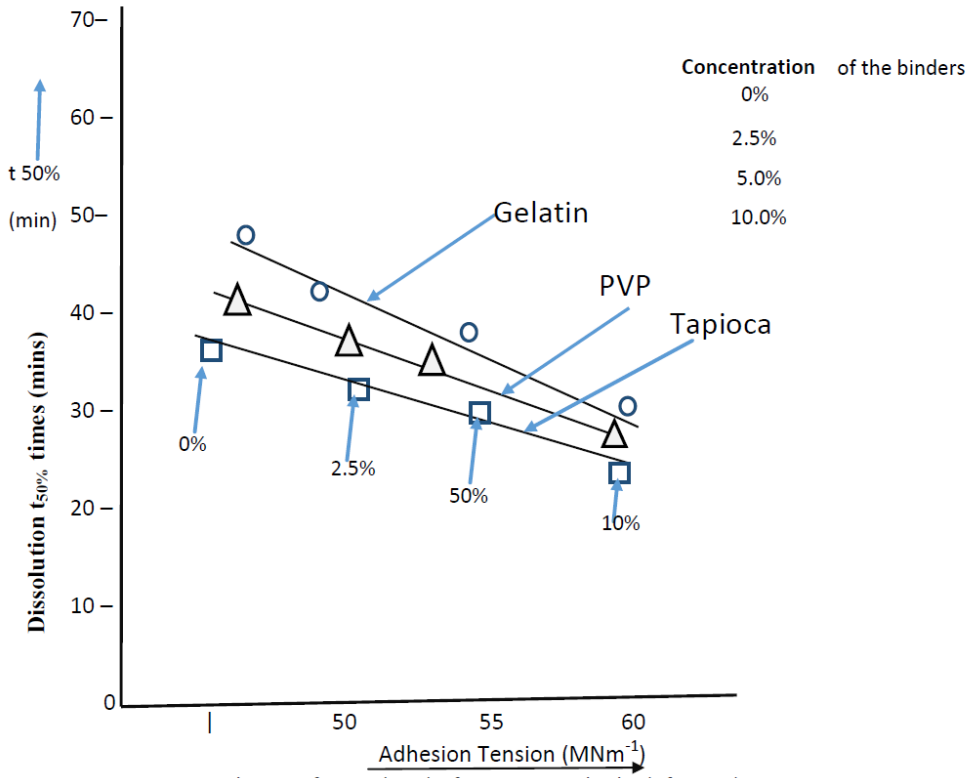


Fig 13. Correlation of t 50%(min) of paracetamol tabs (Pf =0.90) containing between 0 and 10% w/w of binder with Adhesion tension MNm^{-1} of water on tablets

The increase in disintegration and dissolution times of tablets at higher concentrations is due to the influence of the binders on the wetability and penetration of liquid into the capillaries of the tablets. The penetration of liquid into the capillaries of tablets has been shown to be necessary for the process of disintegration and dissolution of tablets to occur.

The presence of binders in tablet formulations would therefore be expected to reduce the size and number and alter the shapes of the capillary spaces between the particles which are contributing to the penetration of water into the tablets. Thus, the nature and quantity of the binder were found to alter the disintegration and dissolution rates of the tablets by reducing their wetability as measured by the Adhesion Tension (AT) of water (see Fig. 13).

EVALUATION OF SOME TABLET DISINTEGRANTS ON THE PROPERTIES OF SULPHAGUANADINE TABLETS

I also evaluated how the packing fraction, (P), the nature, (N), and concentration (C) of 3 disintegrants, (potato starch, alginic acid and methylcellulose M20) added to sulphaguanadine, affected the tensile strengths and disintegration times of the resulting tablets (Esezobo 1989).

The effects of separately varying the packing fraction (P), the nature (N) and concentration (C) of the disintegrants on both tensile strength and disintegration times of sulphaguanadine tablets were found to be in the orders respectively, of P>N>C and N>P>C. The combined effects of these variables on the tensile strength were found to be very close to zero and were in the order of N&C>P&N>P&C while those for the disintegration times were significantly removed from zero and the order was P&N>P&C>N&C. Thus, the

results indicated that the type and relative proportion of the disintegrants in the formulation had a more complex effect on the disintegration times of the tablets than on their tensile strengths.
The ranking of the effects of the various disintegrants on disintegration times was potato starch > alginic acid >methycellulose.

