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Studies on Tablets of Sulphamethoxazole using Chitosan

R. ILANGO*, S. KAVIMANI, JOSPHINE PREMILA, DEEPA K. NAIR AND B. JAYAKAR.
Dept. of Pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Trichy - 21, Tamil Nadu.

In this investigation an attempt was made to study the release of sulphamethoxazole from tablets prepared using chitosan as a granulating agent. Three different sulphamethoxazole tablets were prepared by using 2% chitosan paste, 4% chitosan paste and 10% starch paste respectively. *In Vitro* evaluations were carried out by using Dissolution testing apparatus U.S.P. (XX1). The dissolution pattern indicates the role of chitosan in sustained release. Bioavailability studies on male beagle dogs clearly showed the sustained release from chitosan based sulphamethoxazole tablet with reference to conventional sulphamethoxazole tablet.

POSSIBLE use of chitosan as a new vehicle for sustained release preparation has been examined. Chitosan, a natural poly-saccharide, has structural characteristics similar to glycosamino glycans, Chitosan has been shown to be non toxic and bioabsorbable. It is inexpensive and has been explored in the present investigation as a release retarding agent in sulphamethoxazole tablets.

Chitosan is (1,4)-2-amino -β-D-glucan. Crustacean shells are the usual raw materials of chitin.[1-5] Earlier workers reported LD_{50} and oral toxicity of chitosan in mice and rats.[6-7] Lack of acute oral toxicity of chitosan was noticed as evidenced by an oral LD_{50} of 10 g/kg in mice[8].Controlled release of drug through chitosan has been achieved by Touchi *et al*[4], Chandy *et al*[9] and Maada *et al*[10]. For the present study sulphamethoxazole is chosen as a model drug. The plasma half life is 6-10 h. Crystalluria is the major toxic effect of sulphamethoxazole in multiple dose therapy[11]. To provide a constant blood level for a long period with a low dosing frequency and to suppress the side effects, a sustained release system would be more suitable.

*For correspondence

EXPERIMENTAL

MATERIALS

Chitosan, the deacetylated chitin, is a highly hydrophobic material that is insoluble in water and most other ordinary solvents[5]. Chitosan paste was formed by dissolving chitosan in 10% acetic acid solution. Sulphamethoxazole (U.S.P.), Phosphate Buffer PH 7.4, Starch, Lactose, were the other materials used.

INSTRUMENTS

Digital three stage dissolution testing apparatus, U.V. Visible recording Spectrophotometer-Systronics 118 model, Centrifuge were the instruments used.

Preparation of tablets

Sulphamethoxazole was triturated thoroughly with lactose and passed through a fine mesh. The collected material was granulated using 2% and 4% chitosan paste which was prepared with 10% acetic acid solution. When enough cohesion obtained the mass was passed through sieve No.14 and the

granules so obtained were dried at 50°for 2 h. The dried mass was passed through the sieve No.16 superimposed over sieve No.20.The 16/20 fraction was mixed with 5% of its weight of starch and lubricated with talc and magnesuim stearate. The lubricated granules were then taken for compression. The tablets were punched in a Cadmach single punch tablet compression machine using 3/8" die and punch set at an appropriate compression pressure.

Stability studies on tablets

Physical stability and effect of ageing on the drug release were studied for the following preparations. Sulphamethoxazole control tablets and sulphamethoxazole tablets were prepared with chitosan.

Tablets were kept in small air tight glass containers and stored at 37° in an incubator and at 45° in an oven and at relative humidities of 82.5%., 57% and 17.5% for eight weeks. The tablets were observed every two weeks for the following changes, if any, (i) change of colour and (ii) change in tablet characteristics.

Effect of ageing on the release characteristics were studied after second and fourth week, using dissolution method[12].

Granule-evaluating parameters such as bulk density, total porosity and angle of Repose were studied. Tablet-evaluation parameters such as weight variation, hardness, friability loss,disintegration time and uniformity of drug content were studied.

IN VITRO STUDY

Release of sulphamethoxazole from tablets was determined using Dissolution rate test apparatus U.S.P. (XX1), a rotating basket model using 900ml of phosphate buffer (pH 7.4) as dissolution media, at 37°± 0.5° and 100 rpm.

Samples in 5ml aliquots were withdrawn and passed through a Whatmann filter paper at 0.5, 1, 2, 3, 4, 5, and 6 h intervals. Estimation of sulphamethoxazole is based on diazotisation followed by coupling with Bratton Marshall reagent. The developed colour was measured at 547 nm using an U.V.-Vis, spectrophoto-meter.

IN VIVO STUDY

This study was performed using eight male beagle dogs[13] weighing about 6-8 kg to find the release profile of sustained release and conventional tablets containing sulphamethoxazole. The dogs were starved for 18 h with access to water prior to the experiment. These eight dogs were divided into two groups of four each. The first group received control tablet containing sulphamethoxazole.

