
CHAPTER - TWO

EFFECTS OF
BINDERS ON SULPHAMETHOXAZOLE TABLETS

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RESUME

Five batches of sulphamethoxazole tablets were prepared using different binders viz. starch, acacia, ethyl cellulose, sodium carboxy methylcellulose and povidone (polyvinyl-pyrrolidone P.V.P.) with water in 3% (dry basis) concentration. Comparative data show that granules prepared with PVP have the best flow properties, minimum angle of repose, percentage fines and compressibility. While granule of sodium carboxy methyl cellulose could not be compressed into well defined tablets. Tablets containing starch as a binder posses all quality feature. Tablets from acacia however gives a poor dissolution profile. Ethyl cellulose have less effective granule formation leading to poor quality of tablets. Rank correlation with respect to solubility and absorption characteristics according to granulating agent in the formulation are as starch > ethylcellulose > P.V.P. > acacia.

INTRODUCTION

Solid dosage forms are the most popular category of pharmaceutical formulations. They are in a sense 'convenience' dosage forms and in comparison to the liquid formulations, their stability is of very high order. Within the solid dosage forms unitary forms such as tablets, pills, capsules, cachets, wrapped powders rank high, since they ensure accuracy in dosage.

Compressed tablets offer a number of advantages to the patients as well as the physicians and pharmacists. It is because of these advantage, that their popularity continues to increase(59). From physicians point of view, tablets are significant since their formulation and processing can be manipulated to provide a controlled drug action. The rates of their dissolution as well the sites of dissolution can be fairly accurately controlled giving a preconcieved pattern of action. Tablets also assure 'safety' because of controlled release of drug and reduced chances of high peak blood levels and toxic effects.

The pharmaceutical scientists also have many advantages in compressed tablets. The problems of incompatibilities of medicament and their deterioration due to environmental factors are less significant in solid dosage forms.

Before drawing up a formula for any particular type of tablet it is

essential to visualise its physical and performatonal characteristics, since the two aspects are highly interrelated. The tablets in general should have a certain degree of tensile strength, should provide uniform dose of the medicament, and should posses disintegration/dissolution characteristics as warranted by situation of the case. All these properties are additive dependent(59). Tablets formulations perhaps call for maximum number of additives as detailed below :

- i) Diluents
- ii) Adsorbents
- iii) Binders
- iv) Disintegrating agents
- v) Organaleptic additives
- vi) Glidants anti adhesives, lubricants

Binders :

Binders or adhesives are added to tablet formulations to add cohesiveness to powders, thereby providing the necessary bonding to form granules which under compaction form a cohesive mass or compact referred to as a tablet. The formation of granules aids in the conversion of powders - of widely varying particle sizes - to granules, which may more uniformly flow from the hopper to the feed system, and uniformly fill the die cavity. Granules also tend to entrap less air than powders when compressed. The binder is

usually selected on the basis of previous experience, particular product needs, literature or vendor data, and - unfortunately (or fortunately) - the preference or capabilities of the tablet manufacturing unit. Some of the common binding agents used in tablet formulations are Acacia, Cellulose derivatives, Gelatin, Glucose, Polyvinylpyrrolidone, Starch paste, Sucrose, Sorbitol, Tragacanth Sodium Alginate etc.

The primary criterion when choosing a binder is its compatibility with the other tablet components. Secondary, it must impart sufficient cohesion to the powders to allow for normal processing, yet allow the tablet to disintegrate and the drug to dissolve upon ingestion, releasing the active ingredients for absorption. Different binders can significantly affect the drying rate and required drying time of a granulation mass, and the equilibrium moisture level of the granulation(60).

Tablet Dissolution :

The dissolution profile of a disintegrating tablet is typically a sigmoid curve. The corresponding rate of dissolution is initially zero, then increase until it reaches a maximum and decreases back to zero. Dissolution can be

considered as the reverse process of crystallization, in which individual drug molecules are transferred from the solid surface to the aqueous environment. The reaction at the interface occurs much faster than the rate of transport of molecules from the interface. Therefore, the rate of dissolution is determined by the diffusion or convective transport of solute from the interfacial boundary to the bulk of the solution(61). For most of the drugs of pharmaceutical interest the dissolution behaviour is transport controlled.

The simplest dissolution model involves dissolution from a flat surface into a liquid. Noyes and Whitney in 1897 derived the 'Film Theory' with the equation (62).

$$\frac{dc}{dt} = K (C_s - C) \quad \dots (i)$$

Where K is a model-dependent dissolution rate constant,

C is the concentration of the drug in the solution at the t, and

C_s is the solubility of the drug at the experimental temperature

In this model, it is assumed that there is a stagnant liquid layer (film) at the interface. The concentration of the drug at the solid surface is assumed to be equal to the solubility of the drug and the dissolution rate is determined by the rate at which molecules diffuse from this layer to the bulk solution. Nernst(63) and Brunner(64) later

extended this concept to include the surface area and this can be shown by the equation.

$$\frac{dc}{dt} = \frac{DA}{Vh} (C_s - C) = K'A (C_s - C) \quad \dots (ii)$$

Where A is the area of the dissolving surface,

D is the diffusion co-efficient of the drug,

V is the solution volume

h is the effective diffusion layer thickness and

$$K' = \frac{D}{Vh}$$

Equations have been used to fit tablet dissolution curves and provide parameters which facilitate the storage of data and comparison between various formulations.

Hixson - Crowell Cube Root Law with Lag Time :

Hixson and Crowell proposed a model which accounts for the change in surface area when spherical solids dissolve. In this model, the diffusion rate and the decreasing particle size are linked together by a mass balance. For a powder of uniform particle size dissolving under sink conditions, the following equation is obtained(65).

$$w^{1/3} = w_o^{1/3} - K_{1/3} \cdot t \quad \dots (iii)$$

Where W is the mass of the powder that remains at time t , and W_0 is the initial mass. The constant $K_{1/3}$ is defined to be

$$K_{1/3} = (W_0^{1/3}) \left(\frac{2DC_s}{\rho h^3} \right) \left(\frac{1}{a_0} \right) \quad \dots (iv)$$

Where ρ and a_0 are the density and the initial diameter of the particles, respectively and all the other terms are defined the same as before.

This equation can be reduced to the following form :

$$(W/W_0)^{1/3} = 1 - K_{1/3} \cdot t \quad \dots (v)$$

Where W/W_0 is the fraction of the powder remaining at time t and

$$K_{1/3} = \frac{2DC_s}{\rho h^3 a_0}$$

The constant $K_{1/3}$ is directly proportional to the diffusion co-efficient, the solubility of the drug, and inversely proportional to the diffusion layer thickness and the initial diameter of the particles. It is a model-dependent parameter and must be obtained experimentally.

By including a lag time, the following two parameter results equation (vi).

$$W_0^{1/3} - W^{1/3} = K (t - t_0) \text{ for } t \geq t_0 \quad \dots (vi)$$

$$W = W_0 \text{ for } t \leq t_0$$

In certain cases, the lag time may be related to the tablet disintegration time or the time required for dissolution of the tablet coating and can be determined directly from the dissolution profile. The rate constant can be obtained either by non-linear regression or from the slope of a $W^{1/3}$ Versus $(t - t_0)$ plot.

Sigma Minus Plots :

First order equation have been used to describe tablet dissolution under sink conditions(66).

$$W = W_0 e^{-kt} \quad \dots (vii)$$

This equation can also be expressed as the linearized form

$$\ln W = \ln W_0 - kt \quad \dots (viii)$$

Frequently the data points are non-linear in the early time period, but, at later times, a straight line usually may be fitted to the data points.

