CHAPTER - THREE

EFFECT OF ADDITIVES ON SULPHAMETHOXAZOLE CAPSULES

CHAPTER - 3

EFFECT OF ADDITIVES ON SULPHAMETHOXAZOLE CAPSULES

RESUME

Formulations of Sulphamethoxazole Capsules are prepared and their physico chemical properties have been determined. Formulation of Sulphamethoxazole in combination with Corn starch and silicon dioxide have highest solubility and dissolution characteristics. However, formulation with silicon dioxide and dicalcium phosphate results a poor dissolution profile. Sulphamethoxazole capsules without additives showed higher weight variation and erroneous bioavailability pattern. Formulations incorporating silicondioxide as lubricant has a good flow property. Minimum weight variation was observed with dicalcium phosphate, magnesium stearate and aerosol O.T. A good dissolution and absorption characteristic is observed in formulation with dicalcium phosphate and magnesium stearate in the presence of sodium lauryl sulphate. Rank correlation with respect to bioavailability studies are as Batch V > Batch VIII > Batch I > Batch III.

INTRODUCTION

Capsules are solid dosage forms in whch a drug substance is enclosed in a water soluble shell or envelope(77). The shell is usually made of a suitable form of gelatin.

In addition to the advantages of elegance, ease of use and portability, capsules have become very popular dosage form because they provide a smooth, slippery, very easily swallowed, tasteless shell for drugs, particularly those having unpleasant taste or odour.

They are economically produced in large quantities, in a wide range of colours and generally provide ready availability of the contained drug, since minimal excipient and little pressure are required to compact the material.

Capsules are made principally of gelatin and may contain small amount of certified dye as an aid to identification, opaquing agents, plasticisers and antimicrobial preservatives(78). The hard gelatin capsule, also referred to as the dry filled capsule (DFC) consists of two sections, one slipping over the other, thus completely surrounding the drug formulation. These capsules are filled by introducing the powdered material into the longer end or body of the capsules and then slipping on the cap.

The difficulties encountered in formulation can be classified into two major types.

1. After the powder ingredients have been homogeneously blended by any suitable technique, the flow of the resultant mixture must be adequate to ensure delivery of sufficient powder to the capsules at the time of filling. Demixing must not occur during the powder handling in the filling equipment itself.

2. Physical incompatibilities between active ingredients, between diluents, or between active ingredient and/or diluents and capsule shell may create difficulties(79)(80).

The capsule seldom contains only the active ingredients, hence most of capsule formulations require the use of diluent material especially when the amount of drug to be placed in a single capsule is inadequate to fill the volume of capsule.

In the choice of suitable diluent certain considerations must be taken into account. The powder mixture must provide the type of flow characteristic required by the equipment. In all cases, the powder mixture must retain its homogenous compositions without demixing during the machine handling operations(22).

1. Particle sizes and powder densities of all ingredients should

be matched as closely as possible to assist in prevention of demixing.

2. Potential incompatabilities should be anticipated with each new mixture of materials. Reactions at elevated temperatures and humidities should be studied, not only for the effects on the contained powder mixture, but also on the gelatin capsules and in presence of packing materials(22).

Some of the materials that are useful as excipients in capsules are bentonite, calcium carbonate, lactose, mannitol, magnesium carbonate, magnesium oxide, silicagel, starch, talc and tapioca powder. Materials that may be considered for improvement of flow characteristics (glidants and/or lubricants) may include the following : glycol esters, silicons, silicone dioxide, metallic stearates, stearic acid and talc. Oils that may be considered for use in assisting the control of dusting, as well as in providing additional cohesiveness to a powder mix include any inert edible material(21).

Although small amounts of magnesium stearate are (less than 1%) used as lubricant in capsule to facilitate the flow of the drug fill into the encapsulating machinery, the water proofing characteristics of this insoluble material may pose an obstacle to the penetration of the solid dosage form by the G.I. fluid intended to dissolve it. This obstacle to water and fluid penetration can delay the dissolution of

