COMPARATIVE EVALUATION OF SUCROSE AND POVIDONE AS BINDERS FOR SODIUM SALICYLATE TABLET FORMULATIONS

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CONTENTS

ABSTRACT

This project was particularly intended for comparison of effectiveness and suitability of two different binders namely sucrose and povidone on the tablet characteristics and physical stability with time.

The wet granulation method was employed in making of the tablets where the active ingredient was sodium salicylate.

The finished batches were subjected to both official [Disintegration, Dissolution] and non official tests [mechanical strength, friability, Thickness and Diameter], initially and three months after production.

These tests gave a guideline in comparison of the two binders' suitability.

Disintegration times and dissolution rates are test parameters for which prediction of drug plasma levels can be estimated, if they are the RATE-LIMITING steps, then the in-vitro results are expected to correlate with in-vivo test results.

Mechanical strength and Friability testing give an idea on the suitability of tablet characteristics for convenience of handling in transportation and in use.

Diameter and thickness testing is necessary for patient's compliance and tablet identification.

The project showed that povidone had better binding properties than sucrose.

CHAPTER ONE

Introduction

1.1. Objectives of the Study

Comparison of physical stability of sodium salicylate tablets formulated with two different binders namely povidone and sucrose on aging.

1.2 General Aspects

The use of the tablet as a dosage form can be traced to well over one thousand years ago when a procedure for molding solid form containing medical ingredients was recorded. While the modern counterparts bear little resemblance to the original version, the compressed tablet of today is the most frequently employed dosage form throughout most areas of the world. Other solid dosage form, such as powders, cachets, pills, and grenules, which have been used for centuries, have declined in frequency of use, whereas the tablet has continued to increase in popularity. The technology related to its development and production has grown as well. [Ref: The Theory and Practice of Industrial Pharmacy 2nd Edition].

Tablets are the most widely used of all pharmaceutical dosage forms for a number of reasons. They are convenient, easy to use, and less expensive to manufacture than other dosage form. They deliver the intended dose with high degree of accuracy.

The techniques for preparing tablets may follow one or a combination of several established methods. These are:

1. Dry Method

   (a) Direct compression
   (b) Granulation by Compression

2. Wet Method

   (a) Wet granulation
   (b) Special procedure

The preparation of granulations for tableting by wet granuation is the oldest method and still the most widely used. However, it is laborious involving considerable material handling, as well as several processing steps, and therefore it is costly. The method nevertheless continues to find extensive application for a number of reasons. One reason is that, because of its universal use in the past, the method persists with established products and with new products where for one reason or another - it cannot be replaced by direct compression methods. Although a number of these products could now be made by direct compression, to do so would require a change in the ingredients or, at a minimum, a change to new form of previously used excepients. A change of this nature would be considered a major modification requiring a careful

review to evaluate the need for additional studies of product stability, safety, and efficacy as well as the impact of pertinent practical and regulatory consideration. Since extensive data are likely to have been accumulated on existing product, there is understandable reluctance on the part of the drug industry to undertake such changes unless they are dictated by compelling reasons. A second reason for the use of the method is that some formulators prefer to use wet granulation to assure content uniformity in the resulting tablets. This judgement depends to a great extent upon the personal experience of the formulator in the previous use of different tableting methods. A third reason is that wet granulation is the process of choice to use in tablet formulations of many high-dose drugs where direct compression because of the necessity to add a considerable amount of filler to facilitate compaction becomes unfeasible because of the resulting increase in the tablet size. Another advantage of wet granulation is that the drying cycle of the process can be manipulated to produce a dry granulation with a low moisture content. When such moisture content is not attainable with some direct compression formulation because of the excessive moisture content of the components, the formulation would have to be subjected to a drying cycle, thereby losing much of the benefit of economy of processing.

However wet granulation has limitations. The greatest disadvantage of wet granulation is its cost. It has an expensive process because of the labour, time, equipment, energy, and space requirements. An inherent limitation of wet granulation is that any incompatibility between formulation components will be aggravated by the granulating solvent bringing them into close contact.

1.3 Tablet Additives and Components

In addition to the active or therapeut agent, tablets contain a number of inert materials. The latter are known as additives or "adds". They may be classified according to the part they play in the finished tablet. The first group contains those which help to impart satisfactory comparession characteristics to the formulation. They include:

(1) Diluents
(2) Binders, and
(3) Lubricants

The second group of added substances help to give additional desirable physical characteristics to the finished tablet. Included in this group are:

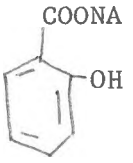
(1) Disintegrators
(2) Colours

and in the case of chewable tablets

(3) flavors and
(4) sweetening agents

Active Ingredient

The active ingredient employed was sodium salicylate structure



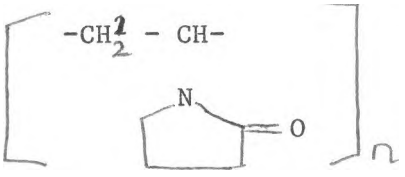
it has antipyretic and analgesic actions. It is a gastric irritant and sodium bicarbonate is often given with it to reduce this effect. However, the bicarbonate also increases the rate of excretion and this lowers the concentration of salicylate in the blood to less effective levels.

Binders

Among the materials used in tablets formulation, none is more critical than the binder used to form the granulation for it is largely the binder which is fundamental to the granulation particle size, uniformity and adequate hardness, ease of compression and general quality of the tablet. Materials commonly used as binders include starch, gelatin, and sugars as sucrose, glucose, Dextrose, molasses, and lactose. Natural and synthetic gums that have been used include acacia, sodium aliginate, extract of irish moss, penwar gum, ghatti gum, mucilage of isapol husks, carboxymethyl cellusose, menthly cellulose, polyvinyl pyrrolidone etc. Binders are used both as solution and in a dry form depending on the other ingredients in the formulation and the method of preparation.