Kitazawa et al(67) plotted $\log (100 \times W/W_0)$ (i.e. log percent of drug undissolved) versus time and found that two straight regression lines

were obtained. The time t_1 at which the two lines intersect was correlated to the tablet disintegration time. The dissolution rate constants K_1 and K_2 , calculated from the slopes of those two lines, were thought to represent the dissolution rate of the drug from the intact and the disintegrated tablet respectively. The change in the dissolution rate constant from K_1 to K_2 at time t_1 was considered as due to an explosive increase in surface area of the drug available for dissolution.

In this case, K_1 is smaller than K_2 . In another case however, K_1 was observed to be greater than K_2 . This was explained by Esezobo and pilpel(68) as a rapid initial break up of the tablets into fairly large fragments and a slow further break up into small fragments. The first order equation has also been modified by introducing an additional parameter lag time t_0 .

$$W = W_0 e^{-k} (t - t_0) \quad \text{for } t \geq t_0 \quad \dots (ix)$$

$$W = W_0 \quad \text{for } t < t_0$$

The dependence of the rate of absorption on the dissolution characteristics of a solid drug in the gastro intestinal tract is an important biopharmaceutical problem. The sartorius solubility simulator* was developed for the in vitro investigation of sulphamethoxazole tablets, capsules and suspensions. To study the absorption pattern * as shown in Fig. 1.

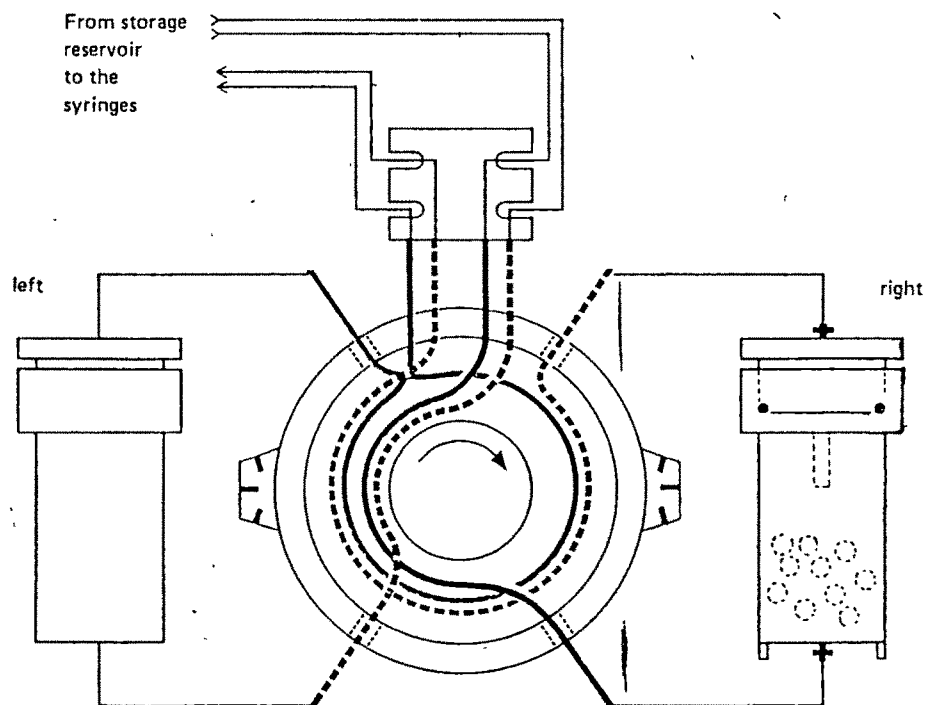
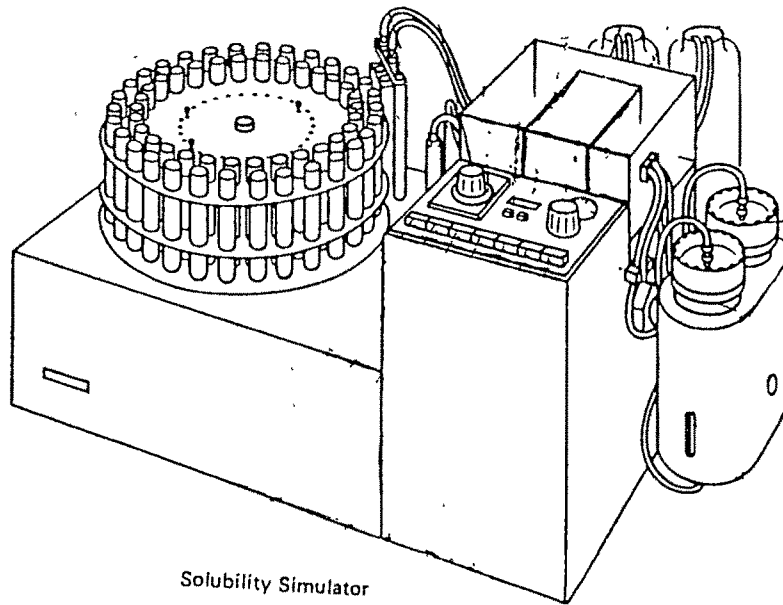
in Vitro Sartorius Absorption Simulator was used as shown in Fig - 2 .

The Sartorius Solubility Simulator :

It consists of two identical separate but mechanically coupled systems, so that two different investigations can be carried out simultaneously. Principle of operation(69). The thermostated (37°C) solubility chamber which contains a definite number of beads (filler) and artificial gastric or intestinal juice in addition to the drug preparation under test rotates around a horizontal axis during the experiment at 1.2 r.p.m. The filler thus simulates a peristaltic movement and the mechanical forces acting in the gastro intestinal tract. As the solid drug slowly dissolves, samples of fixed volume are automatically removed from the chamber through a filler at fixed time intervals. The samples are transferred by means of a syringe to a fraction collector. At the same time as the sample is taken, an identical volume of the appropriate buffer flows from a storage container to the solution chamber, so that the volume of liquid in the solution chamber remains constant. In order to achieve better filtration the pump operate once immediately before and once immediately after sampling. During this pump cycles, no buffer flows into the solution chamber, and the volume which is removed from it, is immediately pumped back into it.

The sample taken from the chamber at time $T = n.t_R$ remains in the screw cap of the filter holder and in the tubing (also in the volume

Fig. 1



Arrangement of the tubing around the rotation axis of the solution chambers

adjustment chamber when used) until the next sampling procedure i.e. it appears in the fraction collector at the $T^1 = (n + 1)t_R$.

At the end of the experiment the instrument is switched off and the pressure valves are set to mid position in order to release the pressure on the tubing.

Contents of the Solution Chamber :

The following are placed in the chamber prior to an experiment - 72 g plexi glass beads (diameter 8 mm) and 100 ml aqueous phase. The aqueous phase is artificial gastric juice of pH 1.2. Time of the experiment is 30 minutes. The liquid volume in the solution chamber remains constant during the experiment (tolerance 95-105 ml). The storage containers should always contain the solutions which are required for the solution chamber. Normally a sample volume of $V_D = 2.5$ ml is used.

Simulator Operating Guidelines :

1. Push button = set number of samples $n = 1$.
2. Round Knob(a) = Set time interval t_R to approximately 20 seconds
3. Press button (a) = Press in
4. Press button (b) = Press in and wait for pump movement.

5. Press button (c) = Press in
6. Press button (d) = Press in according to inlet required for replacement juice.
7. Round Knob (b) = Set sample Volume V_D
8. Round Knob (c) = Set time interval t_R while keeping push button depressed.
9. Fill the storage container with solution. The tubing should hang freely inside the storage containers, to assure free flow.
10. Place the solution chamber in the temperature jacket and turn to lock. Connect the inlet tubing to the bottom of the solution chamber.
11. Place plastic beads and artificial gastric juice in the solution chamber and allow 30 minutes to reach temperature.
12. Place a filter in the dry filter holder base, place the sealing ring in position and then screw the cap on using a pipette, wet the filter completely by adding distilled water through the inlet port on the screw cap and remove excess water by gentle blowing. Connect the tubing to the syringe.
13. Swing the swivel arm into position above the test tubes.