the drug and its absorption. The practice of adding surfactants in capsule and tablet formulation to facilitate the wetting of the drug substances by the bathing G.I. fluids to enhance the dissolution is widely followed in Industry. For e.g. the dissolution of lithium carbonate is enhanced by addition of wetting agents(81). Even in instances in which Magnesium Stearate or some other water insoluble lubricant is not used in capsule formulation, when the gelating shell of a capsule dissolves liquid must displace the air that surrounds the dry powder within the capsule and penetrate the drug before the capsule fill can be dispersed and dissolved. Powders of poorly soluble drugs have a tendency to float on the surface of the fluid and agglomerate to further minimise air liquid contact and if wetting does not occur readily dissolution is delayed(82). Hence in these cases wetting agent is of great necessity. The weight of drug in capsules is governed by volume available for filling and bulk density of drug formulation, which for low weight variation the powder must flow in reproducible manner. The volume of the capsule body cannot be adjusted to accommodate a given weight of powder and therefore bulk density of the powder must be adjusted by the addition of an inhert diluent such as lactose. Care is taken in the selection of diluent as apart from its effect on powder flow properties, that high concentration of lactose (e.g. chloramphenicol capsules) may interfere with drug dissolution.

Rate of absorption of the drugs from hard gelatin capsules may be

highly dependent on formulation(83)(84). Efforts have been made to formulate sulphamethoxazole capsules using various combination of additives. The bioavailability studies on the sulphamethoxazole capsules from nine different combination have been carried, and amongst these the four different formulations have been selected for further study.

EXPERIMENTAL

Materials :

Sulphamethoxazole [British-Pharmacopiea (B.P.), Micro Crystalline Cellulose B.P., Silicondioxide, United States Pharmacopiea (U.S.P.), Dicalcium-phosphate (National Formulary (N.F.), Magnesium Stearate (U.S.P.), Corn Starch (U.S.P.), PEG-6000 (B.P.), PEG-4000 (B.P.), Sodium-lauryl Sulphate (B.P.), Aerosol (O.T.), Capsule O Size.

Equipment :

The following equipments were used :

Seive number 36, Planetory Mixer (Erweka - EMBH. AR 466), Type PRS - 8813). Capsule filling Unit (hand operated Erweka Model). U.S.P. dissolution apparatus, Sartorius dissolution and absorption simulators (GMBH SM 16751 and SM 16750).

Formulation :

Weighed quantities of the raw material was passed through 36 mesh seive in order to obtain a uniform fine powder. The different ingredients were blended together so as to obtain a uniform mix. Hard gelatin capsules of size 0 were chosen to encapsulate the drug formulation. Due to experimental limitations the filling operations were carried out manually with capsule filling equipments (non automatic). Basically it involves three steps.

1. Separattion of the cap from the body.
2. Filling the body half
3. Pressing operation to facilitate uniform and accurate dosaging
4. Rejoining the cap and body halves.

The empty capsules were placed into the two piece filling equipment. As the two piece unit is rotated, a vacuum is created on the underside. This vacuum seats the bodies into the lower half of the unit, while the caps are retained in the upper portion. The two pieces of the unit are separated and the cap containing portion is kept aside.

The powder mix is filled manually in to the body containing portion of the unit. The press plate which is an additional attachment contains an auger for the forced delivery of the powder. Once the fill is complete the two segments of the unit are rejoined. Pressure is applied

manually on the unit which forces capsules body into the cap. For ejection of the capsules the pressure is released, the closing plate restored to its original position and the capsules are expelled through the upper portion of the unit.

Finished capsules required some sort of dusting or polishing operation before the remaining operations of Inspection. This is because small amount of powder formulation adhering to the outside of the capsules may be bitter or unpalatable which must be removed in order to improve the appearance of the capsules and to preserve their quality of being tasteless on administration. Hence the capsules were subjected to cloth dusting.

Formulation of sulphamethoxazole capsules contained a batch size of 200 capsules. Capsule size was zero. The filling figure is 450 mg per capsule. The sulphamethoxazole content in each capsule is 250 mg.

Properties of the Capsules :

Weight Variation :

Weight of the content of an individual capsule is defined as the difference in weight of the intact dose unit and the empty shell. This is done by scooping out the drug content from the capsule after initial weighing and finally reweighing the empty capsule. Twenty intact capsules are weighed individually, maintaining the identity of each capsule, the drug content is removed and the empty capsules are reweighed. The differences in the weights give the content weight(76).

Disintegration [D.T.] :

Place one capsule in each of six tubes of the basket enclosed in the U.S.P. disintegration apparatus. Water contained in the bath is maintained at 37 ± 2°C. The capsules are observed for the time, it takes for complete disintegration. Disintegration is to be completed except for fragments of capsule shell.

