

https://dspace.org/

An evaluation of directly compressible tablet bases on the performance of ibuprofen tablets

Vawda, Naseem

2001-02-02
https://hdl.handle.net/10539/24543

Downloaded from a DSpace repository. https://dspace.org/

Faculty of Health Sciences
Department of Pharmacy
University of the Witwatersrand
7 York Road
Parktown
2193

An Evaluation of Directly Compressible Tablet Bases on the Performance of Ibuprofen Tablets.

Naseem Vawda (BPharm)

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand , in partial fulfilment of the requirements for the degree of Master of Science in Medicine (Pharmaceutical affairs)

Johannesburg, 2001

Declaration

I, Naseem Vawda declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine (Pharmaceutical affairs) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

N Vawda
.....

2nd day of February ,2001

Dedicated to my wife, Mariam and my dear son Zaheer

Abstract

Ibuprofen is a phenylpropionic acid derivative, which has analgesic, anti-inflammatory and antipyretic actions. It is used in the management of mild to moderate pain, inflammatory conditions, peri-articular disorders, musculoskeletal disorders and joint disorders.

Tablets, like ibuprofen, can be manufactured by three different processes *viz.* wet granulation, dry granulation and direct compression. With direct compression, the directly compressible base, along with the active ingredient (ibuprofen) and other suitable excipients, can be compressed directly.

In this project, three directly compressible bases were investigated with ibuprofen. The three bases used were avicel pH 101, ludipress and emcompress. Experiments were done using three different concentrations (40, 50 and 60%) of the directly compressible base. At each concentration, tablets were compressed to three different hardness levels (3-5, 6-8 and 7-9 kg). Therefore a total of twenty-seven formulations were compressed and the tablets from each formulation were evaluated for uniformity of weight, disintegration and friability.

The angle of repose test for powder flow showed excellent results. Emcompress showed the most superior flow, followed by ludipress and then avicel.

The disintegration for avicel was excellent, with all nine formulations of avicel disintegrating almost immediately. Since emcompress is insoluble in water, all nine formulations failed disintegration. Only two formulations of ludipress, at a 60% concentration, passed disintegration. However with the addition of the disintegrant, explotab, both emcompress and ludipress passed disintegration. Therefore a disintegrant will have to be added to an emcompress or ludipress formulation, the percentage of which, will determine the rate at which tablets disintegrate.

The friability of ludipress and emcompress were excellent with all formulations passing. With avicel, only six formulations passed friability. The three formulations that failed were at a higher hardness level.

Overall, the best results were obtained with avicel. Such tablets demonstrated rapid disintegration. This would be ideal for an ibuprofen formulation where a rapid response is needed.

Acknowledgements

Dr Gareth Lowndes - For his supervision and motivation throughout my project.

Pharma Q - For the supply of all raw materials required.

Mariam Vawda - For her support, encouragement and typing expertise.

Table of contents

	Page
Declaration	ii
Dedication	iii
Abstract	iv
Acknowledgements	v
Table of contents	vi
List of figures	ix
List of tables	x
1. Introduction	1
1.1 Background	1
1.2 Manufacturing processes	2
1.2.1 Wet granulation	2
1.2.2 Dry granulation	2
1.2.3 Direct compression	2
1.3 Excipients	5
1.3.1 Lubricants	5
1.3.2 Disintegrants	5
1.3.3 Fillers or diluents	5
1.4.1 Microcrystalline Cellulose (Avicel PH101®)	7
1.4.2 Lactose (Ludipress®)	8
1.4.3 Dibasic Calcium Phosphate (Emcompress®)	8

2. Experimentation 9

2.1 Introduction 9

2.2 Samples 10

2.3 Methods 11

2.3.1 Uniformity of weight 11

2.3.2 Hardness 11

2.3.3 Friability 11

2.3.4 Disintegration 11

2.3.5 Flow properties 12

3. Results 14

3.1 Avicel pH 101 14

3.2 Ludipress 14

3.3 Emcompress 15

3.4 Disintegration 15

3.4.1 Acidic medium 16

3.4.2 Addition of a disintegrant 16

3.5 Powder flow 16

4. Discussion 17

4.1 Introduction 17

4.2 Avicel pH 101 17

4.3 Ludipress 19

4.4 Emcompress 21

4.5 Powder flow 22

5. Conclusion 24

Appendix – Ethics clearance 26

6. References 28

List of figures

Figure		Page
1.1	Schematic drawings of the three different methods in which tablets can be manufactured	4
2.1	Friabilator	12
2.2	Disintegration apparatus	12
2.3	The poured angle on repose	13
4.1	Disintegration for avicel	18
4.2	Friability for avicel	19
4.3	Disintegration for ludipress	20
4.4	Friability for ludipress	20
4.5	Friability for emcompress	21
4.6	Micrograph for emcompress	22
4.7	Micrograph for ludipress	23
4.8	Micrograph for avicel	23
5.1	Disintegration for formulations 4, 5, 29, 30, 31	24
5.2	Friability for formulations 4, 5, 29, 30, 31	24

List of tables

Table		Page
1.1	Comparative properties of some fillers	6
2.1	Formulations at concentrations 40,50 and 60%	9
2.2	Numerical allocation for the formulations	10
2.3	List of excipients with their ingredients	10
3.1	Results for avicel	14
3.2	Results for ludipress	14
3.3	Results for emcompress	15
3.4	Powder flow	16
4.1	Summary of results	17

Introduction

1.1 Background

Solid oral dosage forms are drug delivery systems presented as solid-dose units readily administered by mouth. The group includes tablets, capsules, unit-dose powders and granules. The group constitutes the most popular form of presentation and tablets and capsules account for the greatest number of preparations in this category (Banker and Rhodes, 1990). The prime reasons for this popularity includes: ease of accurate dosage, good physical and chemical stability, competitive unit production costs and an elegant distinctive appearance resulting in a high level of patient acceptability.

Tablets are solid medicaments, which consist of a mixture of powders, which have been compacted into a die to produce a single rigid body. Most formulations will be composed of one or more medicaments plus excipients of various types. For accurate reproducible dosage it is essential that each component be uniformly dispersed within the mixture and any tendency for component segregation be minimized. In addition, the processing operations demand that the mixture has certain minimum flow characteristics, but must be cohesive when compressed.
Pharmaceutical compressed tablets are prepared by placing an appropriate powder mix or granulation in a metal die on a tablet press. At the base of the die is a lower punch, and above the die is an upper punch. When the upper punch is forced down upon the powder mix (single punch press) or when the upper and lower punches squeeze together (rotary press) the powder mix or granulation is forced into a tablet.

A paradox in pharmaceutical tabletting is the need to manufacture a compact of sufficient mechanical strength to withstand the rigours of processing and packaging, yet capable of reproducible breakdown on administration so as to release the drug. Both the formulation and the method of manufacture affect the properties of a tablet, and between these two factors there is a high degree of interrelationship (Lieberman, Lachman and Schwartz, 1989). A suitable formulation is critical to the manufacture of satisfactory tablets. The major unit processes involved in the manufacture of tablets are: solid-solid mixing, solid-liquid mixing, milling, drying and compaction. The

selection of the formulation components and equipment is done to optimize the efficiency of the unit processes involved.

