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DESIGN AND IN VITRO EVALUATION OF A CONTROLLED RELEASE DRUG DELIVERY SYSTEM OF SULFASOMIDINE.

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ABSTRACT

A controlled release oral drug delivery system of Sulfasomidine was developed by spray congealing micropelleting technique using gelatin as the embedding matrix. The pellets were hardened by treating with Formalin-Isopropanol mixture. The in vitro release rate studies of Sulfasomidine from the micropelleted dosage form, revealed that the drug release can be prolonged upto eight hours and not more than 39% of the embedded drug released in the first hour of the in vitro dissolution study. The in vitro release patterns correlated with the reported in vivo studies. The method of formulation was optimized.

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INTRODUCTION

The advantages achievable by prolonging the drug action was described by Wilson.[1] The maintenance of specific minimum plasma concentration with sulfasomidine is essential because an inadequate blood concentration leads to the emergence of resistant strains of the microorganisms. As all the sulfonamides are bacteriostatic in nature, the plasma concentration below the optimum level allows the microorganisms to multiply[2]. A successful controlled release formulation of sulfasomidine could have a better influence over the plasma drug level. In addition, sulfasomidine has very short plasma half-life of 7 ± 1 hours,[3] which necessitates frequent administration, when given in conventional dosage form. The present investigation was undertaken to establish a successful controlled release dosage form of sulfasomidine. The drug was embedded in a gelatin matrix by a suitable modification of spray congealing micropelleting technique reported previously by Tanaka et al[4]. In an attempt to control the release of sulfasomidine from the prepared micropellets, the capsular shell had to be hardened by treatment with Formalin - Isopropanol mixture. It was observed that as long as the integrity of the hydrated polymer was maintained, the release of sulfasomidine from the micropellets was diffusion rate limited.

EXPERIMENTAL

Materials

Gelatin, Iso-electric pH 8.7 (40°C), Bloom strength 277 gm (corrected upto 11.5% water), was supplied by the courtesy of

Eli Lilly and Company, Indianapolis, Indiana, U.S.A.; l-Lysine monohydrochloride was received as gift from Cynamid India Ltd., Lederle Division, Bombay; Liquid paraffin and Light liquid paraffin were of Indian Pharmacopoeia - 1970 grade; Iso-propanol G.R. was from E. Merk (India) Ltd., Worli, Bombay; Sulfasomidine, of British Pharmacopoeia - 1963 grade, was kindly supplied by the courtesy of Hindustan Ciba-Geigy of India Ltd., Bombay.

Methods

Preparation of Micropellets - The following two formulations were studied :

Formulation - 1

Sulfasomidine	-	10.00 gms.
Gelatin	-	14.70 gms.
Lysine	-	0.30 gm.

Formulation - 2

Sulfasomidine	-	10.00 gms.
Gelatin	-	14.25 gms.
Lysine	-	0.75 gm.

In a 250 ml beaker, required quantity of gelatin was taken and dispersed in 32 ml of glass distilled water by the help of a variable speed electrical stirrer. Incorporated specified amount of l-lysine monohydrochloride and allowed to swell during 1 hour. It was then warmed to 60°C on a water bath to form a uniform gelatin sol. 10.0 gms of sulfasomidine in 200 mesh size was slowly

incorporated by an electrical stirrer to form a homogenious dispersion. This mixture was then poured in a constant and steady stream in warm (55-60°C) 400 grams of mixture of liquid paraffins, of absolute viscosity of 23.92 CP, achieved by blending 40% v/v liquid paraffin and 60% v/v light liquid paraffin, kept in 1 litre beaker. The liquid paraffin mixture was kept at continuous stirring at a speed of 200-250 rev min^{-1}. Keeping the stirring on for 15 minutes, the content of the beaker was quickly cooled to about 5-10°C by the external application of ice around the beaker. The system was further stirred for about 30 minutes and 32 ml of ice-cold isopropanol was added very slowly during that time. The Stirring was kept on for another 15 minutes. Then the beaker containing gelled micropellets was kept aside in a refrigerator overnight, to allow the completion of the gelling process.

Recovery of Micropellets

After overnight freezing of the produced newly formed micropellets, the recovery process was started. Firstly, the mixture was stirred slightly to disperse the frozen water and the micropellets throughout the medium, then it was allowed to stand for 5 minutes and the supernatant liquid was decanted off carefully so that the micropellets could be made devoid of liquid paraffin as far as possible. Care was taken to see that the temperature of the micropellets remained below the room temperature during the recovery. Temperature rise might cause

sufficient agglomeration and adherence of the micropellets. About 10 ml of chilled isopropanol was added to the pellets and stirred for about 10 minutes - during which time, the system was slowly allowed to come to the room temperature. Excess isopropanol was again decanted off and a fresh 10 ml quantity of the same solvent was added and this process was continued until the micropellets were completely devoid of adsorbed liquid paraffin. Finally, the micropellets were air dried for 18 hours and then dried in a dessicator under vacuum for 24 hours to a moisture content of about 15-20%. The micropellets were stored in an air-tight, amber coloured, wide mouthed glass container.

