CHAPTER - FOUR

EFFECT OF ADDITIVES ON SULPHAMETHOXAZOLE SUSPENSIONS

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RESUME

Suspensions of Sulphamethoxazole are prepared with the various combinations of additives viz. vehicles, suspending agents, wetting agents, electrolytes and preservatives. Sedimentation studies indicated that formulation IV have a marked increase in the sedimentation volume, clear supernatant fluid with very good redispersability. It has a comparatively high viscosity at negligible shear, however have a poor dissolution profile. Suspension III show low sedimentation volume, severe caking and poor redispersability. Suspension showed Newtonian behaviour when subjected to shearing rate. Dissolution profile indicated slow release rate over a period of 30 min. Suspension II showed great degree of particle particle interaction, resulting in the formation of aggregates thereby leading to quick settling and increased sedimentation rate. Suspension I, II, showed 100% release of the drug within 15 min. Rank correlation in selection of a best combination of Sulphamethoxazole suspension is Suspension I > Suspension IV > Suspension II > Suspension III.

INRODUCTION

Suspensions constitute an important class of pharmaceutical preparation (85)(86). The investigation of their physical and chemical properties stands as a challenge to the Industrial Pharmacist and the research worker because many difficulties arise in the design and manufacture of pharmaceutical suspensios. Principle of sedimentation, electrokinetic phenomena, rheology and micromerities or small particle technology pertain to the preparation and physical stabilization of a suspension. Factors concerned with settling of particle in suspension are(87)(88).

Influence of gravity is constant and hardly can be altered. However the size of the particle can be reduced or increased the consistency or rheological properties of the suspending medium and thus the stability can be improved by reducing the rate of settling.

Caking cannot be eliminated by reducing particle size or by increasing the consistency of the suspension medium, indeed these measures frequently aggravate rather than prevent caking. When particles are held together strongly, they refer to these clusters as agglomerates or aggregates and it is the aggregation of particles into a solid mass at the bottom of the container that is known as caking. When particles are held together in a loose open structure in a suspension it is to disignate these clusters as floccules.

The system is said to be in a certain state of flocculation. The light fluffy flocs settle rapidly in a suspension to form a loosely arranged sediment with a large volume. Conversely the individual particles in a well dispersed or deflocculated suspension settle more slowly but after settling they have a tendency to form a difficult redispersible sediment or cake. Dispersing agents, which bring about the deflocculation of a suspension accordingly may increase the caking tendency of a dispersion, where as flocculating agents tend to prevent it(88).

Let now consider flocculation. One wonder how two particles could come together to form floccules in suspension if a large potential barrier exists between them. In the case of colloidal solution the flocculating agent is concentrated in the double layer and reduces the repulsion of the particles. The potential barrier is lowered and the particles come together in the primary potential well. In the case of coarse suspensions the energy barrier is too large to be surmounted during flocculation, however a secondary minimum exists at a distance of perhaps 1000 to 2000 A° separation(89). The particles can approach each other to this distance to yield a loosely arranged structure in suspension. Flocculated particles are weakly bonded, they settle rapidly in suspension but they are easily resuspended and do not produce a hard sediment or cake.

Although we can prepare a highly flocculated system, which do not

cake, the particles settle rapidly and leave a supernatant layer even when excess of flocculating agent is added. This is considered undesirable in marketed products. Consequently a suspending agent such as carboxy methyl cellulose, tragacant etc. is added to produce a final product with a more uniform appearance. Slowly developing changes in particle size distribution and crystal system can occur and can be discorned many time, before gross changes in viscosity become evident. Larger particles extend slower dissolving action than smaller particles.

Suspension additives include several variables like nature of the vehicle, electrolyte type, concentration of surfactant preservatives, colour, suspending agent etc(90). They may materially effect the characteristics of the suspension systems. Their effect on the physico chemical properties of sulphamethoxazole suspensions have been studied here. It was shown that flocculated suspensions may be usefully applied to the formulation of pharmaceutically acceptable Suspension of the drug. The general physico-chemical principles applicable to caking and flocculation in pharmaceutical systems are reviewed and are related to practical formulation difficulties. The increasing use of suspensions is a form of pharmaceutical preparation has emphasized the need for further evaluation of the factors controlling the physical stability of these systems and their bioavailability in the human system.

EXPERIMENTAL

Materials :

Sulphamethoxazole [British Pharmacopiea (B.P.), Tween 20 (B.P.), Tween 40 (B.P.), Dioctyl Sodium Sulfosuccinate (B.P.), Sodium-Carboxy Methyl Cellulose (M.V.) (B.P.), Methyl Cellulose (1500) (B.P.), Propylene Glycol (B.P.), Sorbitol (B.P.), Glycerine (Indian Pharmacopiea I.P.), Sodium Chloride (United States Pharmacopiea U.S.P.), Magnesium Chloride (B.P.), Methyl Paraben (B.P.), Propyl Paraben (B.P.), Sodium Saccharin (I.P.), Tartrazine (F.D.C. Yellow No.5), Citric Acid (I.P.).