1.2 Manufacturing processes

There are three different processes in which tablets can be manufactured:

1.2.1 Wet granulation

1.2.2 Dry granulation

1.2.3 Direct compression

1.2.1 Wet granulation

Wet granulation is the oldest method and still the most widely used process for the manufacture of tablets. The purpose of granulation is to enlarge the particle size of a powder and to obtain uniform particles that flow readily through the tablet machine hopper and feed frames into the dies. The enlarged particle (granule) is prepared by moistening the desired powder or blended powder mixture and then passing the moistened mass through a screen of the mesh size that will produce the desired size granules. The granules are then dried before being compressed. A disadvantage with wet granulation is its cost. It is an expensive process because of the labour, time, equipment, energy and space requirements. Examples of tablets that are prepared by wet granulation include paracetamol, thiamine hydrochloride and aminophylline.

1.2.2 Dry granulation

In the dry granulation method, the granulation is formed not by moistening or adding a binding agent to the powdered drug mixture but by compacting large masses of the mixture and subsequently crushing and sizing these pieces into smaller granules. By this method, either the active ingredient or the diluent must have cohesive properties in order for the large masses to be formed.

1.2.3 Direct Compression

This is a process by which tablets are compressed directly from powder blends of the active ingredient and suitable excipients that will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation is necessary.

Direct compression should not be conceived as a simplified modification of the granulation process for making tablets. It requires a new and critical approach to the selection of raw materials, flow properties of powder blends and effects of formulation variables of compressibility. During the wet granulation process the original properties of the raw materials are, to a great extent, completely modified. The materials are mixed together, with a binding solution, dried, passed through a sieve and blended. The granulate, which is now subject to compression, is a combination of the raw materials. Therefore the inadequacies in the raw materials are covered up during the granulation process. This is not the case in direct compression. Therefore the properties of each and every raw material and details of how these materials are blended become extremely critical in the compression stage of tabletting. Probably, one of the least recognized advantages of direct compression is the optimization of tablet disintegration. Tablets prepared by direct compression have a faster drug release rate than tablets prepared by wet granulation (Li, 1992). Each primary drug particle is liberated from the tablet mass and is available for dissolution, resulting in a faster drug release rate. The granulation process, wherein small drug particles with a large surface area are 'glued' into larger agglomerates, is in direct opposition to the principle of increased surface area for rapid drug dissolution. Disintegrating agents added prior to wet granulation are known to be less effective than those added just prior to compression (Lieberman, Lachman and Schwartz, 1989). In direct compression all of the disintegrant is able to perform optimally, and when properly formulated, tablets made by direct compression should disintegrate rapidly to the primary particle state.

Although it is not well documented, it would seem obvious that fewer chemical stability problems would be encountered in tablets prepared by direct compression as compared to those made by the wet granulation process. The primary cause of instability in tablets is moisture. Moisture plays a significant role not only in drug stability but also in the compressibility characteristics of granulations. While some direct compression excipients do contain apparently high levels of moisture, this moisture in most cases is tightly bound either as water of hydration e.g. Lactose monohydrate or by hydrogen bonding to surfaces e.g. Microcrystalline cellulose and therefore does not degrade. (Lieberman, Lachman and Schwartz, 1989).

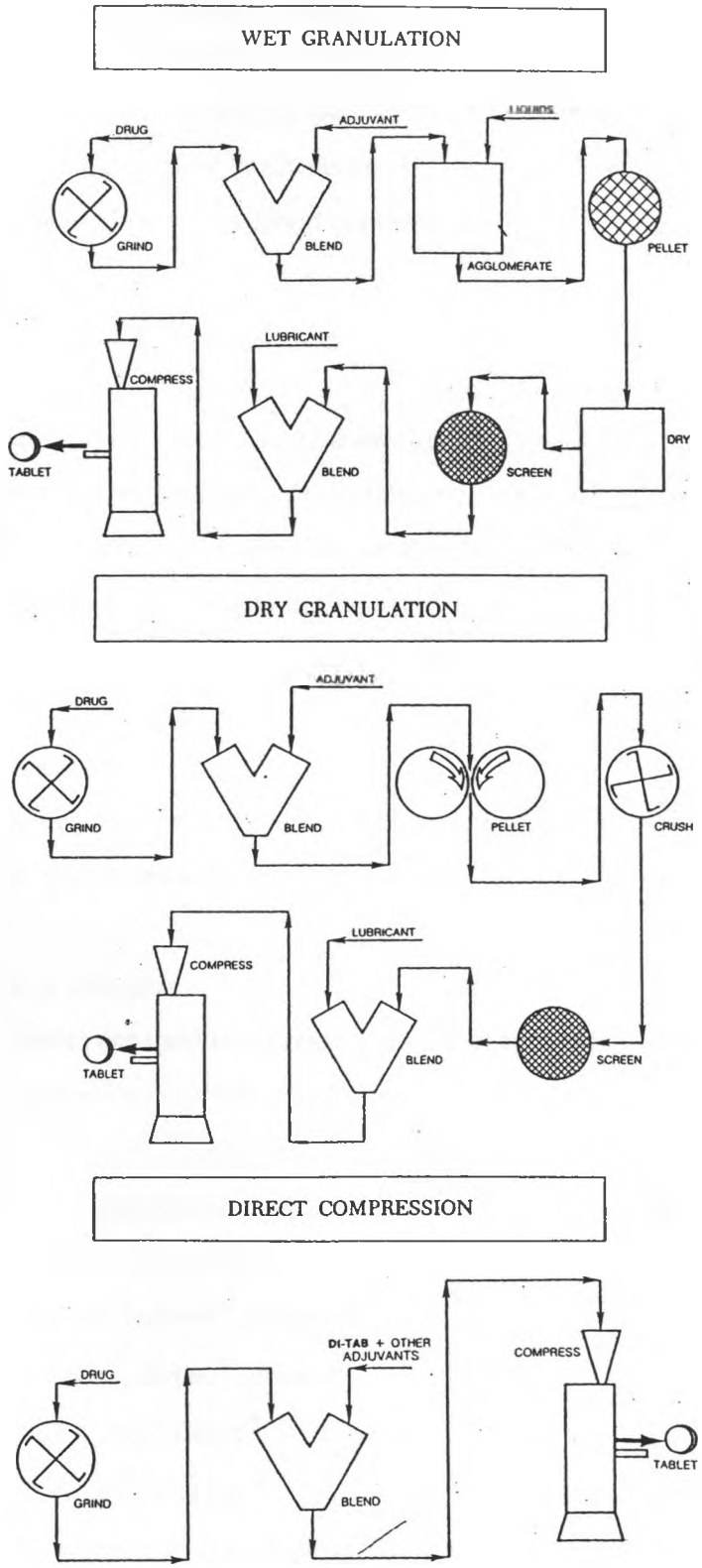


Figure 1.1: Schematic drawings of the three different methods in which tablets can be manufactured (Ansel, 1981).

1.3 Excipients

A tablet formulation contains a number of excipients in addition to the active ingredients. Direct compression excipients should be physiologically inert, colourless and tasteless. They should also be free flowing and highly compressible so as to produce tablets with a good hardness profile (Garr and Rubinstein, 1991). The major types of excipients used for a direct compression formulation are lubricants, disintegrants and diluents.

1.3.1 Lubricants

Lubricants are used in tablet formulations in order to ease the ejection of the tablet from the die, to prevent sticking of the tablets to the punches, and to prevent excess wear on dies and punches. Two of the factors that are critical to lubricant use are the particle size of the lubricant and the type and extent of mixing.
Examples include magnesium stearate and stearic acid.

1.3.2 Disintegrants

A disintegrant causes the compressed tablet to break apart when placed in an aqueous environment. Examples include sodium starch glycolate and croscarmellose sodium.