Content Uniformity :

Contents of 20 capsules were emptied into a crucible and the average weight of each capsule in different batches was carefully transferred into 250 ml beaker. 50 ml of 0.1 N NaOH was added and stirred.

The resultant solution was filtered and the filtrate was taken for suitable dilutions. The final sample was treated with 0.5 ml of 4 M HCl, 1 ml of 0.1% sodium nitrite and the mixture was allowed to stand for 2 min. Then 1 ml of 0.5% W/V ammonium sulphamate was added, allowed to stand for 3 min, before the addition of 1 ml, 0.1% solution of N (1-napthyl) Ethylene diamine dihydrochloride. The mixture is allowed to stand for 10 min, for colour development before the final dilution. A blank is similarly prepared. The absorbance of standard and sample solutions are measured at 538 n.m against a reagent blank with the help of Bausch and Lomb Spectronic 20 Spectrophotometer(76).

Dissolution Rate studies in Vitro(52) :

Apparatus :

U.S.P. dissolution rate apparatus, R.P.M. 100 revolutions. Medium - Simulated gastric fluid without Enzymes, pH 1.3.

In Vivo bioavailability studies carried out in vitro, using Sartorius solubility and absorption simulators. Solubility and absorption characteristics of Sulphamethoxazole Capsules was carried out in vitro.

Dissolution Studies(69) :

(a) pH value in the stomach (1.0 - 1.5 pH); pH 1.3 solution was taken for the 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 min.

T_r = Time Interval = 5 min.

V_D = 2.5 ml (Volume withdrawn each time).

(d) Paper used - Whatman No. 1 filter paper.

Absorption Studies(70) :

In the sartorius absorption simulator phase-I contains 100 ml artificial gastric juice, pH (1.1). Phase-II contains 100 ml artificial plasma, pH (7.5). A lipid membrane simulates stomach wall barrier. Barrier area = 40 cm^2, T_r = 30 min.

RESULTS AND DISCUSSION

In the present study the ingredients used and batchwise formulation composition are given in Tables 6 and 7 respectively. The physico-chemical properties of the Sulphamethoxazole Capsules are given in Table 8. Although filling of capsules was not carried automatically, one could observe sticking qualities of the powder mix to the auger of the press plate in batches I and IV. Batch IV containing lactose and magnesium stearate showed a high degree of sticking. Sticking of the material was not observed in formulations containing silicon dioxide, which serves a better lubricant compared to magnesium stearate, PEG 6000 and PEG 4000. The flow of drug is further facilitated by the combination of diluents viz. micro crystalline cellulose, dicalcium phosphate, corn starch etc. Weight variation study revealed that batch IX have the highest weight percentage deviation. However, very wide variation in weight was not observed in the rest of the batches. Disintegration studies showed that plain sulphamethoxazole capsules without any additives take more time for complete disintegration because of poor wetting of the drug.

Rate of absorption of the drugs from hard gelatin capsules are highly dependent on formulation. Generally the factors which influence the drug dissolution and absorption are dependent on the selection of diluents and fillers, absorption or other interactions of drug and filler, crystal form and particle size and water proofing effect of

TABLE - 6

CAPSULE FORMULAE

Ingredient	Quantity used
Sulphamethoxazole	50.00 gms
Diluent	39.10 gms
Lubricant	0.90 gms
Surfactant	0.09 gms

TABLE - 7

FORMULATION COMPOSITION OF VARIOUS BATCHES

Formulation Composition	Batch								
	I	II	III	IV	V	VI	VII	VIII	IX
Sulphamethoxazole	x	x	x	x	x	x	x	x	x
Micro Crystalline Cellulose	-	x	-	-	-	-	-	-	-
Dicalcium Phosphate	-	-	x	-	-	x	x	x	x
Lactose	-	-	-	x	-	-	-	-	-
Corn Starch	-	-	-	-	x	-	-	-	-
Silicon Dioxide	-	x	x	-	x	-	-	-	-
Magnesium Stearate	-	-	-	x	-	-	-	x	x
PEG 6000	-	-	-	-	-	x	-	-	-
PEG 4000	-	-	-	-	-	-	x	-	-
Sodium Lauryl Sulphate	-	-	-	-	-	-	-	x	-
Aerosol O.T.	-	-	-	-	-	-	-	-	x