Adjustment of the Simulator :

1. Place the sample (tablets, capsules, suspensions) in the solution chamber, screw the filter holder back on.

2. Set the number of samples with the push button, according to the time of stay in the gastric juice which is wanted.
3. At appropriate time intervals the sample is transferred to the fraction collector. The solution collected in the containers are analysed, for the drug concentration.

The Sartorius Absorption Simulator :

Description of the Apparatus :

The Sartorius Absorption Simulator consists principally of the following parts.

Basic Instrument(70) :

Peristaltic Pump (a) to circulate the aqueous phases

Temperature Jacket (b) for the containers h_1 and h_2

Stirrer Motor (not visible) (c) for the magnetic stirrers

Moveable Holder (d) for test tubes

Control Knob (e) for temperature adjustment

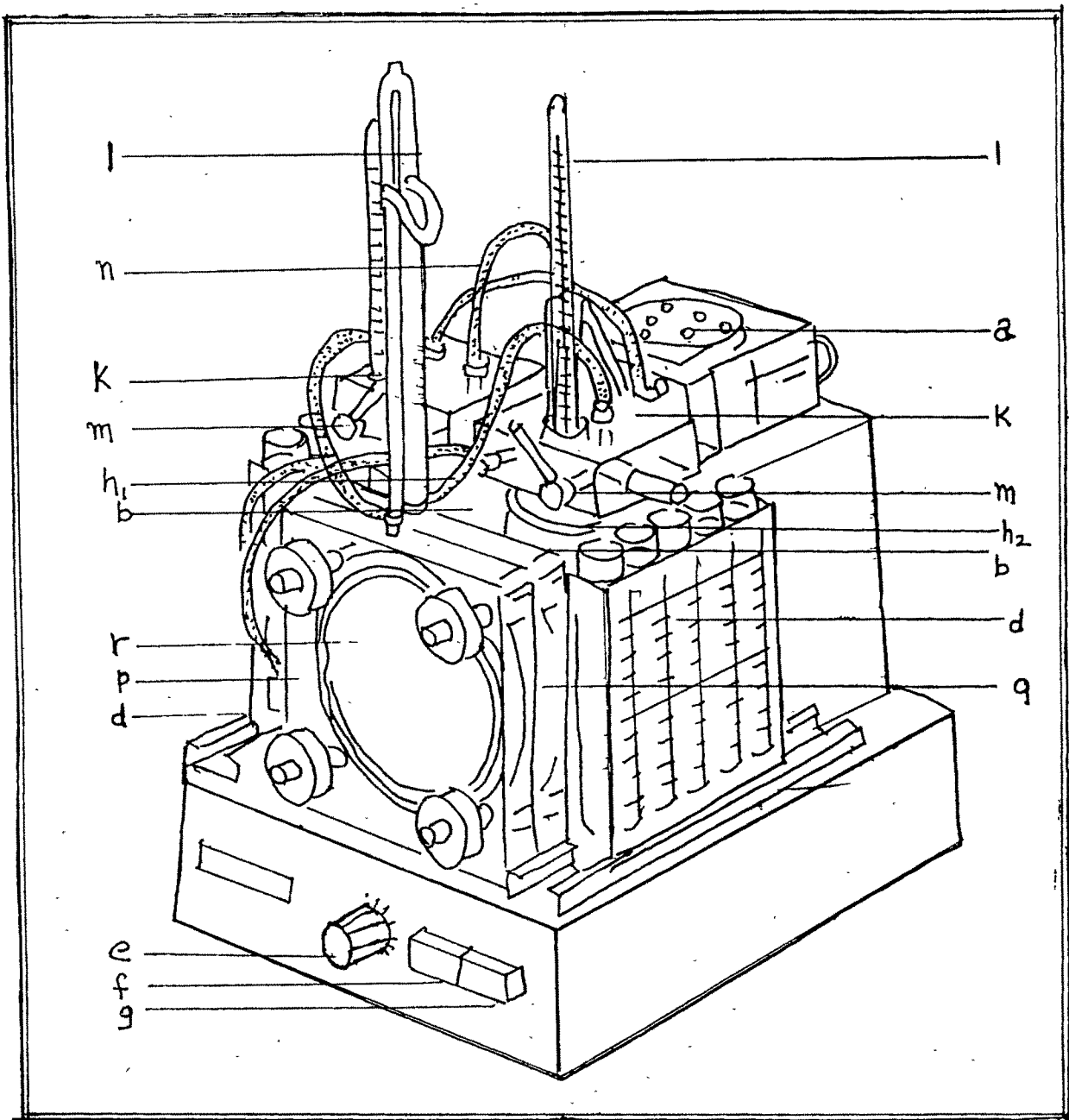
Left Hand Push Button (f) for stirrers motor & pump

Right Hand Push Button (g) for heating and pumping direction of pump

The Containers h_1 and h_2 for the aqueous phases 1 and 2.

Magnetic Stirrer

Fig. 2



Absorption Simulator

Distribution Cap (K)
Thermometer (l)
Taps (m) - for sampling
Tube Connections (n)

The Diffusion Chamber :

Front Plate (p)

Back Plate (q)

Lipid Barrier (r)

Effective area = 40 cm^2

| A | B |
|---------------------------------------|--|
| Phase I | Phase II |
| Lipid Barrier | Lipid Barrier |
| 100 ml of artificial gastric juice | 100 ml of artificial plasma with dissolved substance |

The Sartorius Absorption Simulator allows research to be carried out on the diffusion of organic substances, under conditions approaching those in the gastro intestinal tract. The most important feature of the unit is the lipid barrier whose permeability to passively transported drug is similar to that of the gastric walls.

The absorption simulator therefore enables the absorption from the

gastro intestinal tract to be simulated - an essential process for the effectiveness of orally given drugs.

Scheme - B

| | Phase I Artificial Gastric Juice | Phase II Artificial Plasma |
|---|-------------------------------------|-------------------------------|
| pH | 1.1 | 7.5 |
| Solution | 110 | 750 |
| In HCl (g) | 94.0 | |
| In NaCl (g) | 0.35 | |
| In Glycine (g) | 0.50 | |
| Na ₂ HPO ₄ .2H ₂ O (g) | | 20.5 |
| KH ₂ PO ₄ (g) | | 2.8 |
| Distilled water to | 1000 ml | |

The Lipid Barrier :

Artificial gastric barrier M₁ [Cat.No. SM 15701](70).

The barriers can only be used once and should be prepared. Shortly before the start of the experiment using the components contained in the packages, by filling the pores of an inert frame (Sartorius membrane filter) with a liquid liquid phase. This lipid phase is a mixture of the following two components.

| | Components units by weight | | |
|--------------------------------|----------------------------|------|---------------------------|
| | N | Sl | Density g/cm ³ |
| Lipid Mixture for Barrier M | 4.20 | 0.10 | 0.83 |

Procedure :

A magnetic stirring bar is placed in each of the containers in the thermostated holders. 100 ml artificial gastric juice in which the substance is dissolved is placed in one container, 100 ml artificial plasma in the other. The distribution caps are put on the container and following connections are made with the tubings provided.

The right hand and left hand push buttons are pressed. The heating to $39^{\circ} \pm 1^{\circ}\text{C}$ can be followed on the thermometer.