1.3.3 Fillers or diluents

Fillers or diluents are used to increase the bulk of the tablet so as to enable a formulation to become suitable for compression. In addition to lending bulk to the formulation, fillers are selected to improve binding and flow properties of the formulation. It is essential that fillers be inert and stable.
The major classes of fillers are:
Lactose e.g. fast-flo lactose®, ludipress®
Sucrose e.g. nu tab®, di-pac®, emdex®
Starch e.g. sta-Rx 1500 starch®
Cellulose e.g. avicel®, elcema ®
Dicalcium Phosphate e.g. emcompress®

Table 1.1 compares the properties of these fillers.

Table 1.1. Comparative Properties of some Fillers

Diluents	Compactibility	Flowability	Solubility	Disintegration	Hygroscopicity	Lubricity	Stability
Spray-dried-lactose	3	5	4	3	1	2	4
Fast-flo lactose	4	4	4	4	1	2	4
Anhydrous lactose	2	3	4	4	5	2	4
Sucrose	4	3	5	4	4	1	4
Starch 1500	3	2	2	4	3	2	4
Emcompress	3	5	0	3	1	1	5
Avicel	5	2	0	2	2	4	5

Graded on a scale from **5** (good/high) down to **1**(poor/low) ; **0** means none; (Banker and Rhodes, 1990)

The aim of this research was to evaluate three different fillers on the performance of ibuprofen tablets. To evaluate the three fillers, with ibuprofen, three different concentrations of the fillers were compressed at three different compression forces. By subjecting these formulations to the following tests: uniformity of weight, friability and disintegration; the concentration and compression force of the most ideal filler for ibuprofen would be determined.

The fillers chosen belong to the three major classes of direct compression fillers *viz.* cellulose, lactose and dibasic calcium phosphate.

The three fillers used were:

Microcrystalline Cellulose (avicel pH101®)

Lactose (ludipress®)*

Dibasic Calcium Phosphate (emcompress®)

**Ludipress consists of 93% lactose, 3.5% kollidon 30 and 3.5% kollidon CL.*

1.4.1 Microcrystalline Cellulose (Avicel pH101®)

Avicel stands today as the single most important tablet excipient developed in modern times (Lieberman, Lachman and Schwartz, 1989). Its properties are not far from optimal. It is a white, insoluble, neutral, non-reactive, free-flowing, versatile filler.

It is the most compressible of all the direct compression fillers and has the highest dilution potential. This can be explained by the nature of the particles, which are held together by hydrogen bonds. Hydrogen bonds between hydrogen groups of adjacent cellulose molecules account exclusively for its strength and cohesiveness.

With its smaller particle size, avicel pH101 is more compressible at a low hardness level compared to other grades of avicel, which have a larger particle size (Patel, 1994). It has an extremely low coefficient of friction, and therefore has no lubricant requirements itself. However, when more than 20% of drugs or other excipients are added, lubrication is necessary.

When used in concentrations of greater than 20% it is extremely effective as a disintegrant. This is due to its capillary action or swelling of its granules in water (Bi, 1999). The amount of avicel used in direct compression depends on the flow and compression characteristics of the formulations of other ingredients. Normally the typical range is from 10-50%.

Although it can be used in all methods of tabletting, it is most effectively used in direct compression. Because of its high chemical purity and low moisture content, improved chemical and colour stability of the tablets can result.

1.4.2 Lactose (Ludipress®)

Ludipress is a formulation of auxillaries that have been successfully used for many years in conventional tablet manufacture. It combines the most important functions of the different auxillaries in a single product. The composition of ludipress is:

(i) Lactose acts as a carrier and filler.

(ii) Povidone (Kollidon 30®) acts as a binder.

(iii) Crospovidone (Kollidon CL®) acts as a disintegrant.

It can be combined with almost all active substances.

1.4.3 Dibasic Calcium Phosphate (Emcompress®)

Is the only widely used inorganic direct compression filler. It is relatively inexpensive and possesses a high degree of physical and chemical stability. It is nonhygroscopic at a relative humidity of up to 80%. It is a water insoluble excipient with a good fluidity and glidants are generally not necessary (Mulge and Turco, 1994).

It is compatible with a very broad range of active drug components. Its particles are of a size, shape and density, which create those flow properties demanded by modern tablet presses in which a maximal degree of fluidity is essential for high-speed compaction and tablet-to-tablet weight uniformity.

The particle size distribution is within range of a great majority of active ingredients, therefore ensuring uniform blending, as well as the possibility of stratification in the hopper of the tablet press. It is normally used at levels in the range 20-50% for both tablet and capsule formulations, although it has been used successfully outside this range.

2. Experimentation

2.1 Introduction

The three directly compressible bases *viz.* avicel pH101, ludipress and emcompress were compressed at three different concentrations using three different compression forces. Therefore a total of 27 different formulations were tested.

Avicel is generally used at a concentration of 10-50%, ludipress at 25-75% and emcompress at 20-60%. Therefore the concentrations of the bases used were 40, 50 and 60%. The hardness at which the tablets were compressed was 3-5kg, 6-8kg and 9-11kg. No preformulation or screening studies were performed.

Table 2.1 illustrates the formulations at concentrations 40, 50 and 60%.

Table 2.1

Concentration of D.C. Base	**40%**	**50%**	**60%**
Ibuprofen	200mg	200mg	200mg
Magnesium Stearate	3mg	4mg	5mg
Directly Compressible Base*	150mg	200mg	300mg
Total	***353mg***	***404mg***	***505mg***

*The amount of directly compressible base varied per formulation at concentrations 40%, 50% and 60%

Table 2.2 illustrates the numerical allocation for the 27 formulations.

Depending on the difficulty to achieve the desired concentration and hardness, each formulation weighed approximately 100-200g. The ibuprofen was sieved through a 500μm mesh screen and the magnesium stearate through a 212μm mesh screen.
The ingredients for each formulation were weighed, added together and blended in a cube mixer for 10 minutes. The blend was then compressed on a single punch Manesty (type F3) tabletting machine.

Table 2.2 : Numerical Allocation for the Formulations

Directly Compressible Base	Avicel	Ludipress	Emcompress
Concentration - 353mg (40%)			
Hardness : 3-5kg	1	10	19
Hardness : 6-8kg	2	11	20
Hardness : 9-11kg	3	12	21
Concentration - 404mg (50%)			
Hardness : 3-5kg	4	13	22
Hardness : 6-8kg	5	14	23
Hardness : 9-11kg	6	15	24
Concentration - 505mg (60%)			
Hardness : 3-5kg	7	16	25
Hardness : 6-8kg	8	17	26
Hardness : 9-11kg	9	18	27

2.2 Samples

The excipients are listed in Table 2.3 with their ingredients.

Table 2.3 : Excipients Used

Samples	Constituents	Ratio (%)	Attributes	Manufacturer
Ludipress	Lactose monohydrate	93.00	filler,binder	BASF
	Kollidon 30	3.50	binder	
	Kollidon CL	3.50	disintegrant	
Avicel pH101	Microcrystalline cellulose	100.00	filler,binder	FMC
Emcompress	Dibasic calcium phosphate	100.00	filler,binder	Penwest
Magnesium Stearate		100.00	lubricant	Malinckroft
Ibuprofen		100.00	active ingredient	Albermarle

2.3 Methods

The following tests were carried out on each formulation:

2.3.1 Uniformity of weight

In addition to ensuring that the desired weight had been achieved, it was essential for the tablets to be compressed within a defined range. Too large a variation could result in a too high or too low concentration of ibuprofen. The other parameters including the thickness and hardness of the tablet could also be affected.