TABLE - 8

PHYSICO CHEMICAL PROPERTIES OF
SULPHAMETHOXAZOLE CAPSULES

Batch	Content Average Weight (mg)	Average % deviation	D.T.(')	Content Uniformity %
I	250.7	7.38	8	102.8
II	443.0	4.28	5	99.9
III	445.0	5.38	5	93.4
IV	448.0	6.17	5	97.8
V	453.0	3.15	4	100.0
VI	443.0	4.78	5	100.0
VII	446.0	10.61	5	102.2
VIII	428.0	4.09	5	93.0
IX	451.0	2.41	5	100.0

D.T. - Disintegeration time in min.

lubricants etc.

Dissolution rate studies carried out in Vitro with U.S.P. Dissolution Apparatus (Table 9, Fig.7) indicate that batch III have 50% release, batch I, IV have about 70% release, batch II, VI, VII, VIII and IX have 80% release and batch V have more than 90% release at the end of 20 min. From each of the above class a batch was chosen for the complete study of dissolution and absorption in Vitro using Sartorius solubility and absorption simulator.

The dissolution and absorption studies in vitro simulates the events taking place in the gastro intestinal tract, with respect to peristallitic effect, pH, temperature, are given in Table 10 and 11. The dissolution rate constants have also been calculated. The first order Kinetics for dissolution profile and simulated absorption in Vitro have been shown in Figures 8 and 9 respectively. The dissolution profiles of the capsules is typically a sigmoid curve. The corresponding rate of dissolution is initially zero, then increases until it reaches a maximum and reduced back to zero.

Batch V capsules shows the highest dissolution rate profile compared to capsules batches I, III and VIII. Capsule batch III show the least dissolution profile rate. These data have been fitted to (1) Hixson Crowell Cube Root Law(65) and (2) Sigma Minus Plots(66)(67) (Figures 10, 11) for capsule dissolution curves and provide parameters, which

TABLE - 9

DISSOLUTION RATE STUDIES IN VITRO

Batch	Dissolution Rate (%) at 20 minutes
I	77.9
II	83.3
III	50.0
IV	73.1
V	92.0
VI	85.1
VII	84.3
VIII	86.3
IX	81.8

Fig. 7

Dissolution Rate Of Sulphamethoxazole Capsules at 20 min.