Equipment :

Laboratory stirrer type L56-19, R.P.M. 4000, systronics pH meter. Brook Field Viscometer Model L.V. - 230 V. Sartorius Solubility Simulator. Hitachi Perkin Elmer 139 (UV-VIS) Spectrophotometer, Carl. zeiss Jena, Photomicrographic camera were used.

Formulation :

Different formulations of sulphamethoxazole suspensions were prepared using different vehicle, suspending agents, wetting agents, electrolyte combinations, preservatives, colours and flavours. Keeping in view compatability, suspension with the largest sedimentation volume, uniformity and general acceptance. Four best combinations of vehicles, suspending agent, wetting agent, electrolyte, preservative colour and flavours was selected, suitable for sulphamethoxazole suspension.

Vehicles - glycerine, Sorbitol, Propylene glycal water.

Suspending Agent :

Sodium carboxy methyl cellulose, Methyl cellulose, Hydroxy Propyl ethyl cellulose, poly vinyl pyrrolidone (PVP).

Wetting Agents :

Tween 20, Tween 40, Dioctyl sodium sulfo succinate.

Electrolytes - Aluminium chloride, Magnesium chloride sodium chloride.

Preservatives - Methyl Paraben, Propyl Paraben Sodium Benzoate.

Preparation of Suspensions :

The suspensions 250 mg/5 ml was prepared with the formulae given in Table 12. The various sulphamethoxazole formulation for the present studies are listed in Table 13.

Dispersion Technique :

Dispersion of the sulpha drug is carried out in the small quantities of vehicle, after adding the wetting and flocculating agents, followed by the addition of other ingredients according to the formula and made upto the volume. The pH of the final suspension is adjusted to 5.5 with citric acid 10% (W/v)(22).

Properties of Suspensions :

Sedimentation Studies :

Sedimentation volume of suspension were determined by placing 100 ml of the suspension in a measuring cylinder at room temperature. It was left undisturbed and observations were made every 24 hours over a period of 7 days; and finally after six months(91-93).

This offered a practical approach to the determination of the physical stability, if the system remained undisturbed.

TABLE - 12

SUSPENSION FORMULAE 250 mg/5 ml

Ingredient	Quantity used
Sulphamethoxazole	5.09 %
Wetting Agent	0.20 %
Electrolyte	0.10 %
Vehicle	20.0 %
Suspending Agent	1.00 %
Preservatives	0.20 %
Flavour	0.30 %
Colour	0.01 %

TABLE - 13

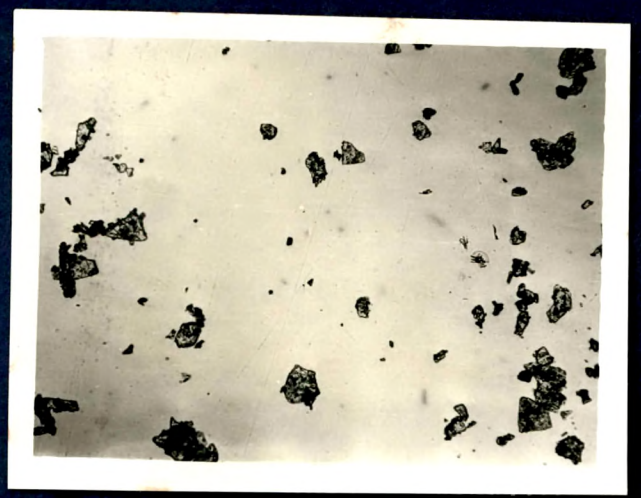
DIFFERENT SULPHAMETHOXAZOLE FORMULATIONS

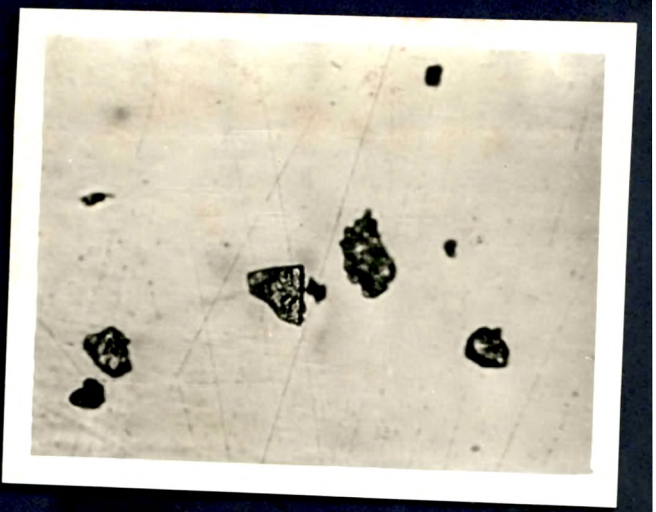
Contents	Batch			
	I	II	III	IV
Sulphamethoxazole	x	x	x	x
Tween 20	x	-	x	-
Tween 40	-	x	-	-
Dioctyl Sulpho Succinate	-	-	-	x
Sodium Chloride	x	-	x	-
Magnesium Chloride	-	x	-	x
Propylene Glycol	x	-	-	-
Sorbitol	-	x	-	-
Water	-	-	x	-
Glycerine	-	-	-	x
Sodium C.M.C.	x	x	-	x
Methyl Cellulose	-	-	x	-
Methyl and Propyl Paraben	x	x	x	x
Sodium Sacharrin	x	x	x	x
Tartrazine	x	x	x	x
Distilled Water Q.S.	x	x	x	x