The weights of 20 tablets were individually recorded. The acceptance criteria was that not more than 10% of the tablets tested could deviate by more than 5% of the average weight of the tablets.

2.3.2 Hardness

The purpose of this test was to ensure that the tablets were sufficiently hard to resist breaking during packaging, shipment and normal handling and yet soft enough to dissolve or disintegrate properly after being administered (Ansel, 1981). A Pharma test (PTB 311) was used to determine the crushing strength of the tablet. This test was carried out on 5 tablets for each formulation, to confirm that the predetermined hardness limits were achieved.

2.3.3 Friability

This test determined the resistance of a tablet to loss of weight and therefore indicated the tablets ability to withstand abrasion in handling, packaging and shipment.

For each formulation, 20 tablets were weighed before being placed in the Erweka friabilator (figure 2.1) with the timer set for 4 minutes. The friabilator allowed the tablets to roll and fall within a rotating tumbling apparatus. The tablets were weighed once the cycle was completed. The loss in weight and the percentage thereof was determined. To pass the friability the percentage loss in weight had to be less than 1%.

2.3.4 Disintegration

In order for the medicinal component of a tablet to become fully available for absorption from the gastrointestinal tract, the tablet must first disintegrate and discharge the drug to the body fluids for dissolution.

The disintegration tests were performed in vitro with a Pharma test (PT2) apparatus (figure 2.2). This apparatus consisted of a basket-rack assembly, which contained 6 open-ended glass tubes held vertically upon a 10-mesh screen.

During testing 6 tablets from a single formulation were placed in an aqueous medium at 37°C, at a frequency of between 29 and 32 cycles per minute.

Six tablets from each formulation were subjected to this test and the acceptance criteria were that the tablets break apart within 15 minutes.

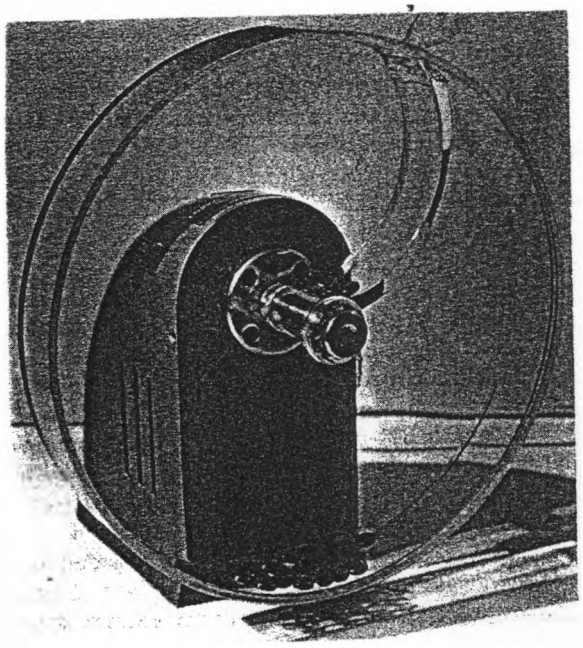


Figure 2.1: Friabilator

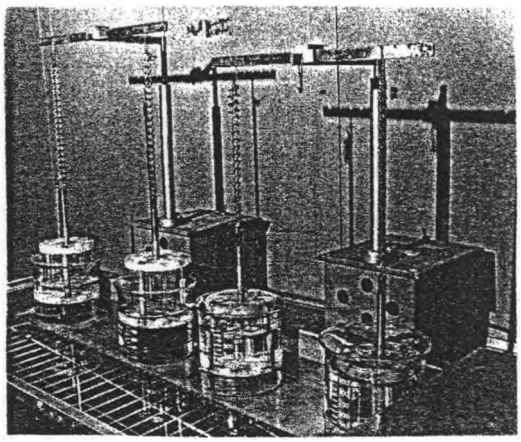


Figure 2.2: Disintegration Apparatus

2.3.5 Flow properties

The flow properties of the different directly compressible bases were evaluated by the angle of repose (θ).

The value of the angle of repose for a given material is dependent upon particulate surface properties that will also affect flowability (Lieberman, Lachman and Schwartz, 1990).

The method used was the so-called 'poured' angle method.

A powder funnel was fixed to a retort stand, so that the bottom of the orifice was 10cm from the bench surface. The outlet was closed and the funnel filled with 5 grams of the directly compressible base. The contents were then allowed to pour out. The diameter of the cone (D) and the two opposite sides, length 1(l1) and length 2 (l2) were measured. The formula below was applied to determine the angle of repose:

Arc cos [D/l1 +l2]

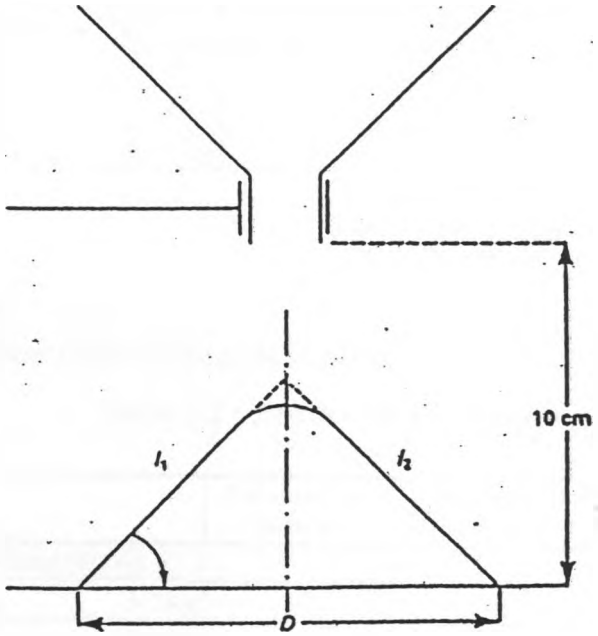


Figure 2.3: The poured angle of repose (Wells)

3 Results

3.1 Avicel pH 101

The results of the nine different formulations for avicel are tabulated below:

Table 3.1 : Results for Avicel

		Formulation Number	Uniformity of Weight	Friability (%)	Disintegration (sec)
Concentration - 353mg (40%)					
Hardness :	3-5kg	1	passed	0.43	30
	6-8kg	2	passed	0.22	36
	9-11kg	3	passed	failed	40
Concentration - 404mg (50%)					
Hardness :	3-5kg	4	passed	0.48	15
	6-8kg	5	passed	0.28	25
	9-11kg	6	passed	0.60	75
Concentration - 505mg (60%)					
Hardness :	3-5kg	7	passed	0.96	15
	6-8kg	8	passed	failed	30
	9-11kg	9	passed	failed	50

3.2 Ludipress

The results of the nine different formulations for ludipress are tabulated below:

Table 3.2 : Results for Ludipress

		Formulation Number	Uniformity of Weight	Friability (%)	Disintegration (sec)
Concentration - 353mg (40%)					
Hardness :	3-5kg	10	passed	0.78	failed
	6-8kg	11	passed	0.58	failed
	9-11kg	12	passed	0.55	failed
Concentration - 404mg (50%)					
Hardness :	3-5kg	13	passed	0.50	failed
	6-8kg	14	passed	0.86	failed
	9-11kg	15	passed	0.63	failed
Concentration - 505mg (60%)					
Hardness :	3-5kg	16	passed	0.92	300
	6-8kg	17	passed	0.89	540
	9-11kg	18	passed	0.80	failed

Since all the results for ludipress failed at a concentration of 40% and 50%, additional tests were performed at a higher and lower concentration. An interval of 10% was chosen for the concentration, which is consistent with the interval of the three original concentrations. At a concentration of 70% all the parameters were met (friability: 0.74% and disintegration: 150 seconds). At 30% the blend was sticking to the punches and the powder flow was poor.