ADDITION OF SOME EXCIPIENTS ON THE PHYSICAL PROPERTIES OF SOME TABLET AND CAPSULE FORMULATIONS

1. **Effects of the addition of the excipients: (sodium lauryl sulphate, sorbitol and aerosil) on the physical properties of paracetamol tablet formulations.**

Effects of the addition of the excipients: Sodium lauryl sulphate (0.25 – 2%w/w), Sorbitol (1 – 8%w/w) and Aerosil(1 – 8%w/w) on the physical properties of paracetamol tablet formulation was evaluated (Esezobo, 1985).

The result showed that increase in the concentration of sorbitol and sodium lauryl sulphate caused a decrease in the hardness with a corresponding increase in the friability, disintegration and dissolution rates of the tablets.

The result also showed that the mode of incorporation of the excipient, aerosil, greatly influenced the physical properties of the paracetamol tablets. When added internally (i.e. before granulation), the strength of the tablets decreased, while the friability, disintegration and dissolution rates increased.

However, when the aerosil was added externally, (i.e. after granulation), the strength of the tablets increased while friability, disintegration and dissolution rates decreased (Esezobo 1985).

2. **The effects of diluent type: (lactose, aerosil and cassava starch) on the physical properties of tetracycline hydrochloride capsule and tablet formulations was also investigated (Esezobo 1990a). (They were used as bulking agent at a concentration of 66.7% w/w).**

The results showed that, in general, the capsules formulated with granules had shorter disintegration times than those formulated with powder blends. The rank order of the release rate from capsules was found to be aerosil > cassava starch >lactose.

For the tablets, those formulated with aerosil exhibited higher tensile strengths and longer disintegration times than tablets formulated with lactose or cassava starch (Esezobo, 1990a).

SOURCING OF AVAILABLE RAW MATERIALS FROM INDIGENOUS PLANTS TO BE USED AS EXCIPINTS IN TABLET MANUFACTURE

We extracted starches from the mature unripe fruits of plantain (Musa Paradisima) (Esezobo and Ambujam, 1982); the tubers of sweet potato (Ipomoea Batatas) (Esezobo, 1986) and the tubers of African bitter yam (Dioscorea Dumatorum) (Esezobo, 1991) respectively (see Table 4).

The starches were employed as binding and/or disintegrating agents in the formulation of paracetamol and chloroquine tablets respectively. The result showed that when the starches were used in the form of mucilage

(i.e. as a binder) they produced harder tablets with longer disintegration and dissolution rates than tablets prepared with maize starch mucilage. But, when they were employed in the form of dry powder (i.e. as a disintegrant) the starches also produced slightly stronger tablets with slower disintegration rates than tablets made with powdered maize starch. However, the starches produced tablets with similar dissolution rates and dissolution efficiencies (see Table 4).

Since the starches of plantain and sweet potato produced tablets comparable to those produced with maize starch, either can thus be employed in place of maize starch for the manufacture of tablets (Esezobo and Ambujam, 1982; Esezobo, 1986; 1991a).

Tapioca is the fibrous remnant material obtained from the tubers of cassava (Manihot Utilisima) after the removal of a large percentage of starch. The material has been evaluated as an excipient in tablet manufacture and found to act as a binding agent when incorporated in a paracetamol tablet formulation but it is a much weaker binder than either gelatin or PVP (Zubair et al., 1988; Esezobo et al, 1989; Esezobo, 1990c) (see Table 4).

Dika fat was extracted from the kernels of Irvingia gabonensia Var excelsia plant and evaluated as an excipient in the preparation of tablets (Esezobo, 1991b). The fat was found to be a good glidant/lubricant in the formulation of tablets. The results obtained compared favourably with stearic acid or magnesium stearate (see Table 4).