Polyvinyl pyrrolidone (PVP) - povidone and sucrose were used and their effect on various tablet characteristics evaluated.

Structure of PVP



This compound first developed as a plasma substitute in the second world war, it is unreactive and has the advantage of being soluble in both water and alcohol. Although it has a tendency to be slightly hygroscopic, tablets prepared with it do not as a rule harden with age. It is a versatile and excellent binder but it is quite expensive compared to e.g. sucrose. It is used in concentration between 2 - 5%. PVP finds particular application in multivitamin chewable formulations where moisture sensitivity can be a problem.

Sucrose

As a binder it is used at a concentration of 2 - 20% of the formulation. Tablets prepared using sucrose are moderately strong but may be brittle and hard.

Diluent or Bulky Agent

Frequently the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size for compression. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar.

The principal substances employed as a bulking agent in tablets is lactose, USP. It is relatively inexpensive. It displays good stability in combination with most drugs whether used in the hydrous or anhydrous form. The hydrous form is most commonly used in systems that are granulated and dried.

While lactose is freely (but slowly soluble in water, the particle size of the lactose employed can affect the release rate of the medicinal.

Disintegrants

A disintegrant is a substance, or a mixture of substances, added to a tablet to facilitate its breakup or disintegrants after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution. Materials serving as disintegrants have been chemically classified as starches, clays, celluloses, algins or gums. The most popular disintegrants are corn and potato starch which have been well-dried and powdered. Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix. However, others have suggested that its disintegrating action in a tablet is due to capillary action rather than swelling, the spherical shape of the starch grains increases the porosity of the tablet thus promoting capillary action. [Ref. Remington's Pharmaceutical Sciences].

When their disintegration effect is desired, starches are added to the powder blends in the dry state.

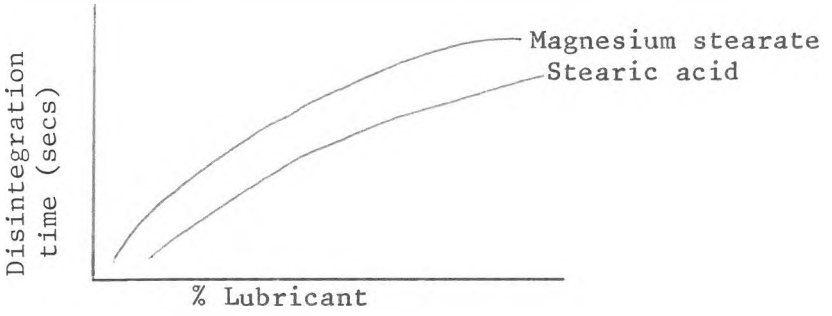
Glidants

They are materials that improve the flow characteristics of granulations. By reducing interparticulate friction and eliminating the problems associated with the flow of materials from larger through smaller apertures in the tablet presses, glidants, in the proper amounts, serve to assure smooth and uniform flow at times. Examples of glidants are talc, starch, lycopodium, magnesium stearate, calcium stearate, boric acid, sugar and sodium chloride.

Lubricants

Lubricants aid in the flow of the granulation, to reduce the die wall friction, to prevent sticking to the surface of the punches and die, and to aid in the ejection of the finished product. The lubricant has a high specific surface area which enables it to coat a large number of granules.

When excessive amounts of lubricant e.g. magnesium stearate is used, it increases the cohesiveness of the granules and hence results in poor flow. Poor flow of granules causes formation of tablets of unequal uniformity and hence variable dosages. Excess lubricant fills the intergranular spaces and renders the material cohesive. Lubricants also have a disadvantage of increasing disintegration time. Most lubricants are hydrophobic and excessive amounts tend to make a tablet water proof.



Effect of the concentration of lubricant in a sodium bicarbonate granulation compressed at 900 kg force upon disintegration time. [Ref. Pharmaceutical Technology - Fundamental Pharmaceutic - Page 84). Magnesium stearate is the best and commonly used lubricant. Others corn starch 5 - 10%, ethylene glycols of high molecular weight e.g. carbowax 5 - 10% sodium benzoate 5 - 10%.

1.4 Tablet Characteristics and Physical Stability

Stability is important not only from the stand point of aesthetics and customer acceptance but also important in maintaining uniform drug strength, identity, quality and purity.

Physical characteristics of tablets may have a stability profile just as chemical characteristics since some of the physical properties of tablets may have a profound influence on drug dissolution and release, including bioavailability. Changes of these physical properties on aging may produce corresponding changes, usually resulting in a reduction in bioavailability. Achieving satisfactory drug dissolution profile is more difficult from tablets than from any other class of oral dosage form.

It is increasingly recognised that the physical and mechanical properties of tablets may undergo change on aging or on exposure to environmental stresses, thus having a stability profile that affects bioavailability and other fundamental tablet properties. Thus it can be seen that the physical and mechanical properties stability profile can be as, if not more important than, the chemical stability of a tablet product.