3.3 Emcompress

The results of the nine different formulations for emcompress are tabulated below:

Table 3.3 : Results for Emcompress

	Formulation Number	Uniformity of Weight	Friability (%)	Disintegration (sec)
Concentration - 353mg (40%)				
Hardness : 3-5kg	19	passed	0.89	failed
6-8kg	20	passed	0.95	failed
9-11kg	21	passed	0.96	failed
Concentration - 404mg (50%)				
Hardness : 3-5kg	22	passed	0.95	failed
6-8kg	23	passed	0.80	failed
9-11kg	24	passed	0.92	failed
Concentration - 505mg (60%)				
Hardness : 3-5kg	25	passed	0.73	failed
6-8kg	26	passed	0.46	failed
9-11kg	27	passed	0.65	failed

All nine formulations of emcompress failed disintegration. Since emcompress is insoluble in water, experiments were carried out at a 20 and 30% concentration. This would determine if disintegration would pass at a lower concentration.
At a 20% concentration the blend was sticking to the punches and the powder flow was poor. At a 30% concentration all parameters were met except for the disintegration.

3.4 Disintegration

Of the twenty-seven formulations, fifteen failed on disintegration (tablets did not break apart in 15 minutes). Additional tests were carried out to determine if the

disintegration would improve in an acidic medium or when a disintegrant was added to the formulation.

3.4.1 Acidic Medium

Instead of an aqueous medium, tests were done in a 0.1 M hydrochloric acid solution. Only avicel disintegrated (in two minutes). Both the ludipress and the emcompress did not disintegrate in an acidic medium.

3.4.2 Addition of a disintegrant

0.5% of the disintegrant, sodium starch glycolate (Explotab®) was added to both emcompress and ludipress formulations (404 mg). The results were positive with emcompress disintegrating in 125 seconds and ludipress in 104 seconds. The recommended concentration for explotab® is 2 – 8%. However at a concentration of 0.5% both formulations passed disintegration.

3.5 Powder Flow

The flow properties of the three directly compressible bases and ibuprofen were evaluated by the angle of repose (θ).

The results are tabulated below:

Table 3.4 : Powder Flow

	Angle of Repose	***Interpretation
Avicel 40%	18	excellent
Emcompress 40%	11.59	excellent
Ludipress 40%	15.94	excellent
Ibuprofen	31.20	passable

*** Relationship between the angle of repose and powder flow

Angle of Repose	Flow
less than 25	excellent
25 to 30	good
30 to 40	passable
greater than 40	very poor

4.Discussion

4.1 Introduction

As can be seen in table 4.1 below, only eight formulations (30%) passed all three tests *viz.* uniformity of weight, friability and disintegration.

Table 4.1: Summary of Results

	AVICEL		LUDIPRESS		EMCOMPRESS	
	Formulation Number	**Result**	**Formulation Number**	**Result**	**Formulation Number**	**Result**
353mg (40%)						
Hardness: 3-5kg	**1**	passed	**10**	failed	**19**	failed
6-8kg	**2**	passed	**11**	failed	**20**	failed
9-11kg	**3**	failed	**12**	failed	**21**	failed
404mg (50%)						
Hardness: 3-5kg	**4**	passed	**13**	failed	**22**	failed
6-8kg	**5**	passed	**14**	failed	**23**	failed
9-11kg	**6**	passed	**15**	failed	**24**	failed
505mg (60%)						
Hardness: 3-5kg	**7**	passed	**16**	passed	**25**	failed
6-8kg	**8**	failed	**17**	passed	**26**	failed
9-11kg	**9**	failed	**18**	failed	**27**	failed

4.2 Avicel pH101

Avicel produced the best results from the three directly compressible bases. Six of the nine formulations (67%) passed all three tests.

The disintegration results for avicel were superior when compared to ludipress and emcompress (figure 4.1). All nine formulations disintegrated almost immediately. This is due to avicel being able to maintain a porous structure in the compressed tablet. It shows a low interfacial tension towards aqueous liquids and enhances the action of capillary forces in producing a rapid penetration of water throughout the

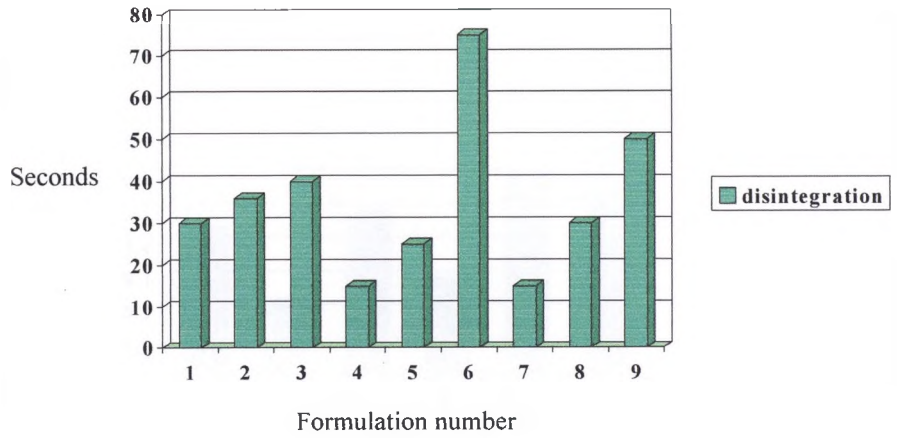


Figure 4.1 Disintegration for avicel

entire tablet matrix. The penetration of water is a prerequisite for disintegration because it activates the mechanisms that lead to disintegration. With avicel the water uptake is rapid. The penetrating water disrupts the hydrogen bond between cellulose and therefore causes an increase in pore volume (Pesonan, Paronen and Ketolainen, 1989).

As can be seen in figure 4.1, as the hardness increases, so does the disintegration. An increase in pressure causes fragmentation and deformation of particles. The smaller fragments occupy void spaces and the tablet is denser. The particles are closer and therefore more extensive hydrogen bonding occurs. Therefore water uptake is not as rapid and disintegration is longer.

Only six of the nine formulations (67%) passed friability (figure 4.2) in comparison to ludipress and emcompress, where all formulations passed friability. However the actual value of the formulations that passed is lower than that of ludipress and emcompress. Five formulations obtained results of 0.60% or lower.

This is due to the morphology of this cellulose type. Apart from hydrogen bonding, mechanical interlocking occurs. The depicted tablet surface reveals partially deformed granules and cellulose fibres, which act as "bridges" between larger agglomerates (Schmidt and Rubensdorfer, 1994).