Table 4: Some raw materials obtained from local plants and were evaluated as excipients in tablet manufacture,

Botanical Name/ Plant Source	Local Name	Functional use as excipients	References
Starch extracted from (a) Musa Paradisiaca (from the mature unripe fruits) (b) Ipomoea Batatas (from the tubers) (c) Dioscorea Dumatorum (from the tubers)	 Plantain Sweet potato African bitter yam	 As disintegrants and binders for tablets As disintegrants in capsules	Esezobo and Ambujam, 1982; Esezobo, 1986; 1988; 1991.
A fibrous material obtained from the tubers of Manihot Utilisima after the removal of a large percentage of starch	Tapioca (Kpokpo gari)	As a weak binder for tablets (as a bulking agent)	Zubair et al, 1988; Esezobo et al., 1989 Esezobo, 1990
Dika fat extracted from the kernels of Irvinga gabonensia var excelsia	Dika fat (Ogbonor)	As a lubricant and/or glidant	Esezobo, 1991b

QUALITY CONTROL OF SOME COMMERCIAL PHARMACEUTICAL PRODUCTS AVAILABLE IN NIGERIA.

As you all are aware, most pharmaceutical products consumed in the country today, including antibiotic capsules are imported into the country from such countries as India, China, Korea, Bangladesh, UK, USA, etc. and a few are manufactured here in Nigeria.

We have observed that of the numerous generic brands of these products that are available, any brand is dispensed or sold in our health institutions or chemist shops, for such reasons as consideration of cost or shortage of drugs without any knowledge of the quality of these brands.

A few studies carried out on some of these products have indicated that many are of low standard in terms of quality and efficacy. It was for these reasons that the present studies were undertaken on 11 commercial brands of chloramphenicol, 10 commercial brands of ampicilin and 5 commercial brands of oxytetracycline capsules. Also included in the study was the stability of 5 commercial brands of ampicilin oral suspension following reconstitution.

The results of the study on the capsules showed that they contained varying amounts of the antibiotics and the rate of their release from the capsules differed significantly. For example, 3 brands of chloramphenicol capsules did not release up to 50% of the drug after an hour. A brand of the ampicilin capsules had an average drug content of 74%, while 90% dissolution of drug from another brand was not achieved after an hour. One brand of the oxytetracycline capsules released only 20% of the drug after 2 hours (Esezobo and Adefisan, 1980; Esezobo and Aloba, 1981; Esezobo and Effiong 1986).

The results of the stability profiles of the active drug in 5 generically equivalent brands of ampicilin for oral suspension investigated showed that considerable variations existed in the initial concentrations of the active drug among the 5 brands. One brand contained approximately 80% of ampicilin. The result also showed that 2 brands did not comply with the official pharmacopoial stability specifications when stored at the recommended conditions (i.e. at room temperature for 7 days or at refrigerated temperature for 14 days). This was because the potency of these 2 brands fell below the minimum 90% value when stored at the above conditions (Esezobo, 1980).

CONCLUSION

Mr. Vice Chancellor, Sir, in this lecture I have made an attempt to present an account of the scientific approach we have adopted in the making of pharmaceutical tablet employing a typical commercial tablet formulation of oxytetracycline.

I have also reported in this lecture that when pharmaceutical powders/granules were compressed into tablets at temperatures ranging from below ambient to well above ambient, the properties (i.e. T, DT, and SR/ER ratio) increased with increase in temperature. When the logarithms of these properties were plotted respectively against the reciprocal of the absolute temperature, the Arrhenius equation was obeyed. The magnitude of the calculated activation energies from the plots were those expected for interaction between particles to be occurring by physical processes and not by chemical processes.

By employing factorially designed experiments in assessing the properties of tablets, it has been possible to show that the compression pressure is by far the most dominant factor that affects the properties of tablets. Whereas, the type and concentration of the excipient (i.e. binder or disintegrant) incorporated in a tablet formulation also affects the properties of the tablets but to a lesser degree.

RECOMMENDATION

Mr. Vice Chancellor, Sir, as of today, all pharmaceutical industries in the country depend on the importation of virtually all their raw materials in order to be able to carry out production.

The government should therefore as a matter of urgency set up a petrochemical plant where a plethora of required chemicals can be synthesized.

The inherent advantage with this is that we can become self-sufficient and become a pivot to our neighbours for finished drug products, Active Pharmaceutical Ingredients (APIs), excipients and chemical needs of other industries and nations.

Some raw materials that are obtained from our local plants (e.g. starches, and the gums) and can be used as excipients in tablet making would serve as good substitutes to imported varieties.

Unfortunately, these materials are not up to pharmaceutical grade. Industries should be set up to purify these materials to the required pharmaceutical specifications.