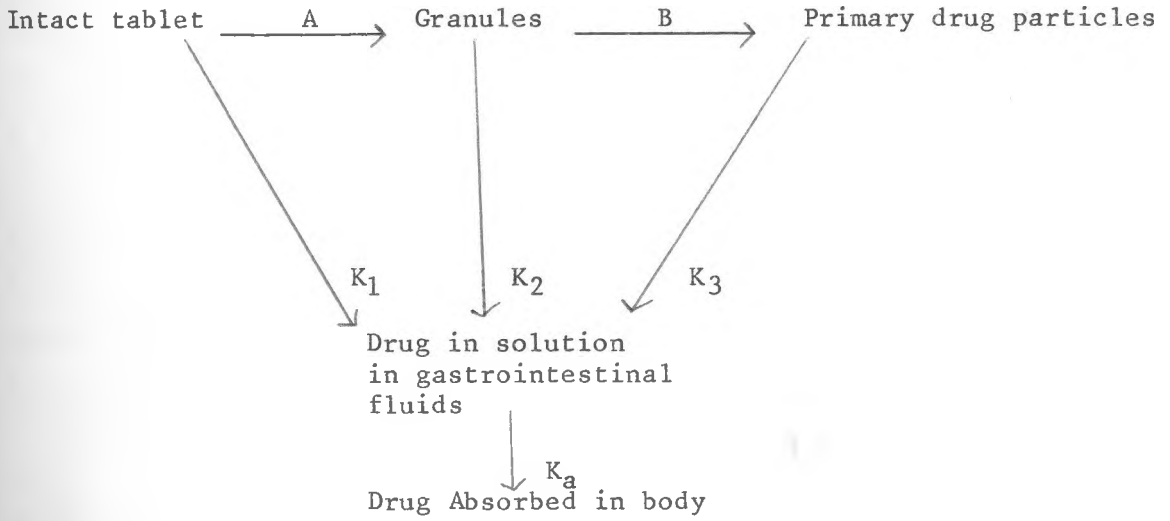
Any variation in tablet thickness with a particular lot of tablets or between manufacturer's lots should not be apparent to the unaided eye to maintain acceptance by the consumer. In addition, it is important to control thickness and facilitate packaging. In addition to the requirements, a tablet requires a certain amount of strength, or hardness, to withstand mechanical shock of handling in its manufacture, packaging, and shipping. Tablets should also be able to withstand

reasonable abuse when in the hands of the consumer (i.e. bouncing about in a purse or pocket in a partially filled prescription bottle). Adequate tablet hardness and resistance to powdering and friability are necessary requirements for consumer acceptance. Friability is related to a tablet ability to withstand both shock an abrasion without crumbling during the handling of manufacturing, packaging, shipment, and consumer use. Tablets that tend to powder, chip and fragment when handled lack elegance, consumer acceptance, can create excessively dirty processes in such area of manufacturing as coating and packaging and can add to a tablet's weight variation or content uniformity problem.

The drug in the tablet must be bioavailable. This property is monitored by two tests, the disintegration and dissolution test. However the bioavailability of a drug from a tablet or other dosage form is a very complex problem, and the results of these two tests do not of themselves provide an index of bioavailability.

Since a drug must normally be in solution before absorption can take place, orally administered tablets must have their drugs dissolved in the contents of the gastro-intestinal tract before the absorption of the drug can occur. Often, the rate of drug absorption is determined by the rate of drug dissolution from the tablet. Therefore, if it is important to achieve peak blood levels for a drug quickly, it will usually be important to obtain rapid drug dissolution from the tablet. For drugs that are absorbed high in the gastrointestinal tract (i.e. acidic drugs), which have a large dose and a low solubility, rapid dissolution may be especially important.

Schematic representation of disintegration and dissolution processes prior to absorption of a drug from a tablet dosage form



K_1 - dissolution rate constant - negligible since the surface area of a drug is so limited in the intact tablet except for very soluble drugs.

A - The primary disintegration step which may influence the absorption of a drug by influencing the dissolution process.

B - Disintegration step only when it occurs will the dissolution rate of the drug approach the dissolution rate of a drug in an aqueous suspension. The comparative magniture of the rate constants decrease in the order $K_3 > K_2 > K_1$.

A tablet that fails, or requires a prolonged period of time to disintegrate in the gastrointestinal tract, shows poor availability of the active ingredient or, at best, an undue delay in onset of the therapeutic effect. However, the rate of absorption is strictly a function of the rate of appearance of drug in solution.

CHAPTER TWO

Experimental

2.1 Equipment

1. Sartorius 2354 Electric balance
   " 2472 " "
2. Spectronic 21 : Baush & Lomb
3. Unicam SP 8,000 Ultraviolet Recording Spectrophotometer
4. Single punch hand tablet machine - Manestry Machines Ltd.
5. Granulating Machine
6. Rotating Basket Dissolution Apparatus : Erweka DT-D
7. Schleuniger - 2E for mechanical strength testing
8. Erweka disintegration apparatus
9. Erweka Friability Testing Machine
10. Calipers
11. 710 um and 250 um sieves
12. Common laboratory apparatus including volumetric flasks, measuring cylinders, syringes, pipettes, beakers, pestle and mortar etc.

2.2 Materials

1. PVP kollidon - MaC's Pharmaceutical Ltd. Nairobi
2. Sucrose - sugarcane BDH - Chemicals Ltd. Poole, England
3. Sodium salicylate-Howse and Mc George Ltd. Nairobi
4. Lactose (Milk Sugar) (I.P.) B.P. $C_{12}H_{22}O_{11}H_2O$
   Molecular weight 360.3 - Sarabhai M. Chemicals (India)
5. Starch maize BDH Chemicals Ltd. Poole, England.
6. Magnesium Stearate - E.T. Monks

2.3. Reagents and Preparation

Sodium salicylate 1% w/v was prepared and the labda max (λ) scanned. To check for absorbance of various concentrations, the following solutions were prepared. 100mg of sodium salicylate was weighed accurately on a sartorius 2472 balance and dissolved in a 100ml of distilled water in a 100 ml volumetric flask.