The lipid barrier is now prepared as follows. Warm 4 to 5 g of the appropriate lipid mixture in a flat bottom glass dish and stir it to a homogeneous mixture. Weigh a membrane filter type RS and place it in the lipid mixture, Swirl gently until it has been wetted to complete transparency, and after allowing a short time for the excess to drop off, press it between two pieces of blotting paper using the roller. Reweigh the filter.

The barrier M1 should have a weight increase of 85 to 105%. This barrier is fitted into the apparatus. Use a glass manometer to measure the pressure difference.

The dosage form is introduced into the chamber containing artificial gastric juice after checking the tube connections, temperature and

pressure. The instrument is made to run with the peristaltic pump working.

Take at least three samples from each container at equal time intervals which must be at least 30 minutes. Samples can be taken by using the taps. Determine the concentration of the substance in the samples collected from the chamber container artificial plasma.

EXPERIMENTAL

Materials :

Sulphamethoxazole, Lactose, Corn Starch, Poly Vinyl Pyrrolidone, Sodium Carboxy Methyl Cellulose, Acacia, Magnesium Stearate of B.P. or S.M. grades were used.

Equipment :

Seives - Numbers 4, 12, 36.

Planetary Mixer - Erweka - GMBH. AR 466.

Type PRS 48813.

Granulator - Erweka. GMBH - Type G.S. 49255.

Sartorius dissolution and absorption.

Simulators GMBH SM 16751 and SM 16750.

Single Punch tablet Kilbern Type F.

I.R. Toshniwal Moisture balance.

U.S.P. disintegration apparatus.

Roche friabilator.

Magumps Hardness tester.

Beckman model Spectrophotometer.

U.S.P. dissolution apparatus.

Manufacture of Tablets :

Manufacture of tablets involves certain well defined steps. viz.

- (a) Pulverising and mixing
- (b) Granulation
- (c) Compression.

In pulverization the different ingredients should preferably be reduced to the same particle size since particles of different sizes will have a tendency to get layered during mixing. Mixing of powders is not difficult except that uniform mixing ought to be assured.

The granulation is done by the wet granulation techniques. In wet granulation the powder mixture is suitably moistured with a liquid binding mix, lumped and then passed through sieves. The granules thus produced are subjected to drying. The major handicaps of wet granulation method are exposure of ingredients to water and differences in granule characteristics from batch to batch due to differences in the qualities of ingredients.

Tablet Compression :

Whatever may be the sophistication of the tablet compression machines, basically compression is achieved by taking granules volumetrically

in a die and compressing them between a set of two punches. To make the process continuous the movements of punches are regulated to ensure die filling, tablet compression, and removal of compressed tablet from the die(60).

In actual experimentation the raw materials were used as received. The drug along with the additives were mixed in a planetary mixer for 10 minutes. The binder mix was gradually added till a dough was passed through sieve (No.4) to obtain large and crude granules. These granules were dried and passed through granulator fitted with sieve to obtain fine granule. The granules were mixed with starch (2%) and magnesium stearate (1%) as disintegrant and glidant respectively. Finally the granular mass was compressed into tablets by compression on a kilburn single punch Type F using a die size 7/16 inch. Batch size : 1000 tablets.

Properties of Granules :

(a) Moisture Content :

The loss on drying was studied on I.R. Toshniwal Moisture balance 5 gms of the sample is weighed into the pan and the pointer is allowed to be zero. The temperature is set to 60°C and kept steady for 10 minutes. Finally the reading corresponding to the pointer directly in percentage is recorded(59).

(b) Flow Properties :

The flow rate and angle of repose 'H' were determined by the fixed funnel method. Generally a weighed amount of the granulation is carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The time taken for the granules to pass through the funnel is recorded, thus $\tan Q = H/R$, where Q is the angle of repose is calculated (59).

(c) Percentage Fines :

A definite weight of the granular mass is taken and the fines are removed by shaking it in Sieve No.36. The contents remaining on the sieve is collected and weighed. The difference in the two weights gives the % fines(59).

(d) Bulk Density and Percent Compressibility :

The method consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of granulation is carefully added to the cylinder with the aid of the funnel. The initial volume is noted and the sample is then tapped until a constant volume is reached. From the initial

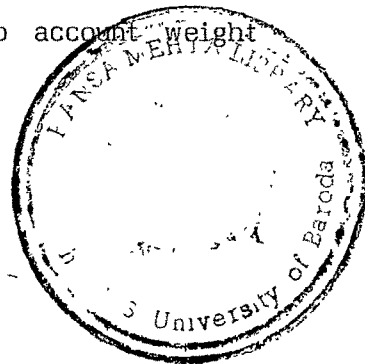
volume and final volume the bulk density and percent compressibility 'C' were calculated taking into account weight of the sample taken for for study(59).

$$\text{Bulk Density } P_b = \frac{M}{V_b}$$

Where M is the mass of the particles and V_b the total volume of the packing.

$$\text{Percent Compressibility } C = \frac{P_b - P_b}{P_b} \times 100 \quad \dots (x)$$

Where P_b = untapped bulk density.



Properties of Tablets :

(a) Weight Variation :

These studies were carried out as per U.S.P. XX N.F. X.V. 1980. Non uniformity in weights can lead to variation in dosaging. Weigh variation can be minimised only by making an effective reproducible granulation. The granulating agent play a significant role in this aspect. Generally 20 tablets are weighed collectively and individually. From the collective weight average weight per tablet is calculated. The weights of individual tablets are then compared with the average weight to ascertain whether the variations in weights are within permissible limits are not (22).

(b) Disintegration Time (D.T.) :

U.S.P. method was employed for the study of disintegration of sulphamethoxazole tablets.

Once the tablet is orally ingested, it should disintegrate within a specified amount of time, so that the active medicament undergoes dissolution and the drug is readily made available for absorption at the receptor sites. The tablet first breaks down to granule and then to primary drug particles. Tablet

disintegration is an important step in absorption process. A tablet that fails to disintegrate or disintegrates slowly may cause incomplete absorption or an undue delay in the onset of clinical response. Tablet binders ordinarily tend to retard dissolution because they delay disintegration and form a layer of viscous solution around the dissolving drug solid. Twenty national pharmacopieas describe tablet disintegration test's with 5' - 30' for reaching end point. The test for disintegration was carried out in U.S.P. disintegration apparatus. A definite volume of water was heated to 37°C. The tablets were placed inside the basket and the apparatus was in motion until all the tablets got completely disintegrated(22).

(c) Friability :

Friability generally refers to loss in weight of tablets in the containers due to removal of fine particles from their surfaces. Chipping and fragmentations can also be included in friability. Friability generally reflects poor cohesion of tablet ingredients. "Friabilators" consists of a circular plastic chamber, divided into 2-3 compartments. The chamber rotates at a speed of 25 r.p.m. and drops the tablets by a distance of 15 cms. A definite quantity of weighed tablets are placed in the Roche friabilator, which is then operated for 100 revolutions at 25 r.p.m. The tablets are then dusted and weighed. The difference in the two

weights represent friability. The weight loss should not be more than 1%(22).

(d) Hardness :

The hardness values of the tablets were determined using a Magumps Hardness tester. Ten independent measurements were averaged for each formulation(22).

(e) Drug Content Studies :

Weight variation and content uniformity go hand in hand. Accuracy of dosage form should be the prime check after a tablet manufacture. This was studied by assaying the tablets. The procedure adopted here is a general method normally adopted for all sulpha drugs, U.S.P. 1980 stated that Sulphamethoxazole on degradation gave sulphanilic acid and sulphanilamide. It also specified the limits for these related substances. Hence initially a thin layer chromatography was done, which excluded the possibility of any sulphanilic acid or sulphanilamide. It is therefore assured the sulpha drug estimate is pure sulphamothoxazole.