Reproducibility of the micropelleting procedure was evaluated by preparing replicate batches and determining the percentage of drug encapsulated in each batch.

Hardening of Micropellets :

Each gram of every size range of micropellets were treated with 10 ml of a mixture of 1.5 gm of formalin 35% w/v and 9.98 ml of isopropanol. After exposing the micropellets for 24, 48 and 72 hours in the above solution, the hardening liquid was decanted and the micropellets were spread to dry in air.

In vitro Dissolution Experiment

Micropellets weighing accurately 500 mg were enclosed into a muslin cloth of 300 mesh, formed into a pouch 200 ml of

simulated gastric fluid[5] was taken in a beaker, and placed on a magnetic stirrer with thermostat controlled hot plate.To get a quantitative relationship between dissolution rate and release rate of sulfasomidine from the micropelleted dosage form, the temperature of the dissolution medium was adjusted to 37±1°C and the stirrer speed was kept fixed at 33 rev min^{-1}. The stirring magnet had the dimensions of 9 x 35 mm and the dissolution fluid was kept in a 250 ml beaker. The pouch containing the pellets was hanged from a stand into the dissolution fluid such that the liquid level remained at least 1 cm. above the upper end of the pouch and the experiment started. After each 30 minutes interval, 25 ml of sample of dissolution fluid was withdrawn and fresh 25 ml of simulated gastric juice,previously maintained at 37±1°C was replenished. One hour after the start of the dissolution experiment fresh volumes of 25 ml of simulated intestinal fluid[5] was replenished, instead of gastric fluid, at each 30 minutes interval.
Table 1 illustrates the pH levels for the designated sample time intervals employed. Sampling was continued till the micropellets dissolved or upto 8 hours whichever was less.

Monitoring of Sulfasomidine Release :

An aliquot of each sample of dissolution experiments was suitably diluted with glass distilled water and subjected to colour development following the method described by Bratton and

TABLE - 1

pH Gradient for the In Vitro Release Rate Test

Cumulative time hour	pH of test fluid
0.5	1.5
1.0	1.5
1.5	2.3
2.0	6.6
2.5	7.3
3.0	7.8
3.5	8.0
4.0	8.1
4.5	8.1
5.0	8.1
5.5	8.1
6.0	8.1
6.5	8.1
7.0	8.1
7.5	8.1
8.0	8.1

Marshall[6]. Blanks for each estimation were prepared separately from placebo micropellets of same size, hardened under identical condition and subjected to dissolution experiment similar to that of test one. Equivalent quantities of sulfasomidine dry powder were subjected to suitable dilution with water and to colour development for the preparation of the standard curve.

RESULTS AND DISCUSSION

Reproducibility of the Micropelleting Technique :

The data in Table 2 show the assayed amounts of drug found in each of the three batches of identically prepared micropellets using both the formulae. The averages were used to calculate the standard deviation of the set of batches prepared using each formulation.

Based on the statistical analysis of the experimental data, it can well be expected with Formulation 1 that approximately 90% of the sample values will fall within ±2.75 of the sample mean (i.e., 193.76±2.75). And in the case of Formulation 2 approximately 90% of the sample values will fall within ±2.89 of the sample mean (i.e., 194.65±2.89). The coefficient of variability in both the formulations fall within the 5% limits that are established for most pharamaceutical preparations.

TABLE - 2

Reproducibility of the Micropelleting Process.

Formulation	mg. of Sulfasomidine per 0.5 g. of pellets Average of two Assays			Sample Standard Deviation
	Batch No.1	Batch No. 2	Batch No.3	
1	192.46	195.20	193.62	± 1.37
2	193.27	196.15	194.53	± 1.44

Particle Size Analysis of the Micropellets

Table 3 and Table 4 illustrate the size distribution of micropellets prepared using Formulation 1 and Formulation 2 respectively. The plots in Figure 1 illustrate the comparative size distribution of the pellets.

In vitro Release Rate Studies

The plots in Figure 2 represent a graphical presentation of the percent of drug remaining to be released against time.

TABLE - 3

Size Distribution of Micropellets Prepared by Formulation - 1.