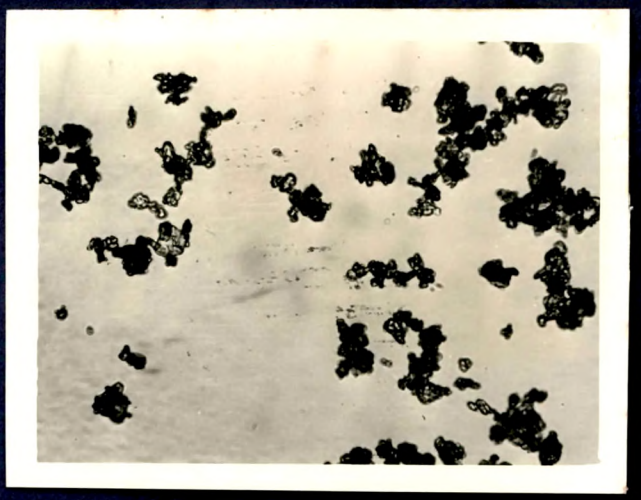
Photomicrographic Studies :

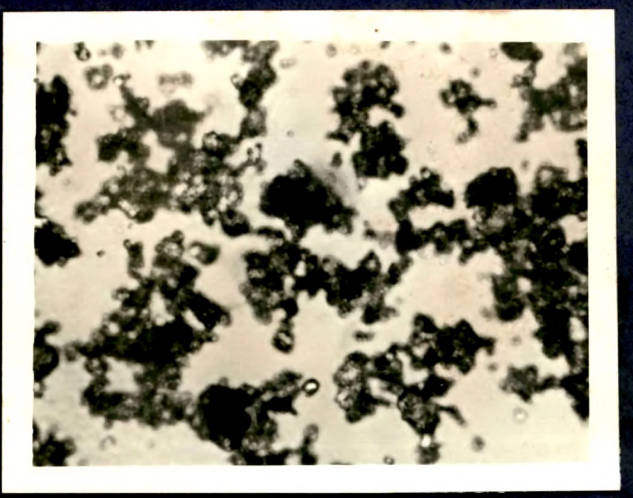
Slowly developing changes in particle size distributions, crystal habit or crystal system will shine forth as red lights and can be discerned many times before gross changes in viscosity become evident(97). Larger particles extend slower dissolving action than smaller particles. Changes in crystal size and shape can take place either soon after the suspension is put together or slowly and unsuspectingly. This question of physical stability of the dispersed phase in suspension is an extremely important problem. Crystal changes in suspensions are due to polymorphic and solvation transformation. The different suspensions were photographed using a Carl. Zeiss Jena Photomicrographic Camera. The photomicrographs are given in Figures 14, 15, 16.

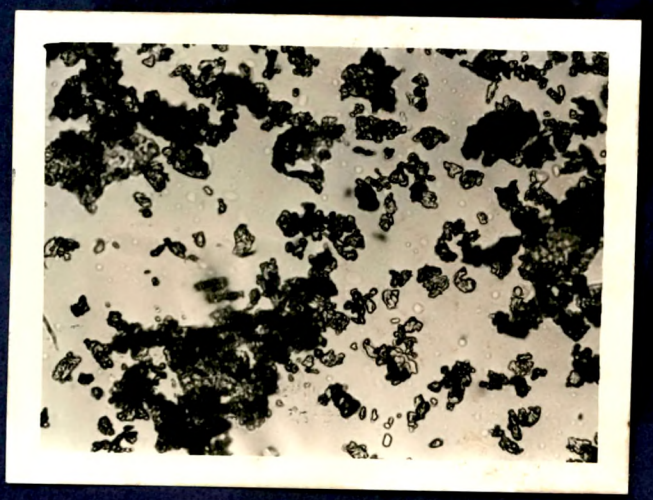
If on this picture is super imposed the element of crystal habit, a supplementary driving force which can be mighty important is brought into play. The habit taken by a crystal be it needles, plates, cubes, rods, prisms etc. is governed by factors which dictate the rate of growth of crystal. Also playing here (Sulphomethoxazole) are additives such as vehicles etc. Problems also arise where distinct new crystalline entities are formed in suspension during storage as a result of solvation and polymorphic transformation. Polymorphs of a drug differ in their solubilities characteristic is very important.