Estimation Procedure :

250 mg of sulphamethoxazole was weighed into a beaker. 50

ml of 0.1 N NaOH was added and shaken well. The sample was then transferred to a 250 ml volumetric flask and diluted with water up to the mark. 5 ml of this was further diluted to 200 ml with water. From this 2 ml was taken for colour development. To 2 ml of the sample solution was added 0.5 ml of 4 M HCl and 1 ml of 1% sodium nitrite. The mixture was allowed to stand for 2'. Then 1 ml of 0.5% W/V Ammonium Sulphamate was added and allowed to stand for 3'. Finally 1 ml of 0.1% solution of N(1 - naphthyl) ethylene diamine dihydrochloride was added and allowed to stand for 10'. Water was then added to make up the volume of 25 ml. A blank was also similarly prepared omitting the sample solution. The colour developed was measured at 538 nm against a reagent blank using Beckman Model Spectro Photometer(75).

$$\frac{CT}{CS} = \frac{AT}{AS} \quad \dots (xi)$$

CT = Concentration of test
 CS = Concentration of standard
 AT = Absorbance of test
 AS = Absorbance of standard

(f) Dissolution Rate :

Dissolution is one of the rate limiting step in the absorption.

process of a large number of poorly soluble drugs. Consequently dissolution rate studies can be useful in evaluating the prospective absorption rate and bio-availability of such drugs. Tablet binders ordinarily tend to retard dissolution because they delay disintegration and form a layer of viscous solution around the dissolving drug solid(65). Dissolution rate is inversely proportional to the granule size, if the granules are non disintegrating.

Dissolution rate studies were conducted according to U.S.P. XVIII.

Medium : Dilute hydrochloric acid (7 in 100) : 900 ml.

Appratus I 100 r.p.m.

Time : 20 minutes.

Procedure :

Determined the amount of sulphamethoxazole dissolved from U.V. absorbances at (265 nm - 1 cm cell) of filtered portions of the solution under test, suitably diluted with dissolution medium in comparison with standard solution having a known concentration of U.S.P. sulphamethoxazole in the same medium.

Each tablet is introduced into the basket of the U.S.P. dissolution apparatus and the apparatus is set in motion at the rate of 100 r.p.m. Exactly after 20 minutes, 10 ml of the sample solution is pipetted out from the glass vessel and filtered. From this 5 ml of the solution is withdrawn and diluted to 100 ml with water. The final solution is taken for absorbance study and the absorbances are read against a sample blank at 265 nm using a Beckman model Spectrophotometer(76).

A standard solution is also prepared containing 250 mg of pure sulphamethoxazole in 1000 ml of media.

Absorption Rate :

Absorption rate of the drug in vitro is carried out using Sartorius Absorption Simulator. Percentage of drug absorbed is calculated at the end of 2 hours. Simulated gastric and plasma fluids are taken for the study. A lipid barrier of 40 cm^2 is chosen for the site of absorption.

Bioavailability(71)(72) :

Dissolution and Absorption Studies using Sartorius dissolution and absorption simulators.

Dissolution Studies :

- (a) pH value in the stomach (1.0 - 1.5) pH 1.3 solution was taken for study.
- (b) Liquid volume in the stomach. Residual gastric juice volume is 40 - 50 ml. Maximum : 100 ml of the medium was taken for study.
- (c) Time of stay in stomach : 30 minutes.
 T_r = time interval = 5 minutes.
 V_d = 2.5 ml = volume with drawn each time.
- (d) Filter paper used. Whatman I.

Absorption Studies :

The absorption studies of sulphamethoxazole tablets was carried out in vitro using sartorius absorption simulator(70).

The apparatus was filled with 100 ml of simulated gastric fluid pH (1.1) and simulated plasma fluid (pH 7.5) in the respective chambers. The lipid barrier area chosen for the experiment was 40 cm². The appropriate connections were made with the tubing and before the start of the experiment the temperature was adjusted to 37°C. One tablet of sulphamethoxazole was dropped into the gastric chamber. The pump was on to simulate the peristaltic movement. The tablet gradually disintegrated and diffused through the lipid barrier into the plasma fluid. The concentration of the drug present in the plasma fluid was analyzed at different time intervals of 30, 60, 90 and 120 minutes respectively.

RESULTS AND DISCUSSION

The properties of the granules and tablets are given in the Tables 1 and 2, respectively. Granules prepared with PVP as binder showed excellent flow rate 3.3 gm/sec angle of repose $18^{\circ} 32'$, proportion of fines as low as 9.0% and this small quantum in no way can hinder flow. Percent compressibility is only 6.5% which indicates a good flow property. Starch can be attributed to be the second best choice as binder for granulation properties. However, starch paste is also acting as a good adhesive which has less retardant effect on disintegration time and dissolution in comparison to other adhesive materials(73)(74). Corn starch is best suited compared to naturally occurring starch in compressibility and flow characteristics.

The granules prepared using sodium carboxy methyl cellulose as the binding agent showed fines as high as 30%. The granules could not be compressed into acceptable tablets. There was a high degree of friability and quick break of tablets. Chipping and fragmentation can also be included. This reflects poor cohesion of tablet ingredients.

Granulation made from ethyl cellulose showed 26.0% of fines resulting in less effective granule formation. However, it was possible to obtain acceptable tablets but the granules required higher compressible loads to produce a cohesive compact. Sticking of the contents was observed and this may hinder uniform flow from the hopper to the feed system

TABLE - 1
STUDIES ON PROPERTIES OF GRANULES

| Batch | Moisture Content % | Flow rate gms/sec | Angle of repose ()° | % fines | Bulk density gms/ml | Compress- ibility % |
|--|--------------------------|-------------------------|----------------------------|------------|---------------------------|---------------------------|
| SS (Starch) | 0.2 | 5.0 | 26.23 | 17.0 | 0.55 | 9.95 |
| SP (PVP with water) | 0.2 | 3.3 | 18.82 | 9.0 | 0.58 | 6.51 |
| SC (Sodium Carboxy Methyl Cellulose) | 0.2 | 3.0 | 20.38 | 30.6 | 0.52 | 11.76 |
| SA (Acacia) | 0.2 | 5.0 | 23.08 | 21.0 | 0.60 | 10.87 |
| SE (Ethyl Cellulose) | 0.2 | 2.0 | 20.55 | 26.0 | 0.58 | 13.98 |

and uniform fill in the die cavity granulation with acacia although showing good granule properties produced harder granules when compared to other binders. The tablets disintegrated readily, but the hard dense granules dissolved less readily.

The dissolution and absorption rate studies has been given in Table-3. Comparative study showed that tablets made from starch as a binder had the best solubility and absorption characteristics in vitro. Weight variation was minimum (Table-2) which indicates an effective reproducible granulation. Average % deviation was 0.33%. Dissolution studies indicated that 73% of the drug dissolved within 20 minutes (Table-3). The inherent nature of starch which serves both as binder and a disintegrant should be responsible for good solubility characteristics. Tablets containing ethyl cellulose as the binding agent falls next in rank with respect to solubility characteristics. However, it proved less effective granules formation in the concentration chosen for study. Average % deviation of tablet weight was 2.66%. Dissolution studies indicated release of 62% of the drug within 20 minutes.

Tablets made from PVP although occupies the first place with respect to granule properties comes next only to ethyl cellulose and starch, with respect to solubility characteristics. Since PVP batch of granules are hard, secondary disintegration was delayed.