Particle Size (Sieve Fraction)	Weight % of pellets of Batch No. 1	Batch No. 2	Batch No. 3	Mean ± S.D.
10 mesh oversize	3.31	4.42	6.75	4.83 1.76
10/12 mesh	5.54	5.75	8.95	6.75 1.91
12/16 mesh	13.76	12.51	15.27	13.85 1.38
16/20 mesh	68.43	67.32	59.82	65.19 4.68
20/22 mesh	7.84	6.53	7.76	7.38 0.73
22 undersize	1.12	3.47	1.45	2.01 1.27

TABLE - 4

Size Distribution of Micropellets Prepared by Formulation - 2.

Particle Size (Sieve Fraction)	Weight % of pellets of Batch No. 1	Batch No. 2	Batch No. 3	Mean ± S.D.
10 mesh oversize	2.12	3.45	1.92	2.50 0.83
10/12 mesh	4.94	5.13	3.87	4.64 0.67
12/16 mesh	12.14	12.95	11.72	12.27 0.62
16/20 mesh	65.76	68.14	62.18	65.36 3.00
20/22 mesh	9.14	7.13	10.87	9.05 1.87
22 undersize	5.90	3.20	9.44	6.18 3.13

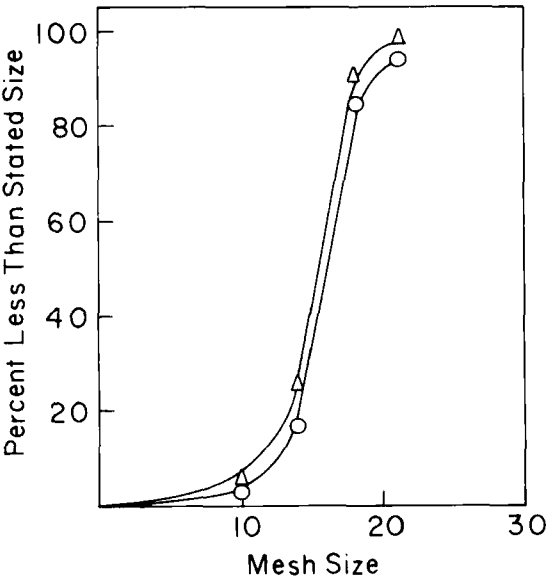

FIGURE 1

Cumulative Distribution Plot for Micropellets, △, Formulation 1; O, Formulation 2.

It was observed that the release of drug from micropellets obeyed first order release kinetics, which was confirmed from several release rate studies. Therefore, the first order release kinetics was used to calculate the release rate constant. Data given in Table 5 and Table 6 represent the release rate constants of three individually prepared batches of the micropellets using both the formulations, which were also hardened for 24, 48 and 72 hours with formalin - isopropanol mixture. Standard deviations of the release rate constants are shown at the bottom of the Tables. In all the cases, the samples of micropellets had been sieved through a 20 mesh sieve.

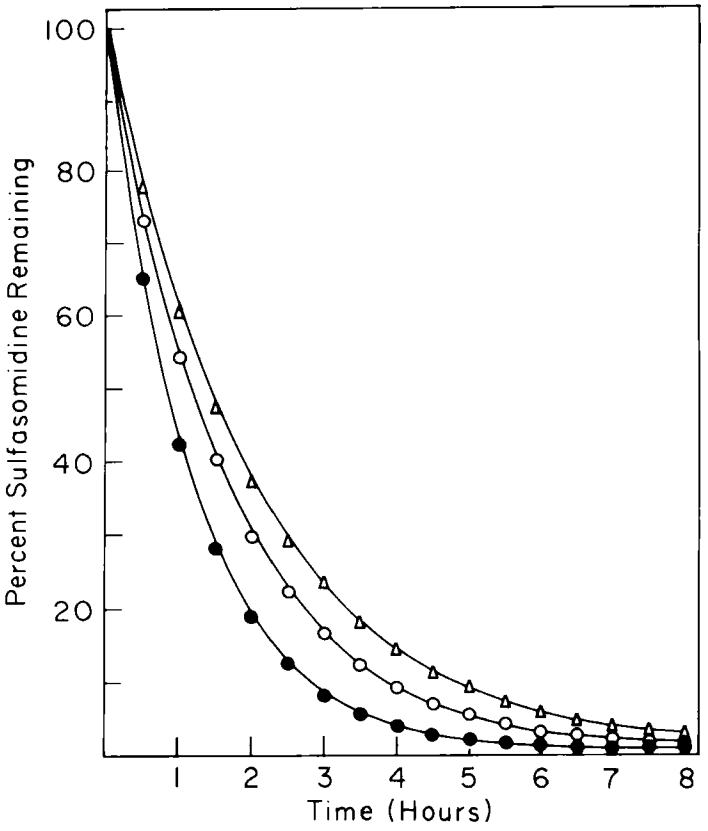

FIGURE 2

In Vitro Release Patterns of Sulfasomidine from Micropellets, Hardened with Formalin-Isopropanol Mixture for Various Hours. △, 72 hours; O, 48 hours; ●, 24 hours.