From this stock solution, 1ml was taken and diluted to 100ml giving a concentration of 10µg/ml of sodium salicylate. Other concentrations were obtained in a similar way.

Volume of Stock Solution	Concentration µg/ml
0.5 ml	5
1.0 ml	10
2.0 ml	20
3.0 ml	30
4.0 ml	40

2.4 Procedures

2.4 (a) Preparation of the Tablets

Four batches with the following composition were prepared. The weight aimed at for each tablet was 500 mg.

Material	Property	Percentage in the Formulation	
Sodium salicylate	Active ingredient	40	
Lactose	Diluent	29	with sucrose Binder
		46	with povidone
Maize starch	Disintegrant/glidant	10	
Magnesium Stearate	Lubricant/glidant	1	
Sucrose	Binder	20	
povidone	Binder	3	

All the weighings were done on a sartorius 2354 electric balance.

Due to the requirements of binder (percentage) in the formulation, the batches with povidone and sucrose binders (being different), the amount of lactose in them had also to vary. The following method was adopted for the different batches.

Tumbling was first done on the sodium salicylate and lactose since it is easier to mix components which are almost equal in amount.

The total amount of disintegrant was divided into half so that one portion was added to the powdered components before the wet granulation process and the remaining portion added to the finished granulation prior to the compression. Use of intra and extra-granular phase addition of disintegrants method is meant for effective disintegration of the tablet. Proponents of this method hold that a disintegrant is required between the granules as well as within them so that the disintegrating action will not only force the tablet apart into the original granules but will also break down the granules themselves [Ref. Theory and Practice of Industrial Pharmacy].

The weighed sucrose was dissolved in warm water. Using a dropper, the syrup was incorporated into the powder with continuous hand mixing. Similarly for the batches with povidone, the povidone was dissolved in water and mixed with the powder. In every batch, it had to be ensured that a suitable mass for granulation was obtained. Granulation was done through a course sieve (aperture 710 um) with a granulating machine.

The wet granules were thinly spread on a piece of paper and placed in a hot air oven for drying. Drying was done at 55°C - 60°C and the granules turned over once or twice using a spatula. The moisture content was checked occasionally by use of an infra-red machine. When proper percentage moisture content was achieved i.e. about 2-4% (but this was almost impossible to achieve even after twelve hours of drying) regranulation was then done using the 710um sieves to break up aggregates.

The granules were sieved in a 250um aperture sieve to remove the fines. 20% of these fines were incorporated back into the granules. The presence of a limited amount of fines help to produce tablets of uniform weight during compression.

The weight of granules was taken so as to calculate for the amount of starch, for extra-granular phase and also for the amount of magnesium stearate.

The granules were then mixed thoroughly with the starch and magnesium stearate and compression done using a single punch tablet machine. A weight of 0.5g for each tablet was aimed at by adjusting the volume of the die.

2.4 (b) Tests for Physical Stability of the Tablets

Precautions - Temperature of the disintegration media was maintained at 37 ± 0.5°C. The disintegration apparatus was set thirty

minutes before the start of any experiment to get constant agitation rate, which was 25 cycles/minute.

The experiment was carried out using the British pharmacopea (BP) 1973 disintegration test for tablets. In all batches, the tablets used were all close in weight, if not equal. Five tablets were placed in one basket in the disintegration apparatus and the time was recorded and the time required in minutes for tablets to disintegrate and completely pass through the sieve pores at the base of the basket.

All the batches passed the B.P. test as none of the five tablets put under test exceeded fifteen minutes. Therefore there was no need for modification of the test.

Friability Tests

Ten tablets weighed very accurately using a sartorius 2472 balance. They were then put in an Erweka friability machine which was fixed at twenty five revolutions per minute for four minutes (therefore, total 100 revolutions). After the fixed time, the tablets were brushed with a soft brush and reweighed again. The percentage loss was hence calculated.

In each batch, for accurate results, two tests were done.

Determination of Rate of Dissolution

Before performing the dissolution test, a solution of 1% w/v of sodium salicylate was prepared. This was used to scan the uv λ max which was to be used in the spectronic 21, in order to read the absorbance and thereby calculate the concentration of the aliquots from the dissolution media. The λ max was 297 um, using this, the absorbance of the standard solutions prepared i.e. 5, 10, 20, 30, 40 ug/ml were read in the spectronic 21.

CHAPTER THREE

3.1 Results and Treatment of Results

Friability Test

Two tests were done for every batch. The results are given as an average. Method of calculation.

Weight of tablets before Testing	4.9821g
Weight of tablets after Testing	4.9799g
Loss	0.0022g

$$\text{Percentage loss} = \frac{\text{weight lost}}{\text{Initial weight}} \times 100$$

$$= \frac{0.0022}{4.9821} \times 100$$

$$= 0.04415\%$$

The other figures were obtained in a similar way. The percentage change is the difference between the percentage loss - initially and after 3 months.

Table 1:

BINDER	BATCH I			BATCH II		
	Initial	3 months later	% Change	Initial	3 months later	% Change
SUCROSE	0.04415	0.00197	0.0423	0.501	0.57207	0.0711
POVIDONE	0.21413	0.5343	0.3202	0.40816	0.1550	0.25316

Disintegration Test

The results are given as an average of two tests done on each batch, initially and after three months. The time is given in minutes.

$$\text{Percentage change} = \frac{\text{Initial disintegration time} - \text{Disintegration time after 3 months}}{\text{Initial disintegration time}} \times 100$$

Example

% change for batch I with sucrose binder

$$= \frac{5.335 - 5.33}{5.335} \times 100 = 0.094$$

Table 2:

BINDER	BATCH I			BATCH II		
	Initial	3 months later	% Change	Initial	3 months later	% Change
SUCROSE	5.335	5.33	+ 0.094	5.292	5.33	+ 0.718
POVIDONE	7.50	7.50	NONE	7.792	7.60	- 2.464

KEY

- \- Indicates a decrease in the time of Disintegration.
- \+ Indicates an increase in the time of Disintegration.