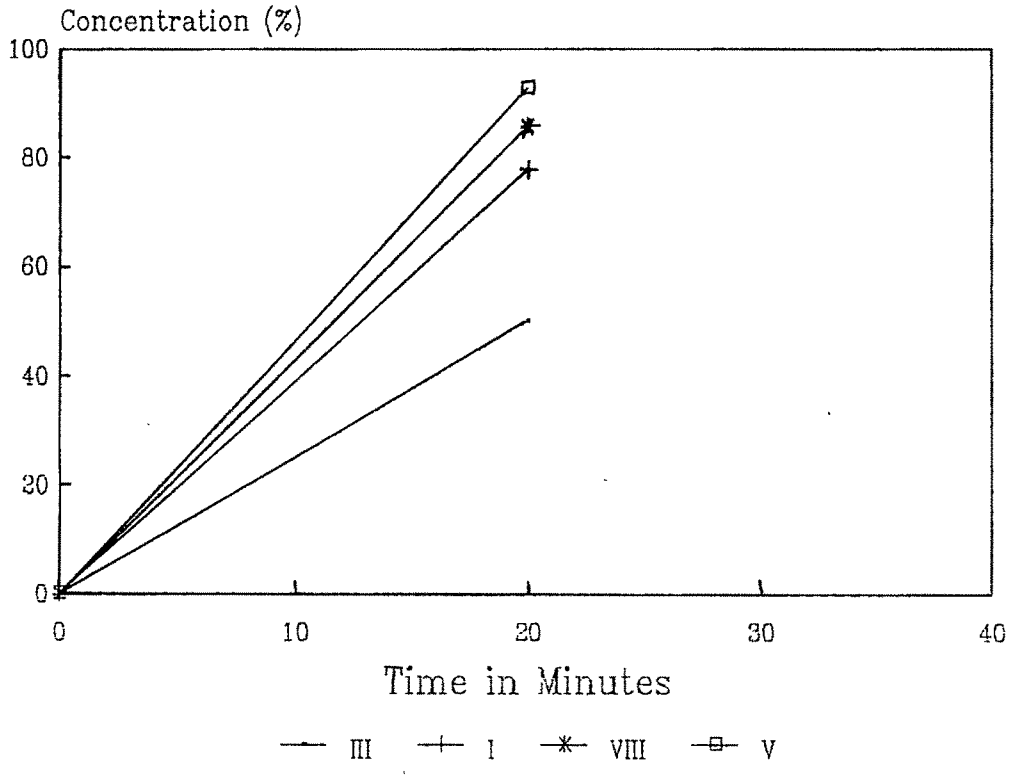


TABLE - 10

DISSOLUTION PROFILE OF SULPHAMETHOXAZOLE CAPSULES

Batch	Concentration = log a / (a - x)						
	Minutes						
	5	10	15	20	25	30	K
I	0.025	0.115	0.284	0.474	0.745	0.935	0.06
III	0.063	0.095	0.207	0.416	0.613	0.627	0.05
V	0.180	0.225	0.434	0.775	1.220	-	0.08
VIII	0.185	0.291	0.506	0.754	0.807	0.966	0.07

K = Dissolution Rate Constant Mole/Min

TABLE - 11

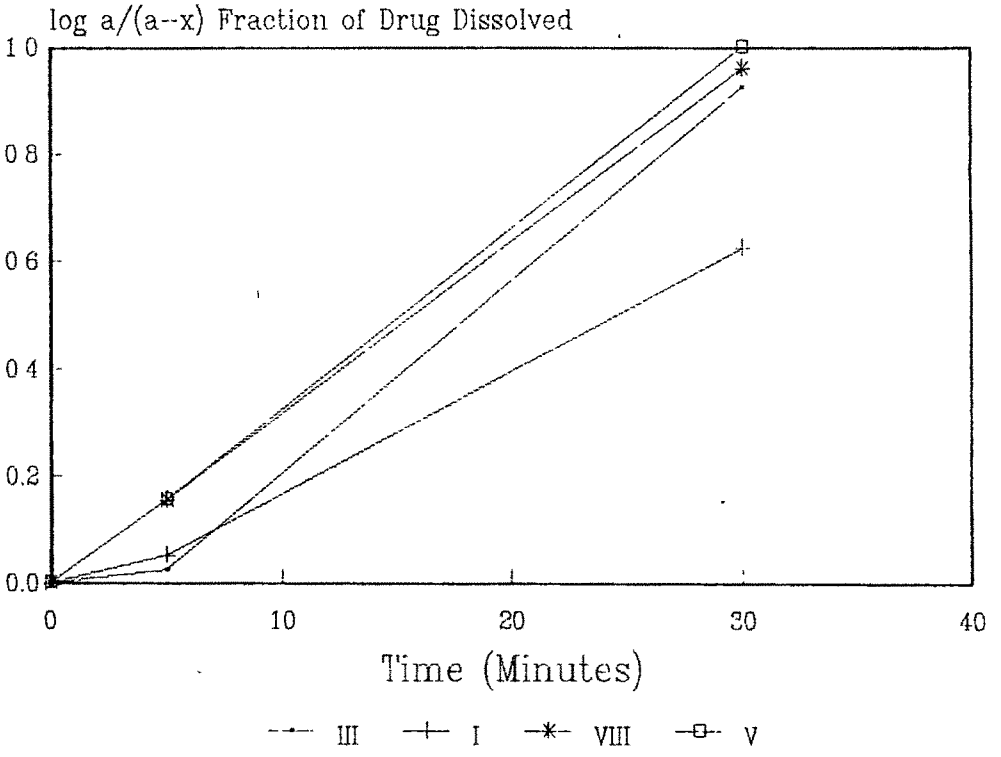
ABSORPTION STUDIES ON SULPHAMETHOXAZOLE CAPSULES

Batch	Concentration of drug in plasma/40 cm^2 area = log a / (a - x)				
	Time in minutes				
	30	60	90	120	K
I	0.0043	0.0128	0.0334	0.0569	0.0006
III	0.0043	0.0170	0.0334	0.0569	0.0006
V	0.0086	0.0212	0.0453	0.0755	0.0009
VIII	0.0086	0.0212	0.0414	0.0682	0.0009