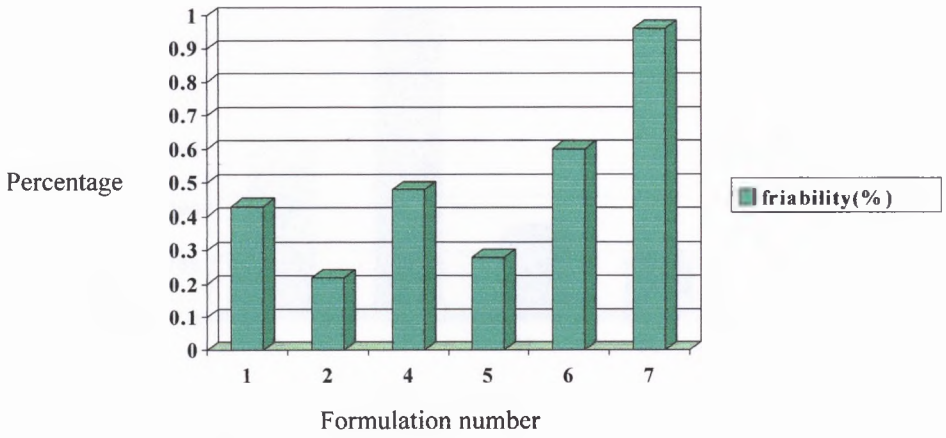


Figure 4.2 Friability for avicel

Formulations 3, 8 and 9 failed friability due to capping. With avicel, robust compacts are formed at comparatively low compaction pressures due to interparticulate bonding. Therefore higher compaction pressures have a negative effect on friability. When comparing the disintegration and friability of the nine formulations, the best results are obtained at a hardness of 3-5kg irrespective of the concentration of avicel. The results for the six formulations that passed are similar, with formulations 4 and 5 yielding the best results.

4.3 Ludipress

Only two of the nine formulations (22%) passed all three tests. Disintegration was a problem with ludipress in that seven formulations (78%) failed. Ludipress consists of kollidon CL (3.5%), which is a disintegrant. At low concentrations less disintegrant is available and the disintegration time is therefore increased.

When the disintegrant, explotab, was added to a 50% concentration of ludipress (404mg), it took only 104 seconds for the tablets to disintegrate (formulation 30). Explotab granules absorb water rapidly and swell, but do not break. The swollen granules remain intact, causing disintegration without bursting. It is neutral, inert and because the granules do not rupture, it is unreactive.

The two formulations (16 and 17) that passed disintegration were at a 60% concentration (figure 4.3). At this concentration, more kollidon CL is available and,

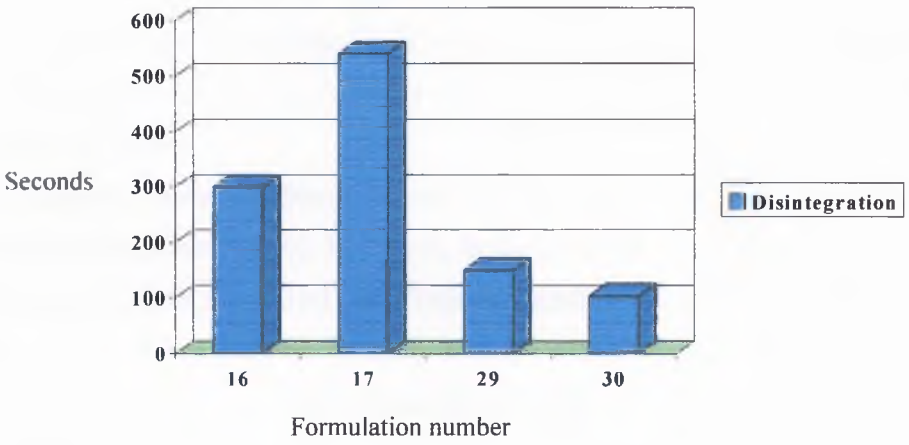


Figure 4.3 Disintegration for ludipress

therefore, these two formulations were able to disintegrate. Formulation 18 failed disintegration due to a higher compaction pressure. This produced a brittle fracture of the lactose crystals and a strong decrease of tablet porosity. Consequently water uptake was impeded and disintegration time increased. As the concentration of ludipress increased, the disintegration time decreased (Goto et al, 1999). Additional tests were done at a concentration of 70% ludipress (formulation 29). All three tests passed.

However all nine formulations passed friability. Figure 4.4 illustrates the friability for fomulations 16, 17, 29 and 30.

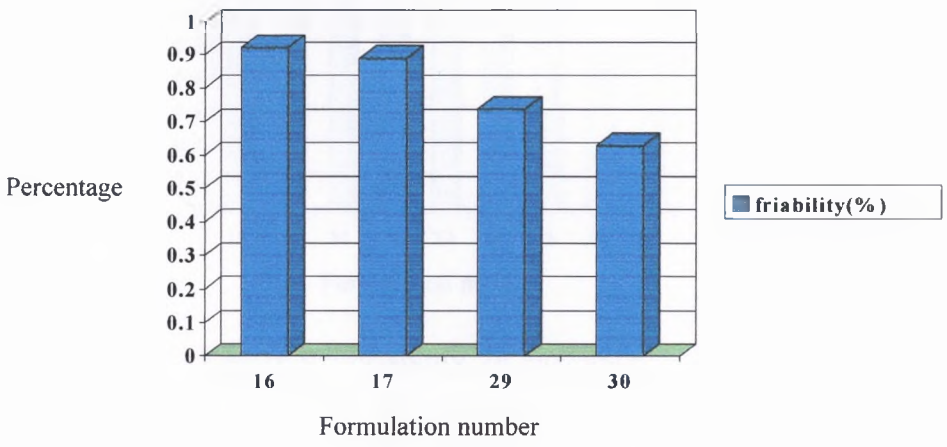


Figure 4.4 Friability for ludipress

Ludipress is a multipurpose excipient. It consists of kollidon 30, which is a binder. During compaction the lactose glass, in ludipress, undergoes plastic deformation, which increases the binding capacity of ludipress and therefore improves the friability of the formulation.

On comparing these four formulations, the best results were obtained when explotab was added (formulation 30). However, as the concentration of ludipress increased, the disintegration time decreased. The friability results for all the formulations were fairly constant. Therefore, ludipress should ideally be used at a concentration of at least 60% with ibuprofen. At lower concentrations of ludipress, a disintegrant must be added to the formulation.

4.4 Emcompress

All nine formulations with emcompress failed disintegration but passed friability (figure 4.5). Emcompress is practically insoluble in water and therefore does not disintegrate readily. A disintegrant must therefore be added to a formulation when emcompress is used. As discussed previously, experiments performed at a lower concentration (20% & 30%) were unsuccessful.

However, with the addition of 0.5% explotab to a 50% concentration of emcompress, the tablets disintegrated in 125 seconds.

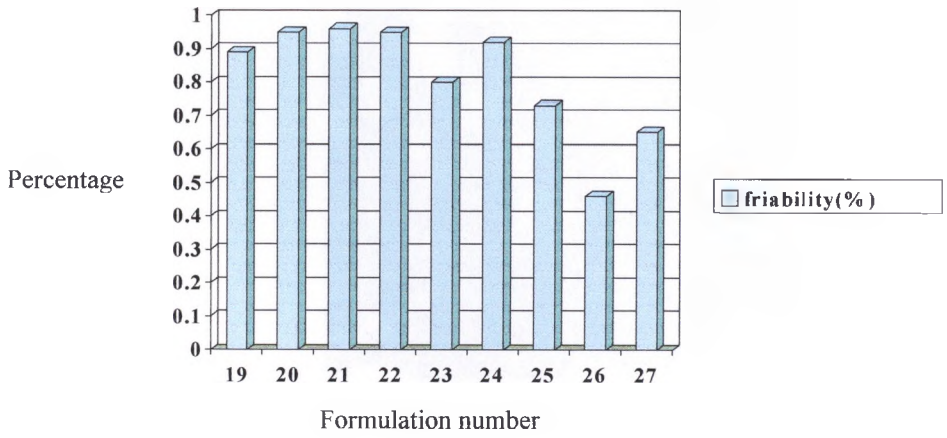


Figure 4.5 Friability for emcompress

Emcompress has good compression characteristics. It deforms by brittle fracture, when compressed; forming clean bonding surfaces which improves friability. Since emcompress is insoluble in water, it must be used in combination with a disintegrant. It appears that a higher concentration of emcompress yields superior results with formulation 26 showing the lowest friability.