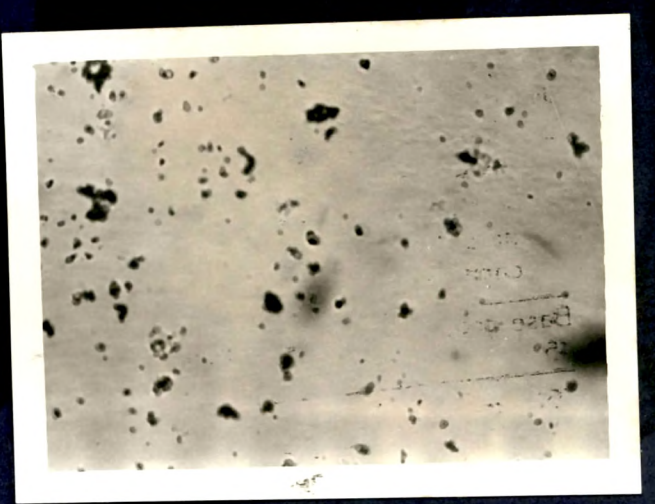


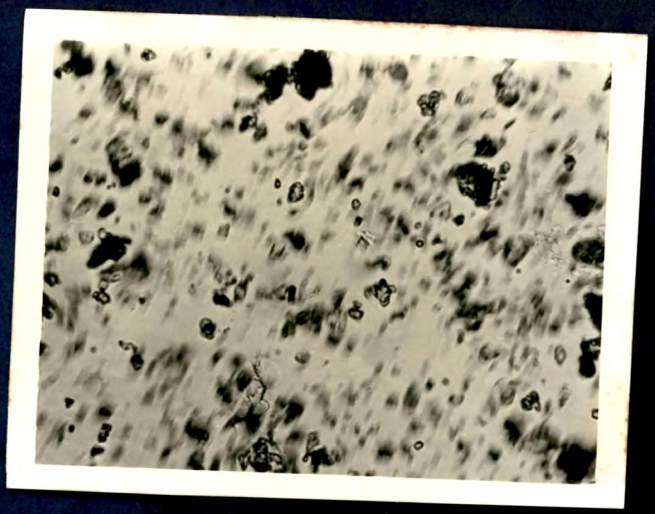


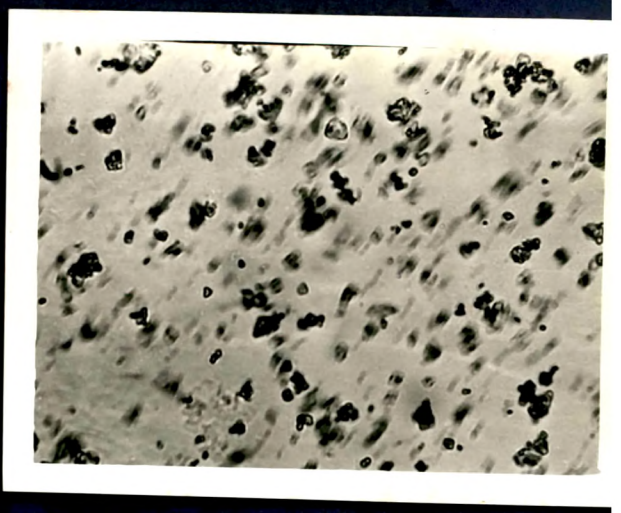


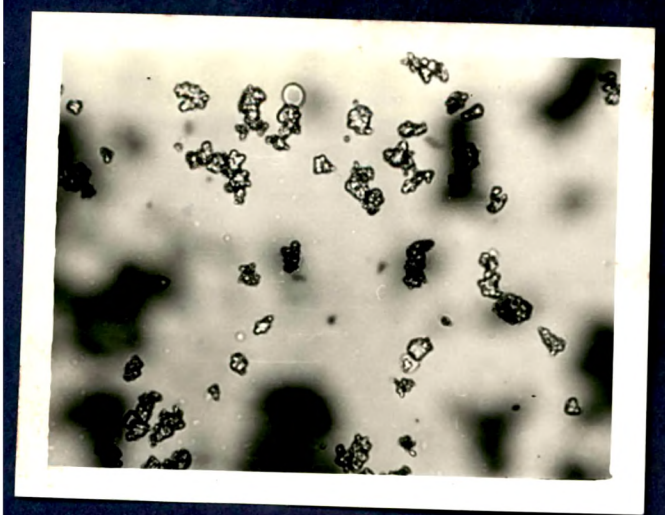


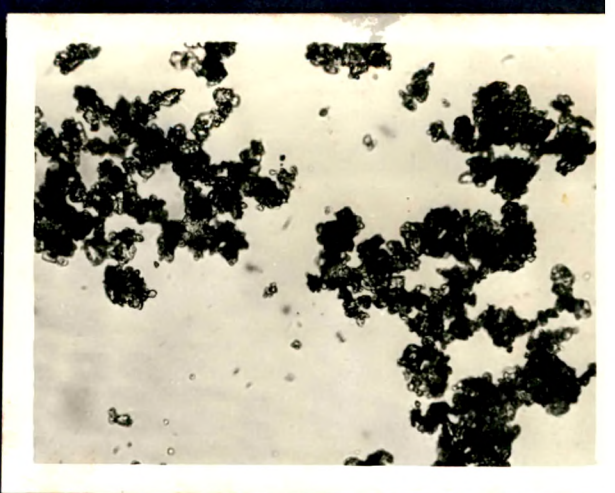












Dissolution Studies :

In Vivo bioavailability studies was carried out in Vitro, using Sartorius solubility and absorption simulators(69) solubility and absorption characteristics of Sulphamethoxazole Suspensions.

(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 = 3 min.

V_D = 2.5 ml = Volume withdrawn each time

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

Absorption Studies :

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 simulated stomach wall barrier. Barrier area = 40 cm^2, Tr = 30 min.(70).

Rheological Studies :

Viscosity of the suspension is measured at 30°C with the use of the Brookfield Viscometer [LVT] mounted on a helipath stand. The spindle is made to descend into the suspension to a predetermined depth and as it rotates with a particular r.p.m., the dial reading on the Viscometer is then, a measure of the resistance the spindle meets at particular level within the suspension(94-96).

RESULTS AND DISCUSSION

Different combinations of Vehicles, Suspending agents, Wetting agents, Electrolytes and Preservatives were studied in formulations maintaining the same concentration(98-100). The general physico-chemical principle applicable to caking and flocculation suspension characteristic was studied and finally four best formulations of Sulphamethoxazole