Heimlich et al attempted to correlate in vitro release rate patterns with in vivo results[7]. The reported in vitro release values, shown in Table 7, were for those products exhibiting suitable sustained action properties (usually 10-12 hr.). When the same products were evaluated in vivo by urinary excretion studies, there was excellent correlation as was also earlier reported by Goodman and Banker[8]. The experimental datas depicted in

TABLE - 5

Release-Rate Constants (hr^{-1}) of the Micropelleted Sulfasomidine Hardened with Formalin-Isopropanol Mixture

Formulation - 1.

	Release-Rate Constants Hardening Time in Hrs.		
Batch No.	24	48	72
1.	0.8329	0.5982	0.4902
2.	0.8384	0.6009	0.4925
3.	0.8349	0.5998	0.4913
Mean	0.8354	0.5996	0.4913
±S.D.	0.0028	0.0013	0.0012

TABLE - 6

Release-Rate Constants (hr^{-1}) of the Micropelleted Sulfasomidine Hardened with Formalin-Isopropanol Mixture

Formulation - 2.

	Release-Rate Constants Hardening Time in Hrs.		
Batch No.	24	48	72
1.	0.8663	0.6307	0.4982
2.	0.8720	0.6364	0.5020
3.	0.8684	0.6328	0.4971
Mean	0.8689	0.6333	0.4991
±S.D.	0.0029	0.0029	0.0026

TABLE - 7

Comparison of Reported Release Values with Experimental Results

Time, hr.	Cumulative Percent Release		
	Reported values	Experimental values	
		Formulation - 1	Formulation - 2
0.5	32 - 43	21.59	21.89
1.5	-	51.71	52.27
2.0	39 - 69	62.06	62.63
2.5	-	70.16	70.72
4.5	60 - 90	88.39	88.74
6.5	-	95.22	95.40
7.0	86 - 98	96.12	96.26

Table 7 were found to lie within or very close to the values reported for satisfactory sustained action properties.

The results shown in Table 8 illustrate the effect of gelatin-lysine ratio on the release rate pattern. The gelatin-lysine ratio may be another means of controlling and changing release rate patterns, but in the present studies, the inclusion

TABLE - 8

Effect of Gelatin-Lysine Ratio

on the Release Rate Pattern.

Time, hr.	Gelatin-Lysine Ratio 49:1 (Formulation-1) Cumulative Percent Release	19:1 (Formulation-2)
0.5	21.59	21.89
1.5	51.71	52.27
2.5	70.16	70.72
3.5	81.46	81.93
4.5	88.38	88.74
5.5	92.62	92.88
6.5	95.52	95.40
7.5	96.81	96.93
8.0	97.36	97.45

of lysine into the formulations did not significantly change the release rate patterns, which also indicate that the drug release prolongation is dependent mostly on the amount of gelatin in the formulation and the cross-linking of formalin with lysine did not contribute any important role in controlling the drug release.

Formulation Optimization

Several trials were performed to optimize the formulation method. The process was expensive due to the use of bulks of liquid paraffin, isopropanol and also due to wastage of drug-gelatin mixture which had been gelled and remained in the beaker being unpourable. Experiments showed that the liquid paraffin medium, isopropanol and the gelled mass could be used again with high degree of success.

After the preparation of each batch, the gelled mass obtained was dried in air then at 60°C under vacuum, cooled and stored in air tight jar. These dried materials were minced to 12 mesh size and then used for the preparation of next batch of the formulation.

The liquid, remained after recovery of the micropellets, had the approximate composition as follows :

Liquid paraffin	- 83% w/w
Isopropanol	- 9.3% w/w

and the rest was water and floating fine gelatin masses. The floating matters were removed by vacuum filtration and the oily portion separated from the isopropanol-water mixture. Per 400 gm of the oily part, 50 gm of anhydrous sodium sulfite was added, and dispersed throughout the oily part and kept aside for overnight. On the next day, it was filtered and the filtrate warmed to 50°C for 10 minutes and used for successive formulation manufacturing.

The isopropanol could be recovered from the water layer collected from previous separation, by fractional distillation.

The in vivo evaluation of the controlled release dosage form of sulfasomidine is under progress and results would be communicated in due course.

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