Tablets made from acacia as the binding agent showed a poor

TABLE - 2

STUDIES ON THE PROPERTIES OF TABLETS

| Batch | D.T.(a) min. | Gauge m.m. | Friabi- lity % | Average Weight mg | % Average | Hardness kg. | Content % |
|--|-----------------|---------------|----------------------|-------------------------|--------------|-----------------|--------------|
| SS (Starch) | 2 | 17.5 | 1.00 | 507.0 | 0.33 | 4.5 | 101.83 |
| SP (PVP with water) | 6 | 16.5 | 0.25 | 511.0 | 0.19 | 8.0 | 101.71 |
| SC (b) (Sodium Carboxy Methyl Cellulose) | - | - | - | - | - | - | - |
| SA (Acacia) | 2 | 17.0 | 0.50 | 500.5 | 1.91 | 5.0 | 102.32 |
| SE (Ethyl Cellulose) | 2 | 17.5 | 2.50 | 518.5 | 2.66 | 4.5 | 102.26 |

(a) Disintegration time.

(b) Tablet could not be compressed in well defined form.

TABLE - 3

STUDIES ON DISSOLUTION AND ABSORPTION RATE

| Batch | Dissolution Rate at 20' (%) | Absorption Rate at 2 hours (%) 40 cm ² area |
|--|--------------------------------|--|
| SS (Starch) | 72.87 | 7.10 |
| SP (PVP with water) | 61.96 | 5.54 |
| SC (Sodium Carboxy Methyl Cellulose) | - | - |
| SA (Acacia) | 50.42 | 4.14 |
| SE (Ethyl Cellulose) | 61.04 | 6.01 |

dissolution profile studies have indicated that hardening is observed with tablets made from acacia on ageing. Dissolution studies indicated 50% of the drug release within 20 minutes.

Interest in the bio-availability of active ingredients in oral drug products has grown rapidly in recent years. The attributes of a drug product that make possible full and consistent utilization of its active ingredient are dependent upon product formulation and an exercise of production control and in turn, such attributes determine what is now commonly termed bioavailability. Tablets are particularly significant because the rate of dissolution has been correlated closely with the bioavailability. The dissolution and absorption studies in vitro using sartorius dissolution and absorption simulators simulates the events taking place in the gastro intestinal tract with respect to peristaltic effect, pH, temperature are given in Tables 4 and 5 respectively. The dissolution rate constants have been also calculated. The first order kinetics for dissolution profile and simulated absorption in vitro has been shown in Figures 3 and 4 respectively.

$$\text{Concentration} = \log \frac{a}{a - a_t} \quad \dots (xii)$$

The constant K is calculated using the formula

$$K = \frac{2.303}{t} \times \log \frac{a}{a - a_t} \quad \dots (xiii)$$

TABLE - 4

DISSOLUTION PROFILE OF SULPHAMETHOXAZOLE TABLETS

| Batch | Concentration [$\log a / (a - x)$] Minutes | | | | | | |
|--|--|--------|--------|--------|--------|--------|-------|
| | 5 | 10 | 15 | 20 | 25 | 30 | K |
| SS (Starch) | 0.0822 | 0.2190 | 0.3853 | 0.5432 | 0.6791 | 0.8154 | 0.061 |
| SP (PVP with water) | 0.0336 | 0.1277 | 0.2604 | 0.4065 | 0.5200 | 0.5800 | 0.044 |
| SC (Sodium Carboxy Methyl Cellulose) | - | - | - | - | - | - | - |
| SA (Acacia) | 0.0391 | 0.0990 | 0.2190 | 0.2993 | 0.4242 | 0.4522 | 0.035 |
| SE (Ethyl Cellulose) | 0.0448 | 0.1300 | 0.2635 | 0.3979 | 0.5314 | 0.6430 | 0.045 |

K = Dissolution Rate Constant Mole/Min.

TABLE - 5

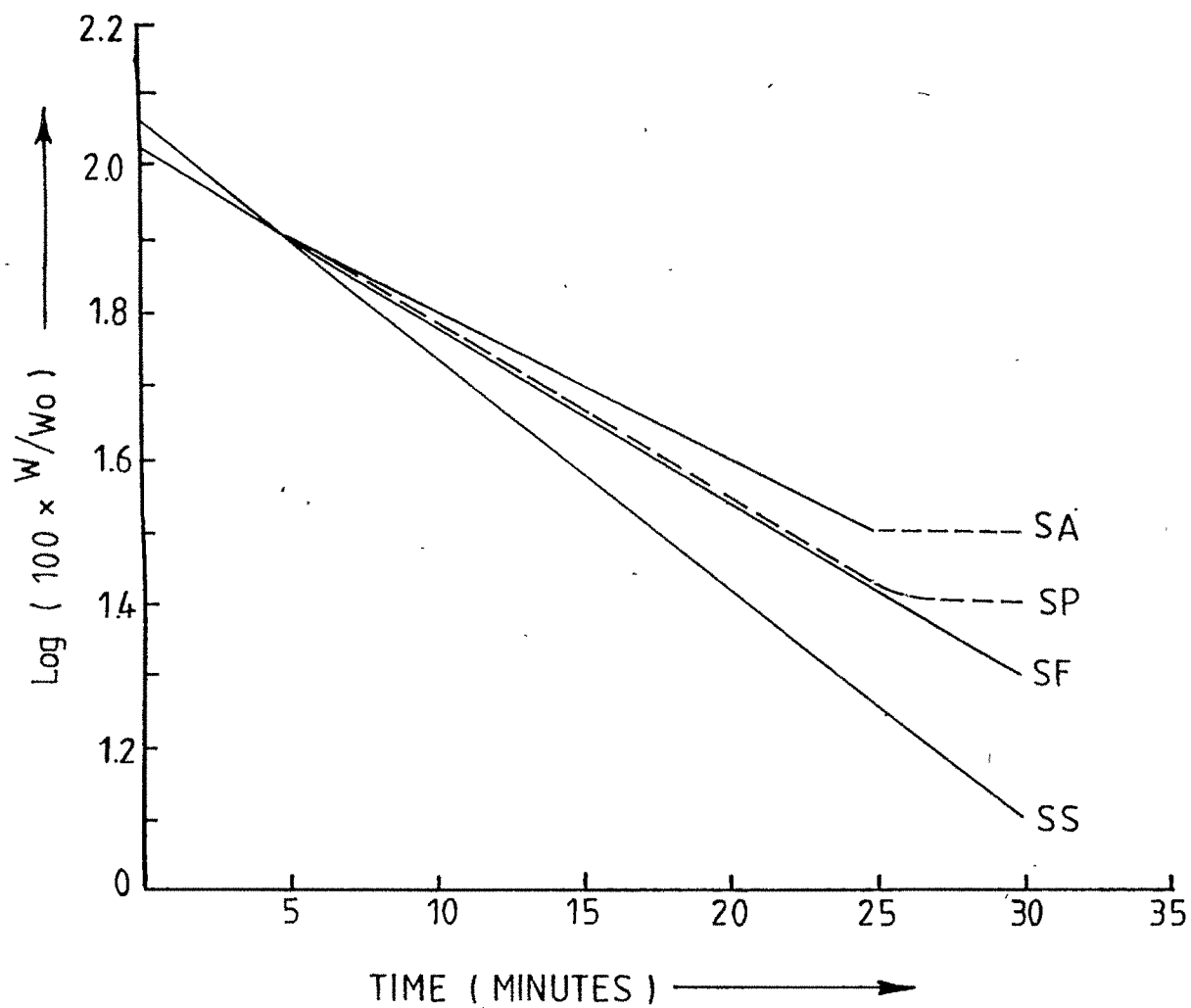
ABSORPTION STUDIES ON SULPHAMETHOXAZOLE TABLETS

| Batch | Concentration of [the drug in plasma/40 cm ² area (log a / (a - x))] | | | | |
|--|--|--------|--------|--------|--------|
| | Time Minutes | | | | |
| | 30 | 60 | 90 | 120 | K |
| SS (Starch) | 0.0064 | 0.0140 | 0.0240 | 0.0313 | 0.0005 |
| SP (PVP with water) | 0.0051 | 0.0112 | 0.0170 | 0.0242 | 0.0004 |
| SC (Sodium Carboxy Methyl Cellulose) | - | - | - | - | - |
| SA (Acacia) | 0.0033 | 0.0068 | 0.0147 | 0.0179 | 0.0003 |
| SE (Ethyl Cellulose) | 0.0060 | 0.0100 | 0.0190 | 0.0260 | 0.0004 |

K = Dissolution Rate Constant Mole/Min.