Suspension were considered for the detailed study. Polyvinyl Pyrrolidone, hydroxy propyl ethyl cellulose in 1% concentration did not serve as good suspending agents compared to sodium carboxy methyl cellulose and methyl cellulose.

Incompatability with other additives was noticed in suspension containing aluminiumtrichloride as an electrolyte in 0.1% concentration. Interference with sodium benzoate was noticed in formulation containing Sorbitol but could not be observed in suspensions containing glycerine or propyleneglycol. $AlCl_3$ could not be incorporated due to its incompatability with tartrazine and Sodium Sacharin.

The results given in Tables 14, 15, 16 and Fig. 12 showed that Suspension IV has the highest sedimentation volume of 88 ml and 68 ml after 24 hours and seven days, respectively(101). The preparation was highly stable with clear supernatant. Redispersibility was very good, without any tendency for caking. Suspension I was also stable with slightly less sedimentation volume of 75 ml and 60 ml, respectively.

TABLE - 14

SEDIMENTATION STUDIES AFTER 24 HOURS

Formulation	Volume of Sediment (ML)	Nature of Supernatant	Redispersability
I	75	+	Good No. tendency of caking
II	60	++	Good
III	30	+++	Good
IV	88	+	Very good

+ = Clear

++ = Turbid

+++ = Very turbid

TABLE - 15

SEDIMENTATION STUDIES AFTER 1 WEEK

Formulation	Volume of Sediment (ML)	Nature of Supernatant	Redispersability
I	60	+	Easily dispersable
II	54	+	Easily dispersable
III	24	++	Dispersable
IV	68	+	Easily dispersable