Mechanical Strength Test

The strength was measured in Newtons (N)

Binder - Sucrose

Table 3:

Weight of Tablet	BATCH I Initial	BATCH I After 3 months	BATCH II Initial	BATCH II After 3 months
0.48g	82.0	91.0	38.0	78.0
0.48g	80.5	85.0	69.0	70.0
0.48g	71.0	72.0	45.0	77.0
0.48g	49.0	61.0	67.0	86.0
0.48g	81.0	97.0	62.0	70.0
0.48g	84.0	78.0	77.0	58.0
0.48g	43.0	80.0	65.0	57.0
0.48g	74.0	103.0	42.5	79.0
0.48g	46.0	74.0	73.0	80.0
0.48g	41.0	125.0	58.0	67.0
Mean Mechanical Strength	65.15	86.6	59.65	72.2
Standard Deviation	18.07	18.31	13.48	9.56
Relative Standard Deviation	27.73	21.14	22.60	13.241

Binder - Povidone

Table 4:

Weight of Tablet	BATCH I Initial	BATCH I After 3 months	BATCH II Initial	BATCH II After 3 months
0.48g	94.0	102	83.0	114
"	83.0	160	95.0	127
"	88.0	128	68.0	135
"	87.0	137	84.0	90.0
"	68.0	154	76.0	40.0
"	84.0	101	75.0	110.0
"	91.0	112	90.0	112.0
"	98.0	144	101.0	141.0
"	87.0	125	83.0	40.0
0.48g	89.0	107	92.0	118.0
Mean Mechanical Strength	86.9	127	84.7	102.7
Standard Deviation	8.0	21.4	10.0	35.9
Relative Standard Deviation	9.21	16.85	11.81	34.96

Diameter and Thickness Test

Binder - Sucrose

Units - Measurements are in millimeters (mm)

Table 5:

	DIAMETER		THICKNESS	
	Initial	After 3 months	Initial	After 3 months
	11.17	11.295	5.15	5.0
	11.15	11.30	5.145	5.135
	11.182	11.315	4.95	5.105
	11.15	11.27	4.85	5.13
	11.11	11.26	4.88	4.92
	11.165	11.23	4.99	5.07
	11.145	11.285	4.88	5.16
	11.145	11.27	5.13	5.15
	11.224	11.32	5.10	4.94
	11.20	11.295	5.06	5.11
Mean	11.1641	11.284	5.01357	5.072
Standard Deviation	0.03	0.02	0.11	0.08
Relative Standard Deviation	0.268	0.177	2.194	1.577
Percentage Change After 3 months		1.074		1.167
Percentage Change After 3 months (on RSD)		(-) (33.95)		(-) 28.122

Binder - Povidone

Units - Measurements are in millimeters (mm)

Table 6:

	DIAMETER		THICKNESS	
	Initial	After 3 months	Initial	After 3 months
	11.15	11.20	4.96	5.0
	11.18	11.19	5.11	5.135
	11.19	11.18	4.99	5.105
	11.19	11.22	5.716	5.13
	11.19	11.18	5.08	4.92
	11.155	11.17	5.06	5.07
	11.185	11.17	4.84	5.16
	11.16	11.175	5.635	5.15
	11.19	11.19	4.935	4.94
	11.195	11.295	5.06	5.11
Mean	11.1785	11.1885	5.2116	5.26312
Standard Deviation	0.01	0.018	0.35	0.34
Relative Standard Deviation	0.089	0.161	6.715	6.46
Percentage Change After 3 months	0.0895		0.988	
Percentage Change After 3 months (on RSD)	(+) 80.9		(-) 3.797	

Dissolution Rate Data

The results in the table is an average from three tablets. The concentration of each test sample was calculated using the concentration of the prepared sodium salicylate (the standard).

Binder - Sucrose

Table 7:

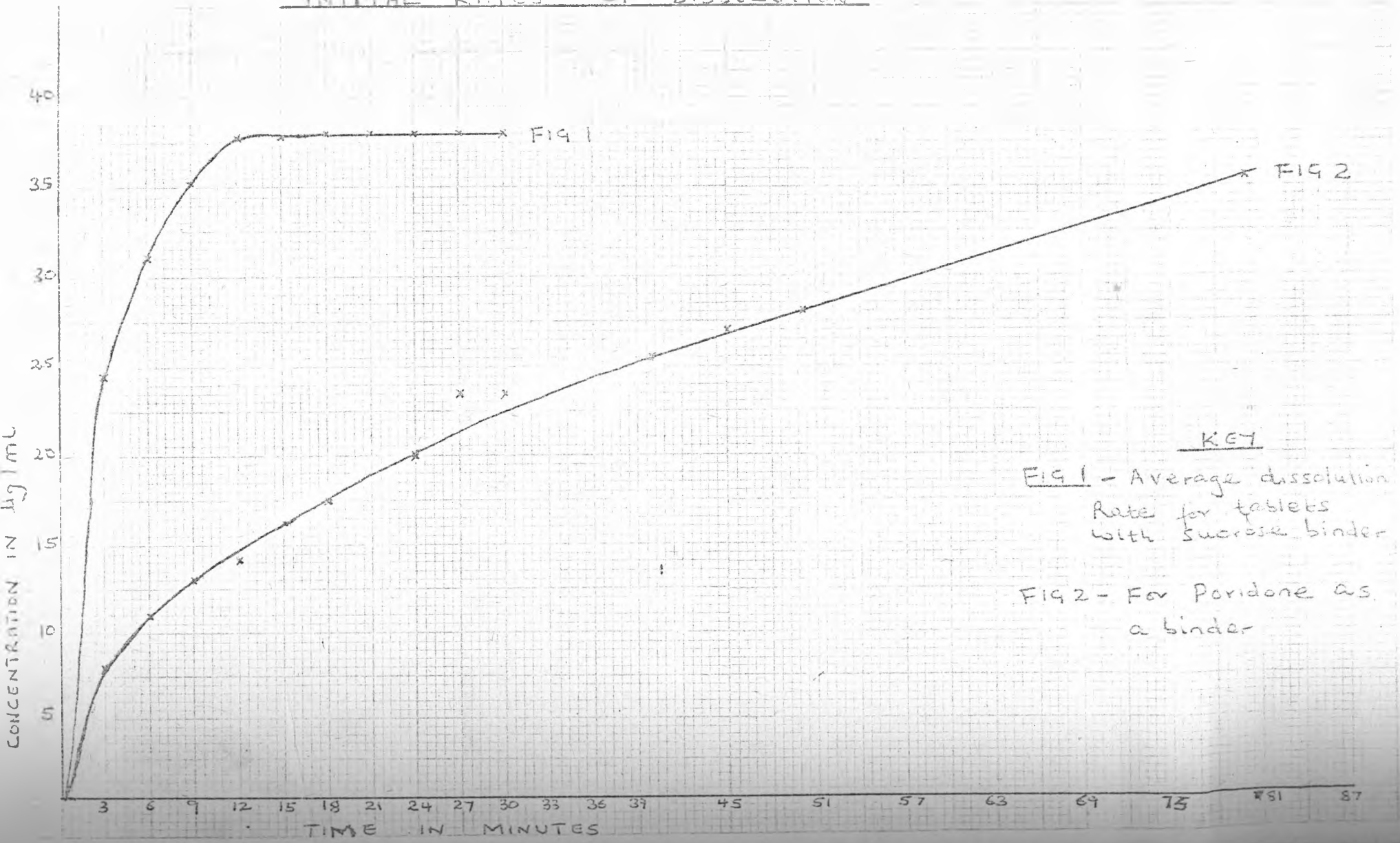
Time (Minutes)	Absorbance	Concentration Ug/ml
3	0.375	24.457
6	0.48	31.3043
9	0.54	35.2174
12	0.58	37.8261
15	0.58	37.8261
18	0.58	37.8261
21	0.58	37.8261
24	0.58	37.8261
27	0.58	37.8261
	0.46 (std)	30.00

Binder - Povidone

Table 8:

Time (Minutes)	Absorbance	Concentration Ug/ml
3	0.0.125	8.33
6	0.145	9.667
9	0.170	11.333
12	0.190	12.667
15	0.210	14.00
18	0.225	15.00
21	0.250	16.667
24	0.250	16.667
27	0.315	21.00
32	0.325	21.667
37	0.335	22.333
42	0.34	22.667
47	0.375	25.00
52	0.38	25.333
62	0.44	29.333
107	0.59	39.333
	0.45 (std)	30.00