K = Dissolution Rate Constant Mole/Min

Fig. 8

Dissolution Profile of Sulphamethoxazole Capsule



According to Ist order kinetics

Fig. 9

Absorption Profile of Sulphamethoxazole Capsules

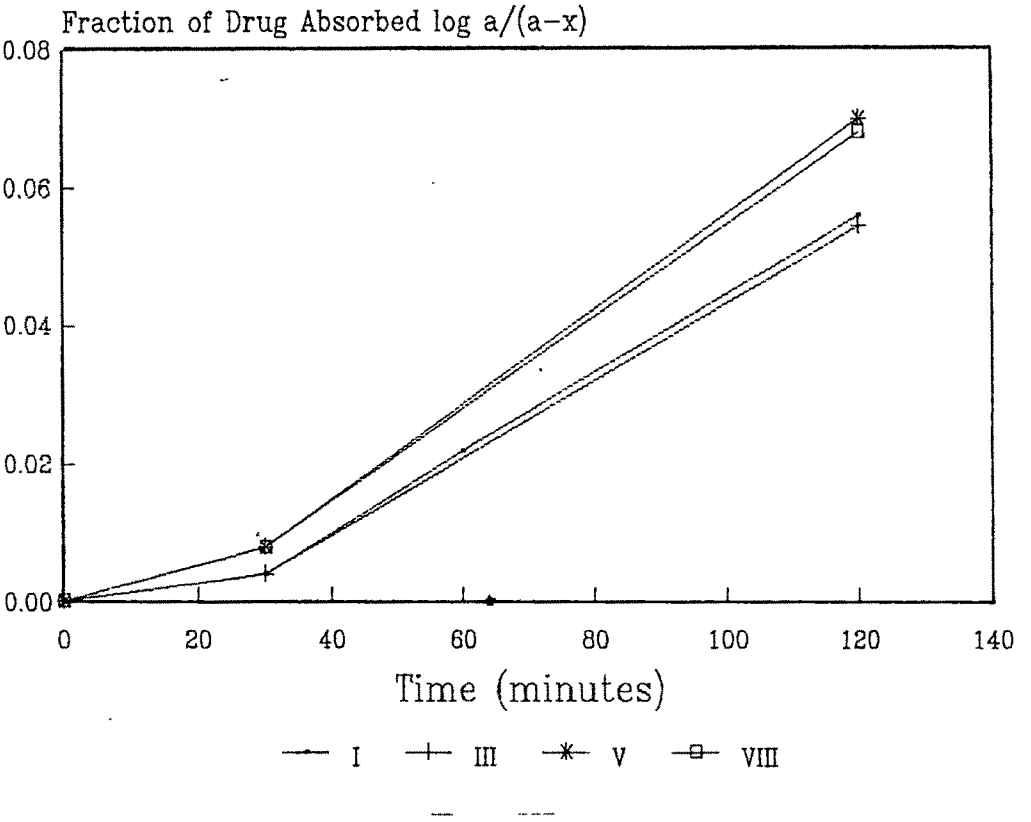
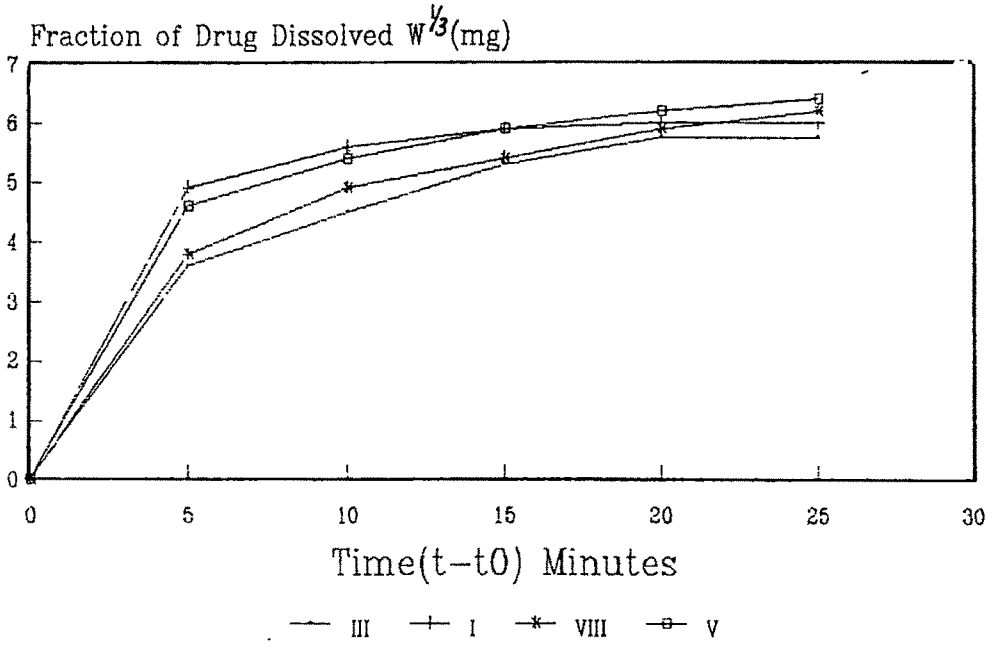