Fig. 3

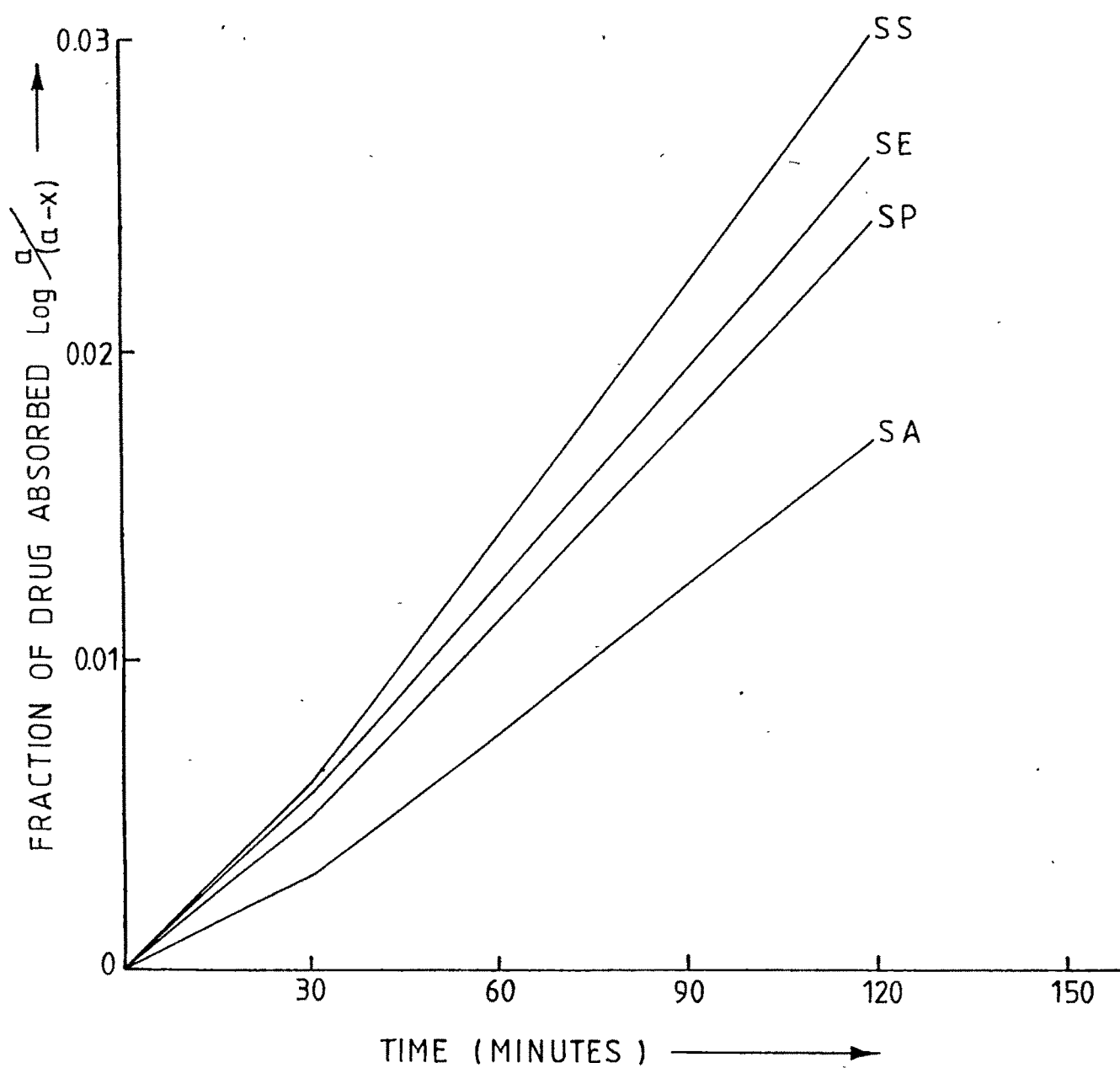
DISSOLUTION PROFILE OF SULPHAMETHOXAZOLE TABLETS



ACCORDING TO SIGMA — MINUS PLOTS

Fig. 4

ABSORPTION PROFILE OF SULPHAMETHOXAZOLE TABLETS



The dissolution profiles of the disintegrating tablets is typically a sigmoid curve. The corresponding rate of dissolution is initially zero, then increases until it reaches a maximum and reduces back to zero. SS tablets show the highest dissolution rate, profile compared to SE, SP and SA batch of tablets. During the period that the dissolution rate is increased surface area is generated by disintegration. After the peak, the disintegration process approaches the final stage and dissolution is the rate determinant for the decrease of surface area.

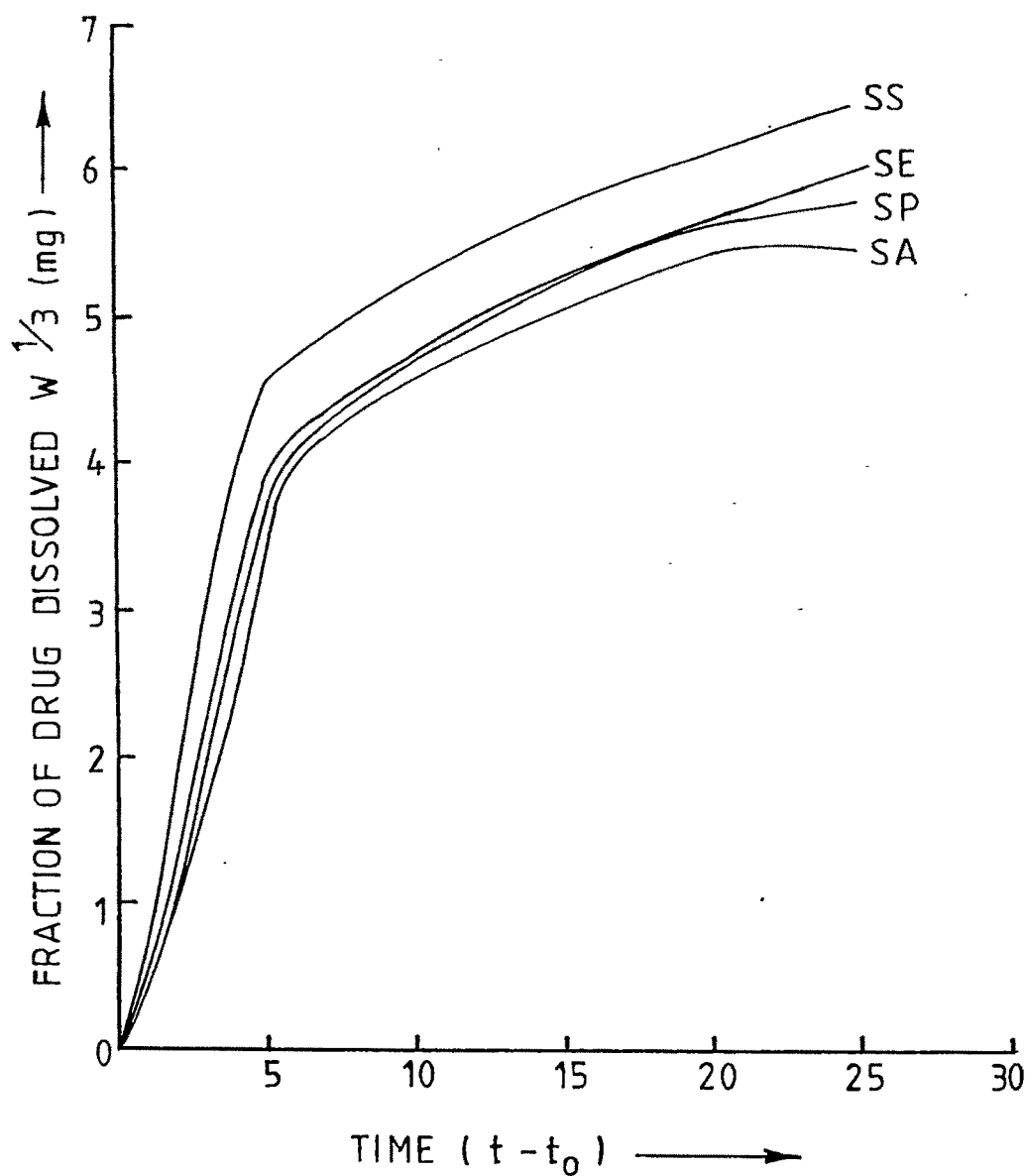
The data have been fitted to (a) Hixson - Crowell Cube Root Law and (b) Sigma Minus Plots (Figures 5 and 6) for tablet dissolution curves and provide parameters which facilitate the storage of data and comparison between various formulations. Figure 5 is according to Hixson - Crowell Cube Root Law with lag time.