INITIAL RATES OF DISSOLUTION

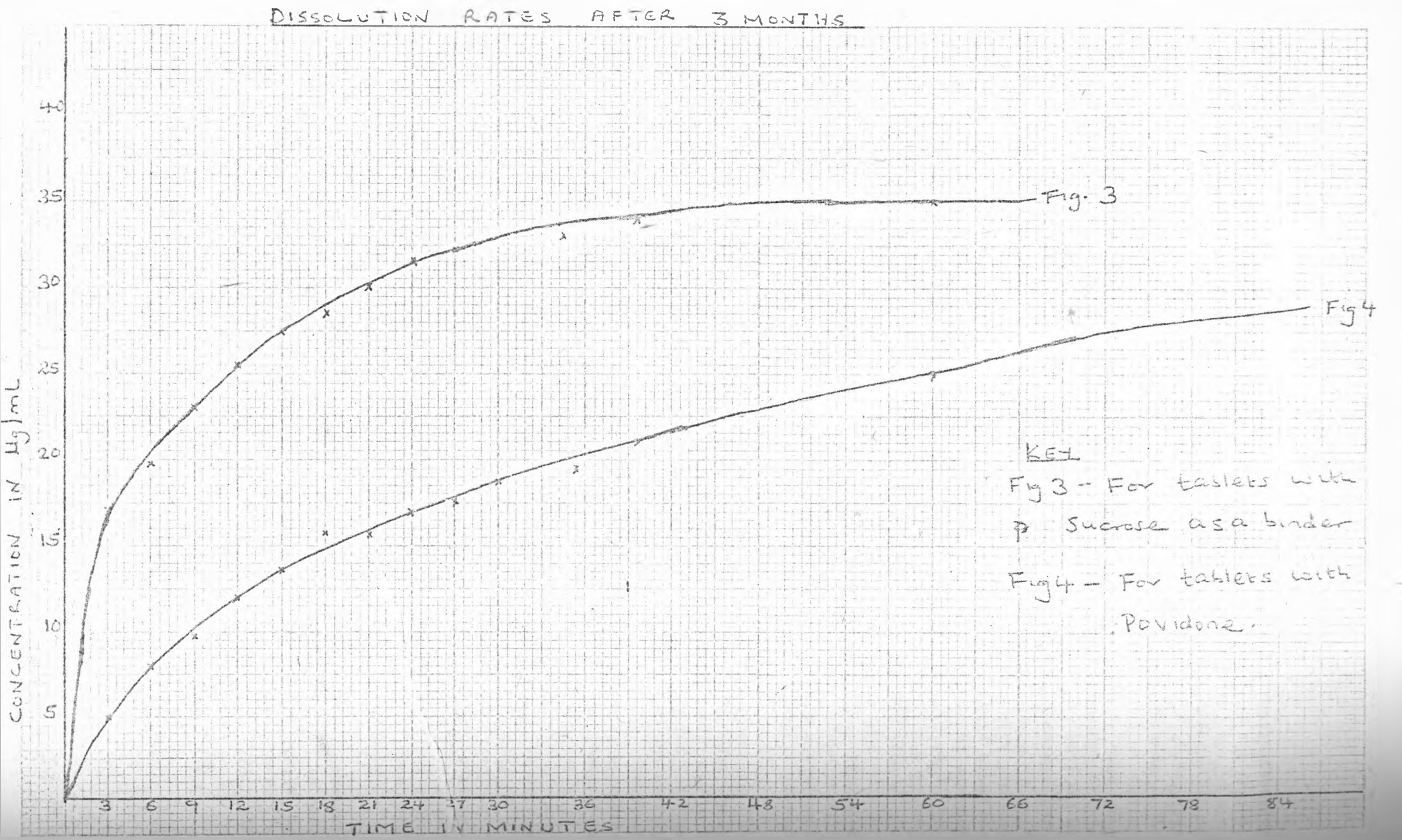


KEY

FIG 1 - Average dissolution Rate for tablets with Sucrose binder

FIG 2 - For Poridone as a binder

DISSOLUTION RATES AFTER 3 MONTHS



Key

Fig 3 - For tablets with Sucrose as a binder

Fig 4 - For tablets with Povidone.

CHAPTER FOUR

4.1 Discussion

Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability machine used induces self abrasion of the tablets as the cylinder section rotates. The tablets also undergo shock as they fall six inches on each turn. The loss due to abrasion or fracture is the measure of tablet friability.

Acceptance limits of weight loss for each size tablet must be based upon correlation with other physical factors, although friability values are usually considered satisfactory when the product exhibits a weight loss of less than 0.8% [Ref. The Theory and Practice of Industrial Pharmacy].

From the experimental results, all batches had a percentage loss of less than 0.8% initially and even after 3 months.

Therefore all the batches were within acceptable limits. However those formulated with sucrose binder (Table 1) show less percentage change in friability on aging of the tablets than those formulated with povidone. This could give a guideline on the binder more effective between the two on production of tablets which can withstand shock and abrasion without crumbling during handling with time. But this cannot give absolute conclusion since there are other factors that affect friability.

Tablet friability for instance is influenced by the moisture content of the tablet granulation in the finished tablets. Very dry granulation that contain only fractional percentages of moisture will often produce more friable tablets than will granulations containing 2-4% moisture.

Disintegration

For the two batches with sucrose binder, there was an average increase in the time taken for the five tablets to disintegrate while in one batch with povidone there was no change and the other there was a decrease with time.

However the tablets with sucrose binder had lower average increase in the time taken for the five tablets to disintegrate while in one batch with povidone there was no change and the other one there was a decrease with time.

However the tablets with sucrose binder had lower average disintegration time than those formulated with povidone.

From these observations, it shows that tablets formulated with sucrose disintegrate faster than those with povidone but then disintegration rate gets poorer with time (i.e. increases).

Except for the type of binder used, the amount of binder and the method of incorporation, other factors affect the disintegration time. These include:-

(1) Media used
(2) Temperature of media
(3) Nature of drug
(4) The type and amount of disintegrating agent
(5) Presence of excessive amounts of lubricants or overly mixed lubricated mixes can cause an increase in disintegration time
(6) Compaction pressure used to make the tablets.

These six factors were however standardised for the tablets in the two binders and therefore could, if at all, have played a very insignificant role. Therefore it is most probable that the binder contributed to the variation in disintegration time. Povidone appears to have strong binding powers in comparison with sucrose since a concentration of 3% was used while 20% was used for sucrose. Further more povidone at concentration of 1 - 5% of formulation acts as a disintegrant.

Disintegration of a tablet or capsule does not guarantee that the contained drug will be readily available for absorption. However dissolution of drug will normally be retarded if the dosage form fails to disintegrate. Tablets that disintegrate fast are normally preferred.

Mechanical Strength

Looking at the results (Tables 3 and 4), it can be seen clearly that tablets with povidone binder are much stronger than those with sucrose, initially and 3 months later.

On average, the change in mechanical strength was larger with povidone formulated tablets than those with sucrose. However in both cases there was an increase in the mechanical strength with time.

The relative standard deviation was greater for tablets with sucrose than those with povidone. This means that within the tablets, the total variation from the mean was higher. But the tablets did not differ significantly in their strength after 3 months than initially. Povidove, although it has a tendency to be slightly hygroscopic, tablets prepared with it do not, as a rule, harden with age. This was not the case and other factors could have contributed including the storage conditions.

For consumer's acceptance, it seems that it is easier to formulate tablets with povidone than with sucrose to give tablets with closer hardness immediately after manufacturing though the variation will increase on aging of tablets.

Povidone gives tablets which are quite strong in comparison with sucrose ones which would have ability to withstand the rigors of the mechanical treatment involved in the production, packaging, shipment and dispensing.