Multinational pharmaceutical companies operating in the country should be encouraged by way of tax incentives to motivate them make donations of chemicals and equipment for teaching and research to our universities. In addition, to give financial support to students undergoing postgraduate studies.

The results from our studies on the in-vitro quality assessment of some antibiotic capsules sold locally in our markets has shown that adequate quality control measures are necessary, specifically, on imported drug products as well as locally manufactured drug products and proof of their quality established before being permitted into wholesale and retail outlets.

APPRECIATION

First and foremost, I must give thanks to God Almighty for taken me this far! Without Him, I will not have made it to this level in academics and be here today.

Various individuals have also played important roles at one time or the other in my early life. They include: late Mr. J.C. Omailey, late Mr. C.C. Okoye, late Barr. Suru Akele and late Mr. Lawrence Ugbo. May their souls rest in perfect peace, Amen.

Those who have contributed immensely to my success in later life include:

- Professor P.G. Hugbo, the pioneer Vice-Chancellor of Western Delta University, Oghara, Delta State;
- Professor Gabriel Osuide, one time Director General of NAFDAC;
- Professor Bonaventure Obiorah, former Deputy Vice-Chancellor, University of Benin;
- Barr. Gibson Aghomon, former, General Manager of the defunct New Nigeria Bank PLC;
- Mr. and Mrs. Rufus Oikeh and family. I say a big thank you and may God bless you all.

I would like to take this opportunity to thank in a special way the Vice-chancellor of this great university, Rev. Professor Eghosa Osaghae, who relentlessly piled pressure on me to give this inaugural lecture. Left to him, this exercise would have taken place more than seven or eight years ago, but for some unexplained reason(s) it never happened, but it is better late than never.

Furthermore, I wish to appreciate the Vice-Chancellor who despite all odds ensured the successful establishment of our College of Pharmacy in this University. I say a big thank you, Sir.

I will also wish to extend my immense gratitude to other members of the management team of this University: the Deputy Vice-chancellor, Professor (Mrs.) Charity U. Emaviwe, the Registrar, Mr. Edwin Okoro, the Bursar, Mr. Nosa Edogiawere, and the University Librarian, Mr. Yakubu Izebekhai for creating a peaceful and conducive environment for work and studies.

I also wish to appreciate all the members of staff (both academic and non-academic) of the College of Pharmacy and most especially to my colleagues of the Department of Pharmaceutics and Pharm. Technology.

Thank you for listening and God bless you all.

APPENDIX A

THE OPERATIONS AND SETTING OF THE 2 TYPES OF TALETTING MACHINES

The compression speed of the single punch machine was adjusted to 70 strokes/min. The multi-punch (16 stations) machine was modified by blocking off 14 stations so that only **TWO** compression stations fitted with deep concave punches on opposite sides of the revolving turret were used. It was operated at 30 r.p.m.

The setting on each machine was adjusted to produce tablets (about 400 – 500) from each batch of granules with pre-determined weights and packing fractions.

Types of tablets prepared

The following tablets were prepared (all contained approximately 250mg of oxytetracycline dihydrate).

Type of machine	**Shape of tablets**	**Total weight (mg)**	**Paking fraction of tablet (P_f)**
Hand press	Deep biconvex	300 ± 10	0.69 – 0.90
Single punch	Flat face	325 ± 10	0.85 ± 0.05
	Deep biconvex	300 ± 10	0.80 ± 0.05
Rotary punch	Deep biconvex	300 ± 10	0.80 ± 0.05

REFERENCES

Aulton, M.E. (2002). What is Pharmaceutics? In: Pharmaceutics; The Science of dosage from design. 2nd Edition, Churchill Livingston. Elsevier Science Ltd. XIII – XV.

Ashton, M.D., Farley, R. and Valentine, R.H.H. (1964). J. Scient. Instrum. 41, 763 – 765.

Ashton, M.D., Cheng, D.C-H., Farley, R. and Valentin, F.H.H. (1965). Rheol. Acta, 4, 206 – 217.

Britten, J.R. and Pilpel, N. (1997). Tensile testing of powders over a range of temperatures. Lab. Pract. 26, 185-186.