4.5 Powder Flow

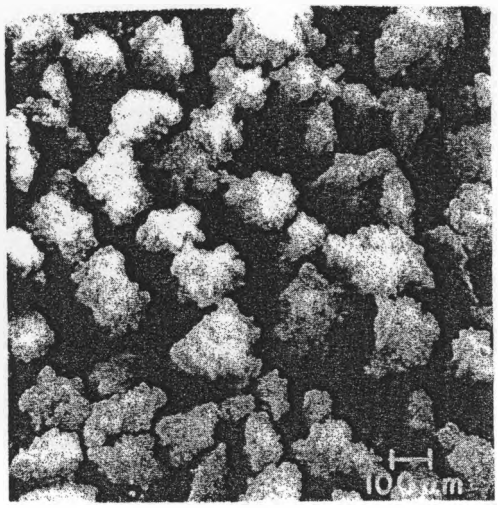
The powder flow for all three directly compressible bases were excellent (table 3.1). Emcompress had the best flow, with an angle of repose of 11,59; followed by ludipress (15,94) and then avicel (18,00).

Emcompress consists of free-flowing aggregates of small micro-crystals. 95% of the granules are less than 420 microns in size.

Ludipress showed good flowability due to the spherical shape of its granules and the lack of fibres (Schmidt and Rubensdorfer, 1994). Its larger granules have a mean diameter of approximately 200 microns.

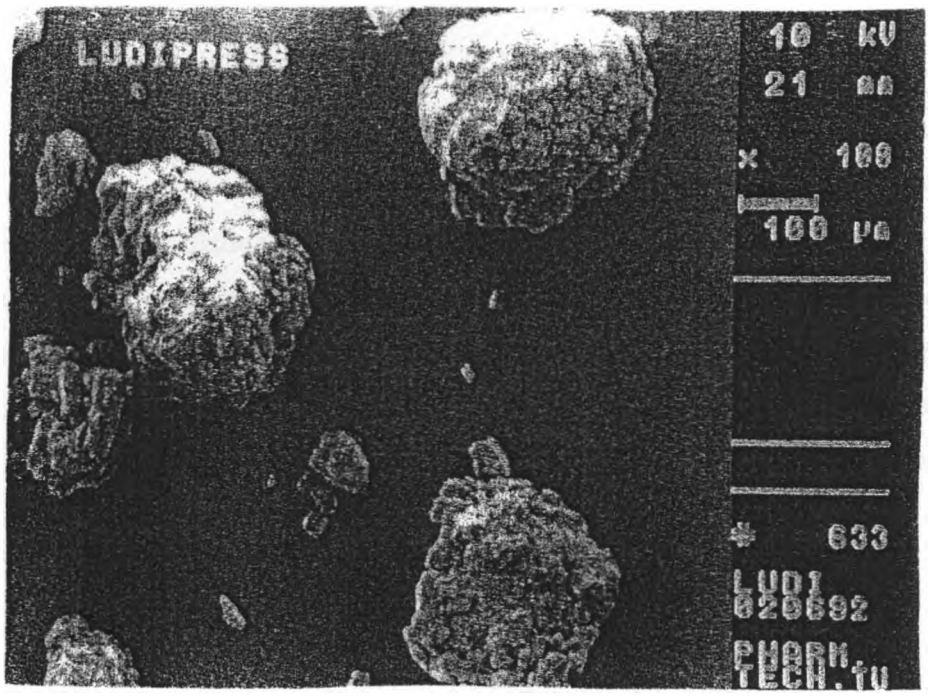
Avicel had the poorest flow. This is due to its fibrous shape, which enhances internal bridging, resulting in poor flow. The average particle size for avicel is 50 microns.

Figure 4.6, 4.7 and 4.8 show micrographs of emcompress, ludipress and avicel at a magnification of 100, 120 and 360 respectively.



Scanning Electron Microscopy(SEM)

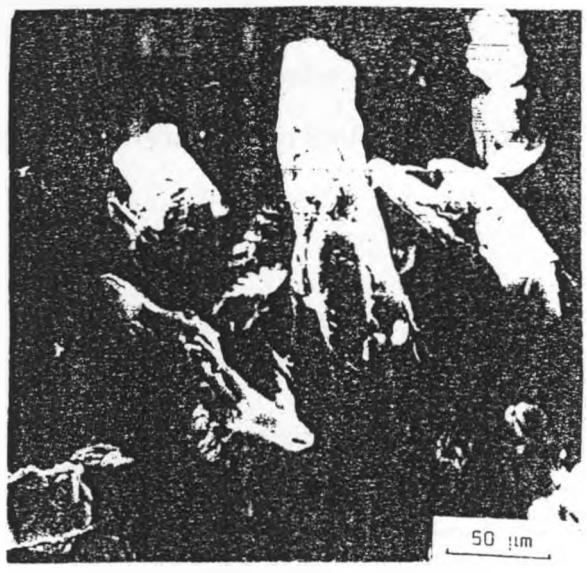
Figure 4.6(Emcompress)



SEM

Figure 4.7(Ludipress)

(Schmidt and Rubensdorfer, 1994)



SEM

Figure 4.8(Avicel)

(Wade and Welder, 1994)

5. Conclusion

On comparing the results of the three directly compressible bases, formulations 4 and 5 of avicel produced the best results. The addition of the disintegrant, explotab, to ludipress (formulation 30) and emcompress (formulation 31) produced very positive results. The use of ludipress at the higher concentration of 70% (formulation 29) proved to be effective. Figure 5.1 and 5.2 show the disintegration and friability for formulations 4, 5, 29, 30 and 31. (BP limits: for disintegration – tablets must break apart within 900 seconds, for friability - % loss in weight must be less than 1%).

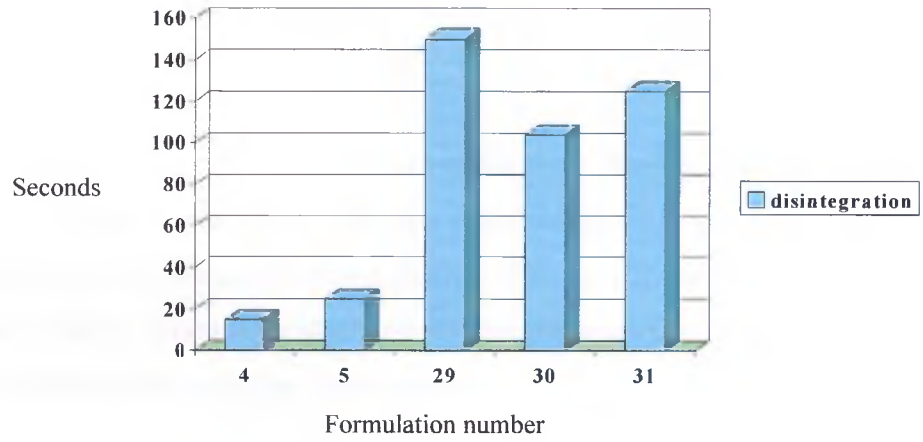


Figure 5.1 Disintegration for formulations 4, 5, 29, 30, 31.