+ = Clear

++ = Turbid

Fig. 12

SEDIMENTATION STUDIES OF SULPHAMETHOXAZOLE SUSPENSIONS

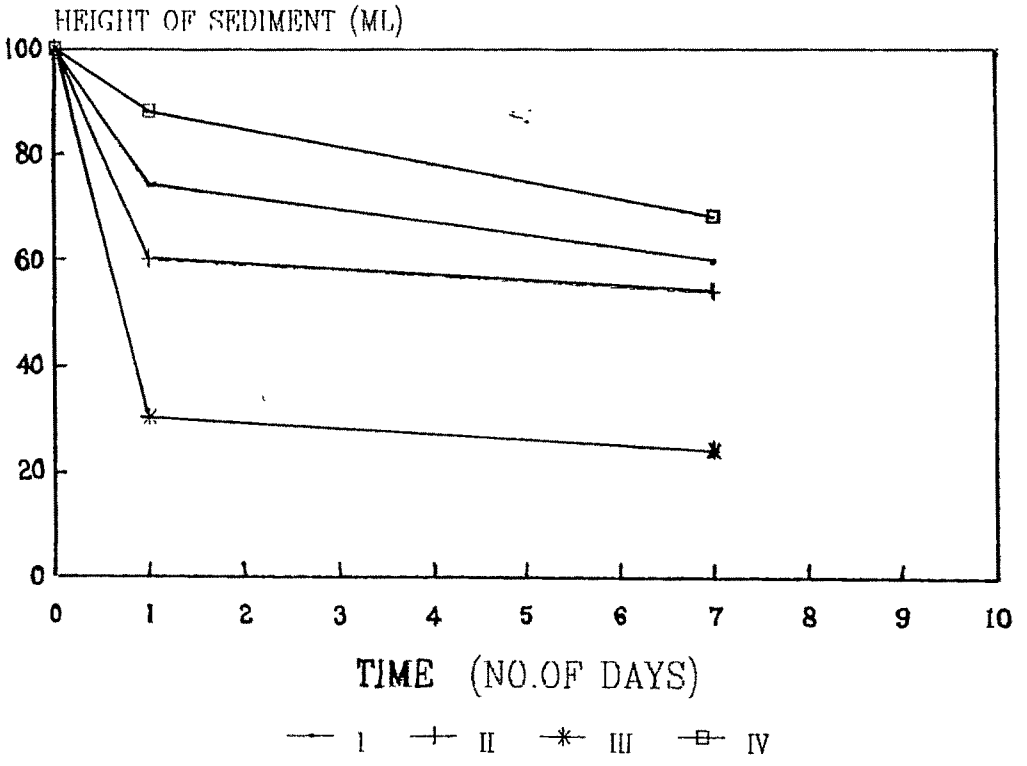


TABLE - 16

SUSPENSION STABILITY STUDIES AFTER 6 MONTHS AT R.T.

Formulation	Suspension Stability
I	No Caking, Very easily disperable
II	Dispersable. Little Caking is observed
III	Caking is observed. Dispersability is poor
IV	No Caking. Very easily dispersable

Supernatant was clear, good redisperability with no signs of caking at the end of six month. Suspension II showed 60% and 54% sedimentation volume. Supernatant was initially turbid yielding a not particularly elegant preparation. Suspensions were dispersable but little caking was observed. In Suspension II flocculent precipitates developed several days after a stock solution was made. This may be due to habit change or delayed incompatability(102), but more frequently are evidence of growth of Yeast, moulds or bacteria. Such growth may be due to indirectly to a chemical incompatability if the preservative system is inactivated by a chemical reaction. However, there was no loss of therapuetic activity.

Suspension III were termed poor suspensions since they indicated a very low sedimentation volume of 30 ml and 24 ml after 24 hours and 1 week respectively. Supernatant was highly turbid. Severe caking was observed with poor redispersability.

The rheological studies can also be used to determine the settling behaviour and the arrangement of vehicle and particle structural feature, for purpose of comparison(96,97). Helipath profile of sulphamethoxazole suspensions, Table 17, Fig. 13 showed that all the different formulations were Non newtonian in behaviour. Suspension IV had the highest viscosity of 500 c.p.s. and Suspension II 360 c.p.s. falling in moderate range. Suspension III with 43 c.p.s. indicated very low viscosities. The suspensions were tried out at