Britten, J.R. and Pilpel, N. (1978). Effects of temperature on the tensile strengths of pharmaceutical powders. J. Pharm. Pharmacol, 30, 673-677.

British Pharmacopoeia (1973) London. HMSO. A131.

Carr, J.F. and Walker, D.M. (1968). Powder Technol, 1(6), 169-173.

Chalmers, A.A. and Elworthy, P.H. (1976). J. Pharm. Pharmacol, 28, 228.

Cheng, D. C-H. (1968). The tensile strengths of powders. Chem. Eng. Sci. 23, 1405-1420.

Eaves, T. and Jones, T.M. (1971). Rheol. Acta. 10. 127-134.

Ejiofor, O., **Esezobo, S.,** and Pilpel, N. (1986). The plasto-elasticity and compressibility of coated powders and the tensile strength of their tablets. J. Pharm. Pharmacol. 38, 409-413.

Esezobo, s. (1976). Ph.D. Thesis, London University.

Esezobo, S. and Pilpel, N. (1974). The effect of moisture content and gelatin binding agent on the mechanical and failure properties of an oxytetracycline formulation. J. Pharm. Pharmacol, 26, Suppl. 47P – 56P.

Esezobo, S. and Pilpel, N. (1976). Some formulation factors affecting the tensile strength, disintegration and dissolution of uncoated oxytetracycline tablets. J. Pharm. Pharmacol. 28, 8 -16.

Esezobo, S. and Pilpel, N. (1977a). Moisture and gelatin effects on the inter-particle attractive forces and compression behaviour of oxytetracycline tablet formulations. J. Pharm. Pharmacol. 29, 75-81.

Esezobo, S. and Pilpel, N. (1977b). Formulation factors affecting the strength and dissolution of uncoated oxytetracycline tablets. J. Pharm. Sci. 66, 852-858.

Esezobo, S. and Adefisan, M.O. (1980). An evaluation of the physical and pharmaceutical factors involved in the in-vitro release of the drug from chloramphenicol capsules available in Nigeria. Nig. J. Pharm. Vol. 2, No. 2. 71-81.

Esezobo, S. (1980). The stability of some commercial brands of ampicillin oral suspensions following reconstitution. Nig. J. Pharm. Vol. 2, No. 5, 199-201.

Esezobo, S. and Aloba, T.O. (1981). An evaluation of some commercial brands of ampicillin capsules available in Nigeria. Nig. J. Pharm. Vol. 12, No. 1, 308-319.

Esezobo, S. and Ibiezugbe, A. (1982). The influence of addictives on the in-vitro release of chloroquine phosphate from capsules. Nig. J. Pharm. Vol. 3, No. 6, 25-28.

Esezobo, S. and Ambujam, V. (1982). An evaluation of starch obtained from plantain (Musa Paradisiaca) as a binder and disintegrant for compressed tablets. J. Pharm. Pharmacol, 34, 761-765

Esezobo, S. (1985). The effects of some excipients on the properties of a paracetamol tablet formulation. J.Pharm. Pharmacol. 37, 193-195.

Esezobo, S. and Effiong, E. (1986). In-vitro studies of some commercial brands of oxytetracycline capsules available in Nigeria. Nig. J. Pharm. Vol. 17, No. 3, 24-28.

Esezobo, S. and Pilpel, N. (1986). The effect of temperature on plasto-elasticity of some pharmaceutical powders and on the tensile strengths of their tablets. J. Pharm. Pharmacol. 38, 409-413.

Esezobo, S. (1986). Evaluation of sweet potato starch as a binder and disintegrant for paracetamol tablets. Nig. J. Phar. Sci. 2, 44-51.

Esezobo, S. and Pilpel, N. (1987). Effects of applied load and particle size on the plasto-elasticity and tablet strength of some directly compressible powders. J. Pharm. Pharmacol. 39, 303-304.

Esezobo, S. (1988). Effect of varying the volume of plantain starch mucilage on the physical properties of chloroquine phosphate granules and tablets. Nig. J. Pharm. No. 19, Vol. 5, 151-154.

Esezobo, S., Zubair, S. and Pilpel, N. (1989). Effects of tapioca obtained from cassava (Manihot Utilisima) on the disintegration and dissolution rates of paracetamol tablets. J. Pharm. Pharmacol. 47, 7-10.