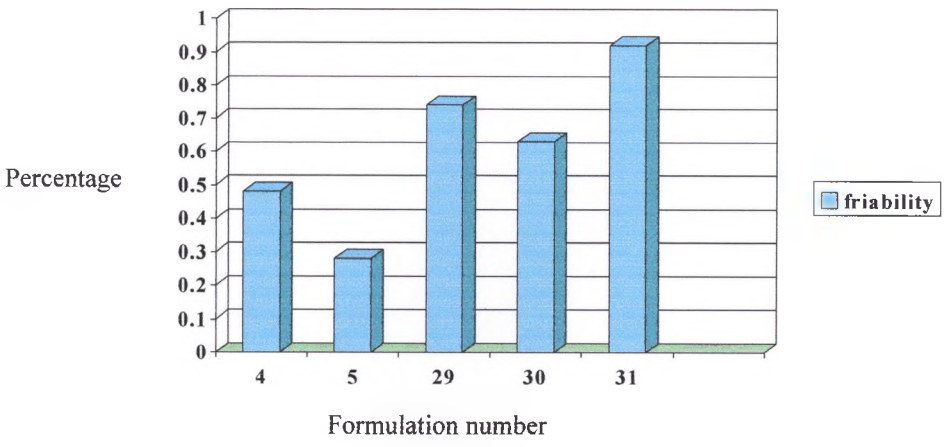


Figure 5.2 Friability for formulations 4, 5, 29, 30, 31.

The two most important factors for a successful formulation are compressibility and fluidity. Friability is related to compressibility and flow to fluidity of a formulation. All three directly compressible bases showed positive results with respect to compressibility and fluidity.

Ibuprofen is a phenylpropionic acid derivative, which has analgesic, anti-inflammatory and antipyretic actions. It is used in the treatment of rheumatoid arthritis and other musculoskeletal disorders. It has also been used in the treatment of acute gout (Reynolds, 1982).

With its rapid disintegration, avicel pH101 would be ideal for an ibuprofen formulation where an immediate response is needed. For a slow release formulation, emcompress and ludipress would be more suitable. A disintegrant will most probably have to be added to the formulation, the percentage of which will determine the rate at which the tablets disintegrate.

Future objectives:

To investigate various combinations of the three directly compressible bases. Avicel pH101 showed good compressibility and disintegration while emcompress and ludipress showed excellent flow/fluidity. The correct combination should, theoretically, produce an ideal directly compressible base with good compressibility, fluidity and disintegration characteristics.

Ethics Clearance

University of the Witwatersrand, Johannesburg

Faculty of Health Sciences

Submission of Masters Dissertation/Research Report/PhD thesis

PLEASE WRITE CLEARLY IN BLOCK LETTERS

1. Name (in full) NASEEM VAWDA

2. Student number 8906761R

3. Present home address 93 MEADWAY MEWS

MEADWAY STREET

KELVIN Postal code

Telephone 083 285 9720

4. If you are likely to move in the next 6-12 months please give the address and anticipated date

N/A

From (date)

Telephone

5. I hereby submit my ~~MSc dissertation~~ / MSc research report / ~~PhD thesis~~
(Delete whichever is not applicable)

6. I have checked **all** copies of my dissertation/research report/thesis and declare that no pages are missing or poorly reproduced.

7. Number of copies: 3 *(bound)* 2 *(unbound)*

8. I confirm that my **signed** declaration in terms of Rule G27 is included in **each** copy of the dissertation /research report/thesis.

9. Title of submitted dissertation/research report/thesis:

AN EVALUATION OF DIRECTLY COMPRESSIBLE TABLET BASES ON THE PERFORMANCE OF IBUBROFEN TABLETS.

PLEASE NOTE: IF THE ABOVE TITLE HAS CHANGED FROM YOUR PREVIOUSLY APPROVED TITLE, NO FURTHER ACTION CAN BE TAKEN BY THE FACULTY OFFICE UNTIL THE AMENDMENT HAS BEEN APPROVED BY THE FACULTY

10. Did your research involve animal experimentation?

a) Yes ☐ No ☑

b) If Yes, please certify that clearance was obtained from the Animal Ethics Committee.

Clearance number(s) _____

11. Did your research involve the use of human subjects, human tissue or other material, or patient records? Yes ☐ No ☑

If yes, has clearance been obtained from the Human Ethics Committee? Yes ☐ No ☑

No clearance required. 29/9/2000 [signature] CRHS(med) Chairman.

12. I understand that I may not graduate unless my University fees have been paid in full.

13. Name of supervisor(s):

Dr GARETH LOWNDES Department PHARMACY

_____ Department _____

Signature of candidate NVanda

Date 2000.10.14.

wcs/sci/subform/gk/5/99

6. References .

Ansel, H.C. 1981. Introduction to pharmaceutical dosage forms, third edition. Philadelphia: Llea and Febiger, pp 167 -205.

Banker, G.S., and Rhodes, C.T. 1990. Modern Pharmaceutics, second edition. New York and Basel: Marcel Dekker Inc, pp 355 -378.

Bi, X,Y., *et al.* 1999. Evaluation of rapidly disintegration tablets prepared by a direct compression method. *Drug Development and Industrial Pharmacy,* **25**(5), pp 571 -581.

Garr, J.S.M., and Rubinstein, M.H. 1991. The effect of rate of force application on the properties of microcrystalline cellulose and dibasic calcium mixtures. *International Journal of Pharmaceutics,* **73**, pp 75 -80.

Goto, K., *et al.* 1999. Pharmaceutical evaluation of multipurpose excipients for direct compressed tablet manufacture: Comparisons of capabilities of multipurpose excipients with those in general use. *Drug Development and Industrial Pharmacy,* **25**(8), pp 869 - 878.

Lieberman, H.A., Lachman, L., and Schwartz, J.B., editor. 1989. Pharmaceutical dosage forms: Tablets. New York and Basel: Marcel Dekker Inc, second edition, **1**, pp 109 -162.

Lieberman, H.A., Lachman, L., and Schwartz, J.B., editor. 1990. Pharmaceutical dosage forms: Tablets. New York and Basel: Marcel Dekker Inc, **2**, pg 300.

Li, L.C. 1992. In vitro controlled release of theophylline from tablets containing a silicone elastomer latex. *International Journal of Pharmaceutics,* **87**, pp 117 -124.

Mulge, N.V., and Turco, S.J. 1994. Use of dicalcium phosphate dihydrate for sustained release of highly water soluble drugs. *Drug Development and Industrial Pharmacy,* **25**(8), pp 869 -878.

Pesonan, T., Paronen, P., and Ketolainen, J. 1989. Disintegrant properties of an agglomerated cellulose powder. *International Journal of Pharmaceutics,* **57**, pp 139 – 147.

Patel, N.K., *et al.*1994. An evaluation of microcrystalline cellulose and lactose excipients using an instrumented single station press. *International Journal of Pharmaceutics,* **110**, pp 203 -210.

Reynolds, J.E.F., editor. 1982. Martindale. London: The pharmaceutical press, twenty eighth edition, pp 256, 257.

Schmidt, P.C., and Rubensdorfer, C.J.W. 1994. Evaluation of ludipress as a multipurpose excipient for direct compression, part 1 :Powder characteristics and tableting properties. *Drug Development and Industrial Pharmacy,* **20**(18), pp 2899 -2925.

Schmidt, P.C., and Rubensdorfer, C.J.W. 1994. Evaluation of ludipress as a multipurpose excipient for direct compression, part 2: Interactive blending and tableting with micronized glibenclamide. *Drug Development and Industrial Pharmacy,* **20**(18), pp 2927 -2952.

Wade, A., and Wedler, P.J. 1994. Handbook of pharmaceutical excipients. London: The pharmaceutical press, second edition, pg 84.

Wells, J.I. Pharmaceutical Preformulation. pp 209-212.