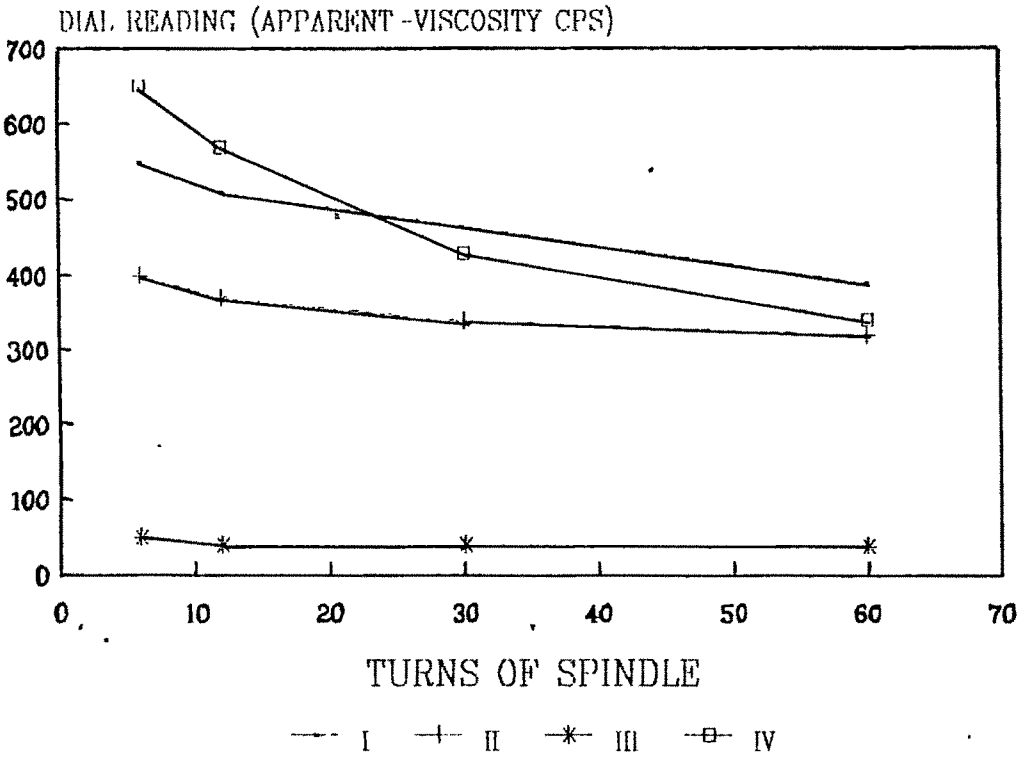
TABLE - 17

SUSPENSION VISCOSITY

Formulation	R.P.M.	Dial Reading	Apparent Viscosity	Average Viscosity
I	6	11.0	550.0	
	12	20.5	512.5	473.10
	30	44.5	440.0	
	60	78.0	390.0	
II	6	8.0	400.0	
	12	15.0	375.0	361.20
	30	35.0	350.0	
	60	64.0	320.0	
III	6	1.0	50.0	
	12	1.5	45.0	43.00
	30	4.5	40.0	
	60	8.0	37.5	
IV	6	13.0	650.0	
	12	23.0	575.0	501.25
	30	43.5	435.0	
	60	69.0	345.0	

Fig. 13

HELIPATH PROFILE OF SULPHAMETHOXAZOLE SUSPENSIONS



different R.P.M. of 6, 12, 30 and 60. It was found that the flocculation increased the viscosity of Sulphamethoxazole suspension. The settling rate of particles in each of the suspension showed a definite correlation between sedimentation volume and viscosity.

Dissolution rate is the primary step in studying the bio-availability of a particular dosage form(103). The dissolution profile shown in Fig. 17 and Table 18 indicates that 100% of the drug in Suspension I and II underwent dissolution within within 18 min. Suspension III took 27-30 min. for 100% drug release. Suspension IV required more than 30 min. for 100% release of the drug. The dissolution rate constant was 0.1 mole/min. in all the cases. Many factors seem to play a significant role in the dissolution pattern of Sulphamethoxazole suspensions. Viscosity in this case is not proportionately affecting the dissolution rate as seen from Suspension I which has 473 c.p.s. and Suspension III Having 43 c.p.s. It is very clear that formulation additives are playing a major role in the diffusion of the drug. In Suspension II although it is very thin suspension, the rate of release of the drug was impaired to a certain extent, may be because of methyl cellulose. The experimental condition maintained at 37°, simulating body temperature might have activated the cellulose to get, obstructing easy diffusion of drug. Comparatively poor dissolution rate in Suspension IV can be largely attributed to the role of additives.