However the tablets should not be too hard to compromise drug release characteristics.

Diameter and Thickness

The relative standard deviation (R.S.D.) in thickness in tablets formulated with povidone is much greater than in those with sucrose while the R.S.D. of diameter for povidone tablets is slightly lower than those with sucrose.

The thickness variation from mean for tablets with povidone shows that in the batch, difference in thickness from tablet to tablet is much more than with sucrose. In both cases the variation decreases with age.

Initially, the tablets thickness and diameter is influenced by the compression force exerted and therefore looking at the results obtained initially, is not a good way of assessing binder's efficiency. In both cases the RSD for diameter is not very much and decreases with time in tablets with sucrose while for povidone there is a great increase in RSD after 3 months in the Diameter of tablets with povidone binder while there is a decrease in those with sucrose. The percentage decrease in RSD after 3 months is greater for sucrose tablets than for povidone ones. Therefore the variation within the tablets from the mean diameter after 3 months is greater for povidone formulated tablets while variation for sucrose ones decrease. In the case of thickness, the variation within the tablets decreases a lot for sucrose formulated tablets than those with povidone.

Therefore the variation within the tablets size is greater for povidone tablets than for sucrose ones.

But looking at whole batch on change in the mean size, the sucrose ones are affected more on aging as shown by the higher percentage.

Any variation in tablet thickness within a particular lot of tablets or between manufacturer's lots should not be apparent to the unaided eye to maintain product acceptance by the consumer. Therefore tablets that change alot with storage are not good since this also affects packaging.

Dissolution

Dissolution characteristic of the formulations are shown in figures I, II, III and IV. In figure I tablets with sucrose binder show that for the first 9 minutes, the dissolution rate is about 3.89 µg/ml/min, this rate then decreases slightly for the next 9 - 15 minutes to 0.43 µg/ml/min. the dissolution rate becomes constant after the 15th minute. Therefore the maxima is at 37.5 µg/ml/min.

Povidone formulated tablets.

The dissolution rate is much lower and the gradient is small throughout, unlike with sucrose where for the first 9 minutes there is a steep gradient. There is no maxima as rate does not go to a steady one even after 84 minutes. This is indicated by figure II.

After 3 months

As shown in figure III, the rate of dissolution of tablets with sucrose decreases and the tablets do not reach any steady state. The gradient decreases but dissolution rate is higher than for tablets with povidone, whose dissolution rate did not seem to have changed (Figure IV).

It appears that tablets formulated with sucrose as a binder have better release characteristics than those with povidone. But those with sucrose binder are affected on storage.

Factors influencing dissolution rate:

- Tablets made with smaller granules dissolve faster than those from larger ones;
- Starch increases the dissolution rate - probably because of more efficient disintegration of the granules to primary particles and increase in surface area;
- Hydrophobic materials e.g. magnesium stearate and stearic acid which are commonly used as tablet lubricants, reduce significantly the rate of dissolution;
- Dissolution may be slow due to strong intra-granular forces or presence of a film of hydrophobic adhesive (binder) around the granules.

In addition to these factors the compression force has a marked effect on the release characteristics of the tablet. A big compression force will decrease the disintegration rate as well as dissolution whereas a weak force will do vice versa.

However, since the compression force was almost standardised, it is not very likely that the force used for the tablets vary considerably to justify the variations in drug release characteristics.

Tablets formulated with povidone were stronger than those with sucrose and therefore it shows that povidone has very strong binding properties than sucrose.

4.2 CONCLUSION

Bearing the aim of the project in mind together with the previous discussion, the following conclusion can be drawn on the better binder of the two on the following physical characteristics.

Initially

In terms of disintegration and dissolution rates, sucrose as a binder produced tablets with better drug releasing characteristics than those with povidone. These two tests are very important in assessing the usefulness of a formulation in its therapeutic use.

After 3 months

Those tablets with sucrose were less friable but there was deterioration in disintegration and dissolution rates. There was also much more increase in both diameter and thickness of those sucrose formulated tablets with storage than those with povidone.

Those with povidone showed no significant change on dissolution and disintegration rates with time. Initially and after 3 months, those with povidone gave stronger tablets than those with sucrose as a binder.

From these, it appears that sucrose is a good binder for tablets which are to be put into use immediately after manufacturing since there is deteriorating effect on the formulation on storage. Tablets with povidone show good keeping properties.

It is too expensive to manufacture small batches for immediate use only and therefore it appears that povidone is a better binder than sucrose.

Povidone is much more expensive than sucrose but since it is only used as 3 - 5% of the formulation, in the long run it is cheaper since large batches can be manufactured at the same time and stored for later use.

The primary criterion when choosing a binder is its compatibility with the other tablet components. secondarily, it must impart sufficient cohesion to the powder to allow for normal processing (sizing, lubrication, compression, and packaging), yet allow the tablets to disintegrate and the drug to dissolve upon ingestion, releasing the active ingredients for absorption.

From the tests carried out on the finished product, povidone appears to be more satisfactory than sucrose as a binder.

C H A P T E R F I V E

REFERENCES

1. The Theory and Practice of Industrial Pharmacy Second Edition by Leon Lachman, Herbert A. Lieberman, Joseph L. Kanic.

2. Pharmaceutical dosage forms - Tablets volume 1 and 2. Edited by Herbert A. Lieberman and Leon Lachman.

3. Remington's Pharmaceutical Sciences.

4. Pharmaceutical Codex.

5. Pharmaceutical Technology - Fundamental Pharmaceutics.

6. British Pharmacopea 1973.

7. United States Pharmacopea.