Esezobo, S. (1989). Disintegrants: effects of interacting variables on the tensile strengths and disintegration times of Sulphaguanidine tablets. Int. J. Pharm. 56(3), 207-211.

Esezobo, S. (1990a). The influence of diluent type on the physical properties of tetracycline capsule and tablet formulations. Nig. J. Pharm. Vol. 21, No. 2, 40-46.

Esezobo, S. (1990b). The effect of temperature on the compression behaviour of some pharmaceutical powders and a paracetamol tablet formulation. West Afri. J. Pharm. Vol. 4, No. 1, 24-28.

Esezobo, S. (1990c). The plasto-elasticity of tapioca and in a mixture of several pharmaceutical diluents. Int. J. Pharm. Tech. and Prod. Manuf. (Accepted for Publication).

Esezobo, S. (1991a). The effect of Dika fat (a new tablet lubricant) on the plasto-elasticity of some pharmaceutical powders. Drug Dev. And Ind. Pharm. Vol. 17, No.2, 295-301.

Esezobo, S. (1991b). An assessment of the disintegration efficiency of some indigenous starches in a paracetamol capsule formulation. West Afri. J. Pharm. (Accepted for publication).

Fell, J.T and Newton, J.M. (1970). J. Pharm. Sci. 59, 688-689.

Gunsel, W,C., Swartz, C.J and Kanig, J.I. (1970). In: The Theory and Practice of Industrial Pharmacy. Pg. 305. Eds. Lachman, Liberman and Kanig, Lea and Febiger, Philadelphia.

Heckle, R.W. (1961). Trans. Metallic. Soc. Aimc, 221, 671-675, 1001-1008.

Itiola, O.A. and Pilpel, N. (1986). Studies on metronidazole tablet formulations. J. Pharm. Pharmacol. 38, 81-86.

Kitazawa, S., Johno,I., Ito, Y., Teramura, S., and Okeda, I. (1975). J. Pharm. Pharmacol, 27, 765-

Kocova, S., and Pilpel, N. (1971- 1972). Powder Technol. 5, 329-343.

Levy, G. and Hayes, B.A. (1960). New Engl. J. Med. 262, 1053-1058.

Little, A. and Mitchel, K.A. (1963). Tablet Making, 2nd Edition, The Northern Publishing co. Ltd, England, pp. 149.

Malamataris, S. and Pilpel, N. (1981). Effect of temperature on the tensile strength of lactose coated with fatty acids: Tablets. Powder Technol. 28, 35-42.

Pilpel, N. (1969). Chemical and Process Engng, 50(7), 67.

Pilpel, N. and **Esezobo, S. (1977)**. The effect of temperature on the tensile strength and disintegration times of paracetamol and oxytetracycline tablets. J. Pharm. Pharmacol. 29, 389-392.

Pilpel, N., Britten, J.R., Onyekweli, A.O. and **Esezobo, S.** (1991). Compression and tableting of pharmaceutical powders at elevated temperatures. Int. J. Pharm. 70, 241 – 249.

Pilpel, N., Malamataris, S., Bangudu, A.B., **Esezobo, S.,** Itiola, O.A. (1992). Plasto-elasticity and tableting of single and multicomponent powders. Powder Technol. 67, 195 – 201.

Wagner, J.G. (1969). J. Pharm. Sci. 58, 1253.

Williams, J.C. and Birks, A.H. (1967). Powder Technol. 1, 199 – 206.

York, P. and Pilpel, N. (1972). The effect of temperature on the mechanical properties of some pharmaceutical powders in relation to tableting. J. Pharm. Pharmacol. 24, 47P – 56P.

York, P. and Pilpel, N. (1973). The tensile strength and compression behaviour of lactose, four fatty acids and their mixtures in relation to tableting. J. Pharm. Pharmacol. 25, 1P – 11P. Suppl.

York, P. (2002). The design of dosage forms: In Pharmaceutics; The science of dosage form design. 2nd Edition, Churchill Livingstone, Elservier Science Ltd. Pg. 1 -11.

Zubair, S., **Esezobo, S.**, and Pilpel, N. (1988). The effects of interacting variables on the tensile strength, disintegration and dissolution of paracetamol tablets. J. Pharm. Pharmacol. 40, 278 – 281.