TABLE - 18

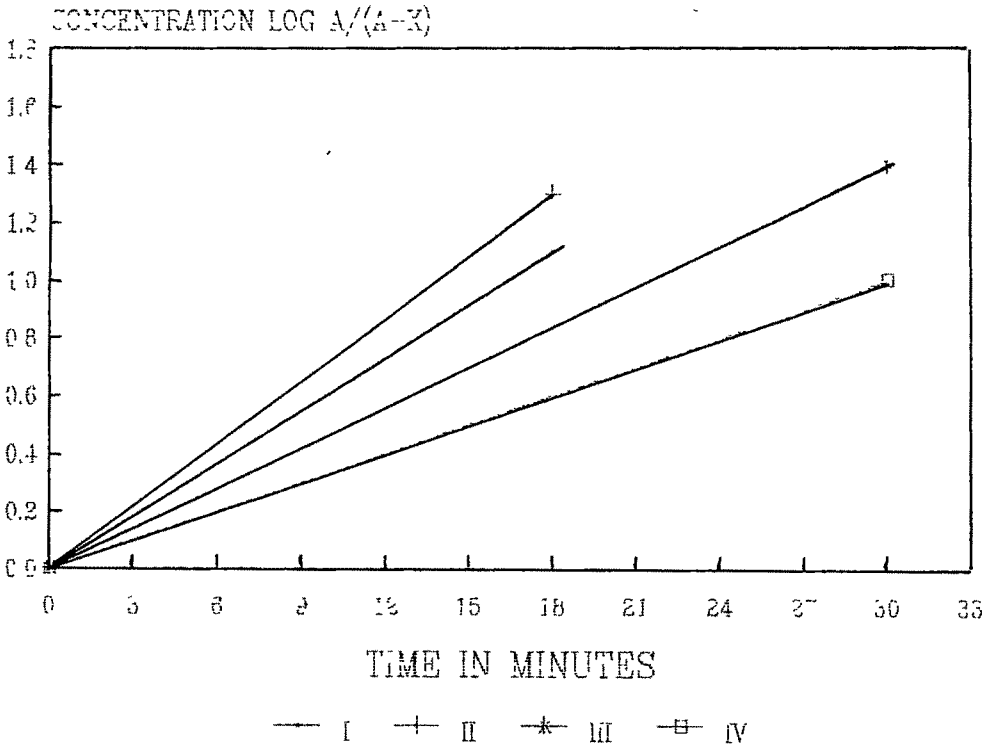
DISSOLUTION PROFILE OF SULPHAMETHOXAZOLE SUSPENSION

Batch	Concentration = log a / (a - x)										
	Minutes										
	3	6	9	12	15	18	21	24	27	30	K
I	0.276	0.469	0.595	0.784	0.915	1.124	1.146	1.146	1.301	1.492	0.14
II	0.325	0.504	0.564	0.826	0.883	1.360	1.660	1.740	-	-	0.17
III	0.192	0.441	0.582	0.636	0.698	0.771	0.870	0.983	1.050	1.410	0.11
IV	0.113	0.301	0.470	0.551	0.707	0.791	0.858	0.923	0.983	1.000	0.10

K = Dissolution Rate Constant Mole/Min

Fig. 17

DISSOLUTION PROFILE OF SULPHAMETHOXAZOLE SUSPENSIONS



Formulation I, II	100% release within 18 min.
Formulation III	100% release within 30 min.
Formulation IV	100% release took > 30 min.

TABLE - 19

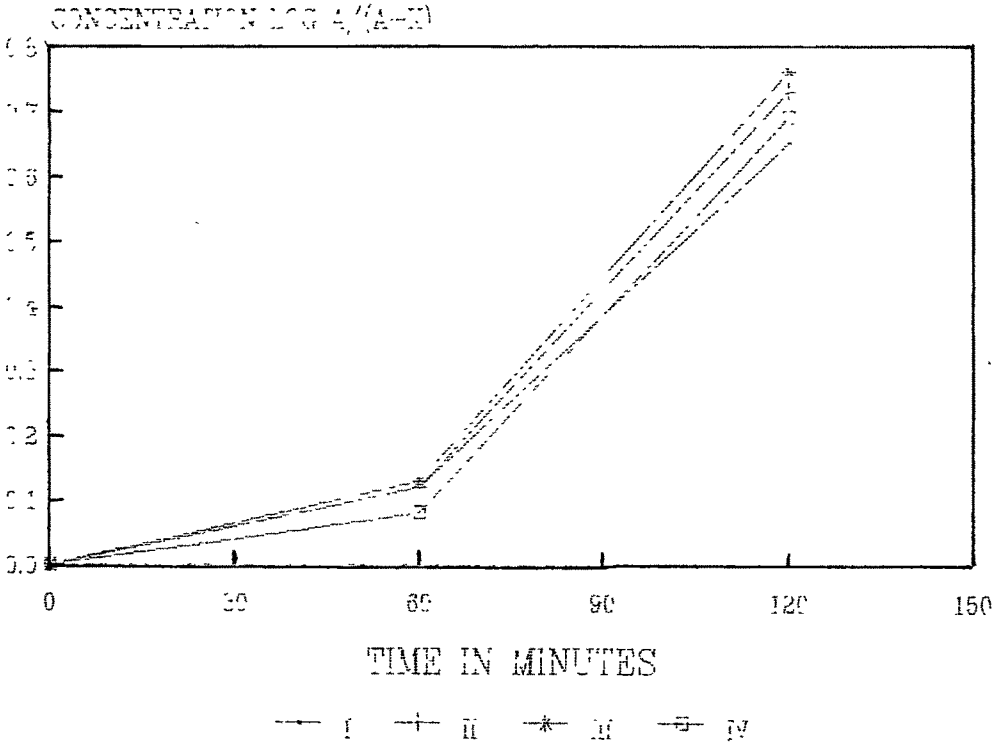
ABSORPTION STUDIES ON SULPHAMETHOXAZOLE SUSPENSIONS

Batch	Concentration of drug in plasma/40 cm^2 area = log a / (a - x)				
	Time in Minutes				
	30	60	90	120	K
I	0.1139	0.2455	0.4183	0.6749	0.010
II	0.1383	0.2553	0.4914	0.7202	0.010
III	0.1239	0.2480	0.3772	0.7372	0.010
IV	0.0828	0.2041	0.3874	0.7050	0.009

K = Dissolution Rate Constant Mole/Min.

Fig. 18

ABSORPTION STUDIES OF SULPHAMETHOXAZOLE SUSPENSIONS



Absorption profile as shown in Table 19 and Fig. 18, however, did not indicate undue differences between the different formulations, may be due to long time interval (30 min.) between each withdrawal of sample. The dissolution rate constant was 0.01 mole/min. Hence small deviations could not be detected. All the formulations followed almost the same path of absorption. The absorption rate of the drug can be given rank correlation as Formulation III > Formulation II > Formulation IV > Formulation I with respect to absorption studies.