Fig. 10

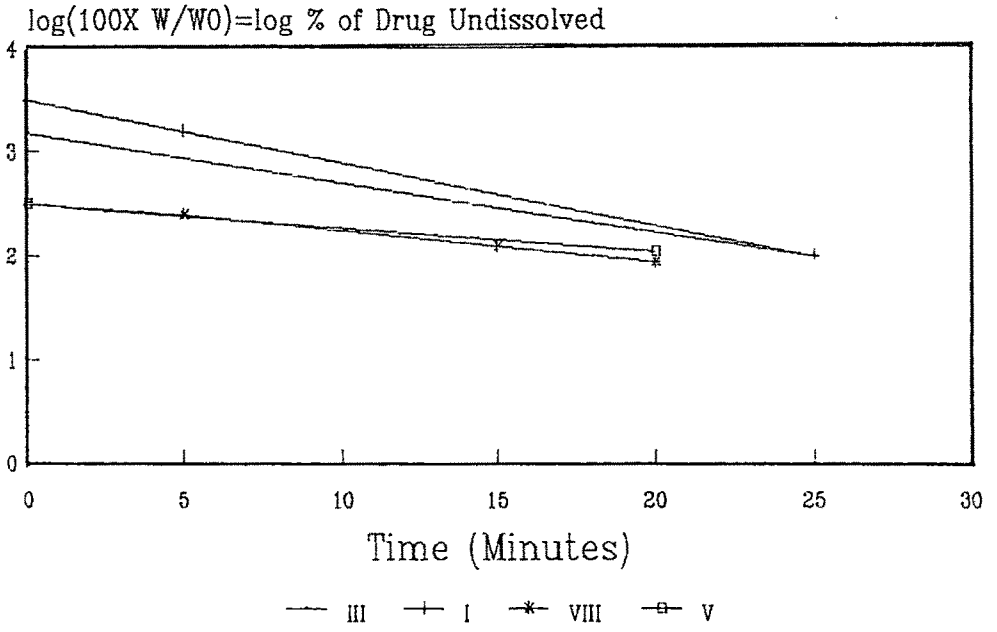
Dissolution Profile of Sulphamethoxazole Capsule



According to Hixson – Crowell cuberoot law with logtime

Fig. 11

Dissolution Profile of Sulphamethoxazole Capsule



According to Sigma minus plots

facilitates the storage of data and comparison between various formulations.

Figure 10 is according to Hixson Crowell Cube Root Law with lag time(65). Including a lag time the following two parameter equation results :

$$W_o^{1/3} - W^{1/3} = K (t - t_o) \quad \text{for} \quad t \geq t_o$$

$$W = W_o \quad \text{for} \quad t < t_o$$

Lag time is related to the capsule disintegration time. Fig.10 represent a plot of $W^{1/3}$ (mg) versus time ($t - t_o$) min. Batch V shows the best dissolution profile, batches V and VIII follow almost the same dissolution rate. Batch III has the lowest dissolution profile compared to all the formulations.

Figure 11 shows the dissolution profile according to Sigma - Minus Plots(7). First order equations have been used to describe capsule dissolution under sink conditions.

$$W = W_o e^{-Kt}$$

Figure 11 shows a plot of log [100 x W/W_o] i.e. log percentage of drug undissolved versus time, shows straight regression lines.

Thus all equations used for the study of dissolution profile followed the same pattern of release rate providing parameters which facilitite 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.