Lag time is related to tablet disintegration time. Figure 5, represent a plot of $W^{1/3}$ (mg) versus time ($t - t_0$). SS shows the best dissolution profile. SE and SP follow almost the same dissolution rate. SA has the lowest dissolution profile compared to all the formulations.

Figure 6 shows the dissolution profile according to Sigma-Minus Plots. First order equations have been used to describe tablet dissolution under sink conditions.

Fig. 5

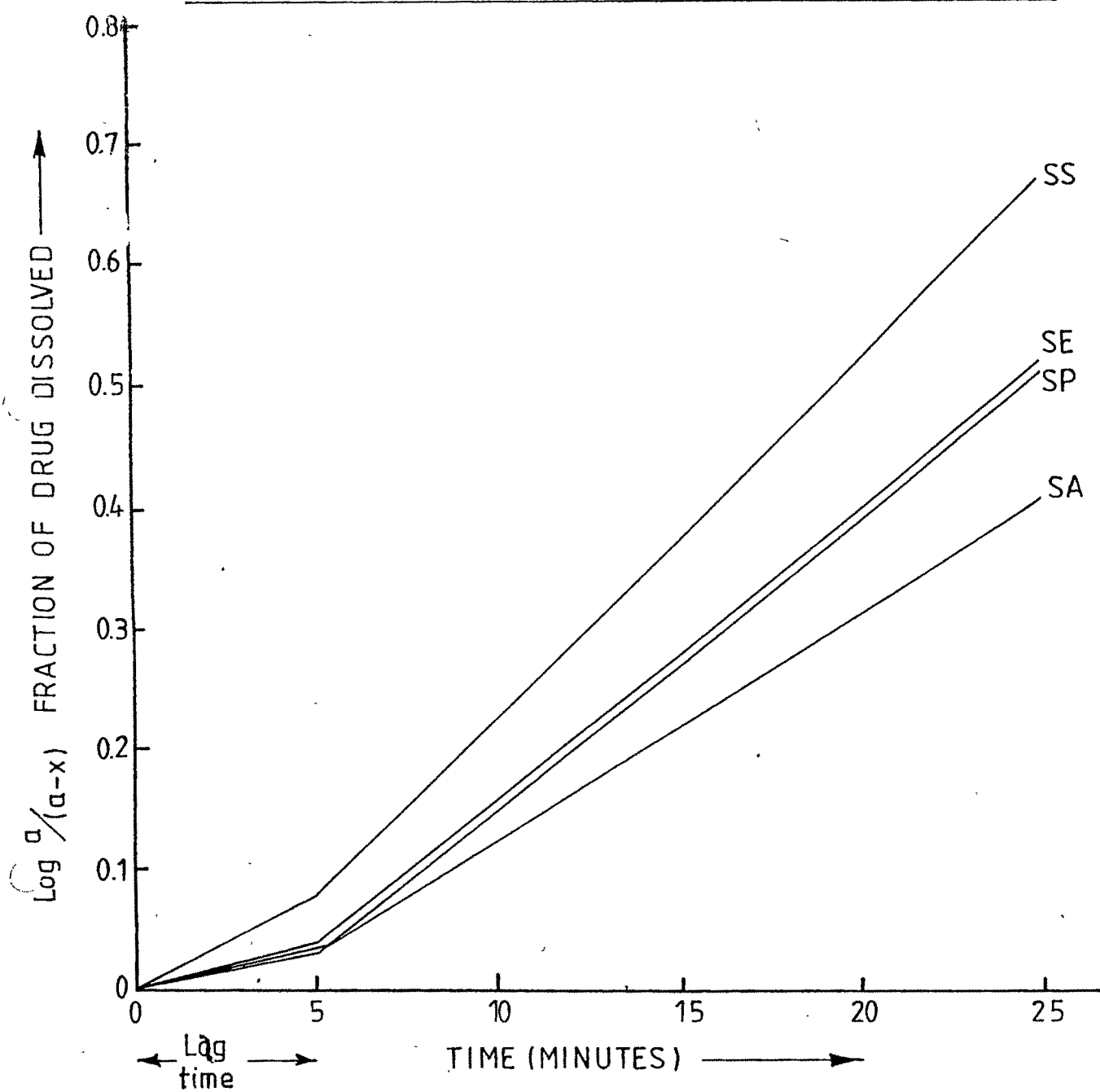
DISSOLUTION PROFILE OF SULPHAMETHOXAZOLE TABLETS



ACCORDING TO HIXSON CROWELL CUBE ROOT LAW
WITH \log TIME.

Fig. 6

DISSOLUTION PROFILE OF SULPHAMETHOXAZOLE TABLETS



ACCORDING TO — I ORDER KINETICS

Figure 4 shows a plot of $\log (100 \times W/W_0)$ i.e. log percent of drug undissolved versus time. Graph shows straight regression lines and the time t_1 at which the lines intersect was correlated to the tablet disintegration time. Amongst the four different formulations SS had the highest dissolution rate profile. SP and SE followed the same rate of dissolution and SA showed the least dissolution rate. Even when dissolution rate study was done at random Table 3 considering a time of 20 minutes SS showed a release rate of 72.87%, SP - 61.96%, SE - 61.04% and SA - 50.42%.

Thus all equation used for the study of dissolution profile followed the same pattern of release rate providing parameters which facilitate the storage of data and the comparison between various formulations. Frequently the data points are non-linear in the early time period but at later times, a straight line usually may be fitted to the data points.

The changes in the dissolution rate, at time it may be considered as due to an explosive increase in the surface area of the drug available for dissolution. In cases where the dissolution rate constant is less it could be explained as a rapid initial break up of tablets into fairly large fragments and a slow further break up into small fragments.

As granulation properties are more clearly defined and the exact

relationships of these properties to tablet quality features are established, optimization of the properties of tablets will become more realistic and feasible.