Calculated doses of drug were administered through oral intubation technique. After the 1st hour, 5ml blood was collected through the femoral Vein from each batch. Blood samples were collected at intervals of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h. The blood samples were centrifuged at 2500 rpm for 20 min and the plasma was separated in to a clean sample tube. To 1 ml of plasma sample, 0.2 M Phosphoric acid was added and mixed well. Then 3 ml of carbontetrachloride was added, mixed well and centrifuged for separation. The organic layer was collected and shaken well with 4ml of 0.1 N sodium hydroxide and centrifuged. To the aqueous layer 1 ml of sodium nitrite, 1ml of 4n hydrochloric acid, 1 ml of ammonium sulphate and 1ml of Bratton Marshall reagent were added with intermittant shaking. The developed colour was measured at 547 nm.

Drug interaction study

There was no interaction between chitosan and sulphamethoxazole which was confirmed by infrared spectrum of the physical mixture of chitosan and sulphamethoxazole.

Table 1
Characteristics of granules in various sulphamethoxazole tablets

Formulation	Bulk density g*/ml	True density g*/ml	Total porosity	Angle of Repose
Control	0.322 ± 0.013	0.81 ± 0.01	63.8 ± 3.1	38.4 ± 0.15
2% Chitosan	0.410 ± 0.01	1.18 ± 0.02	64.3 ± 2.0	35.7 ± 0.36
4% Chitosan	0.400 ± 0.01	1.20 ± 0.02	70.00 ± 3.3	36.2 ± 0.02

* n = 5, ** n=8, Each value is the mean of five or eight determinations with standard deviation.

Table 2 : Characteristics of sulphamethoxazole tablets

Formulation	Hardness** (Kg/cm)	Friability* Loss (%)	Disintegration** time (min)	Diameter of tablet (mm)	Average Weight (mg)
Conventional Tablet	1.5 ± 0.06	0.52 ± 0.06	5	3/8"	800 ± 0.33
Chitosan 2% Tablet	1.56 ± 0.02	0.47 ± 0.08	20	3/8"	800 ± 0.033
Chitosan 4% Tablet	1.54 ± 0.02	0.32 ± 0.06	30	3/8"	800 ± 0.55

* n = 5, **n = 8, Each value is the mean of five or eight determination with standard deviation

RESULTS AND DISCUSSION

Physical properties of the granules and tablets of sulphamethoxazole prepared using chitosan or starch paste showed no significant difference. It is summarieed in tables 1 and 2. Stability studies of tablets were carried out by placing the samples at different temperature (37° ± 1°, 45° ± 1°) and at three different relative humidities. There is no appreciable change in release characteristics,colour and character of the tablets used in the release study.

The mechanism by which chitosan retards the release rate in granules and tablets may be explained on the basis of its high insolubility. The figure 1 depicts the dissolution profile of sulphamethoxazole from tablets prepared using different concentration of chitosan in comparison with those prepared using conventional starch paste as a binding agent. It is possible to decrease the rate of dissolution by increasing the concentration of chitosan solution over the formulation of sulphamethoxazole granules.

In the animal studies, conventional sulphamethoxazole tablet dosage form attained peak plasma drug concentration at 3.5 h, while, 2% chitosan paste-based sulphamethoxazole tablet attained maximum plasma drug concentration at the 5th h. Pharmacokinetic parameters are summarised in table 3. Control tablets attained the highest concentration of 8.0 mcg in this study. However, chitosan-based tablets maintained 6.7 mcg for a prolonged period of time.Conventional sulphamethoxazole tablets dissolved immediately, while the chitosan-based tablets showed a lag time

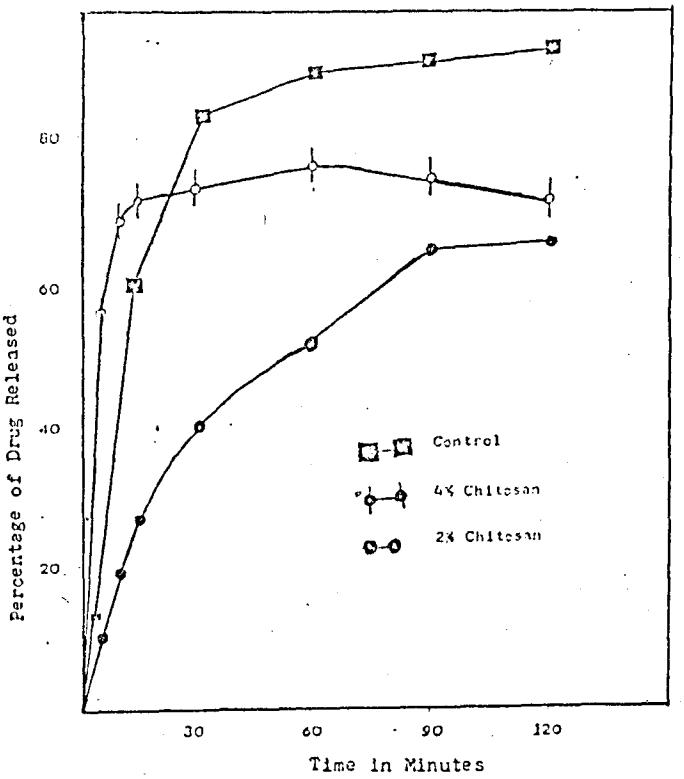

Fig. 1: Dissolution profile of Sulphamethoxazole from tablets prepared using different concentration of chitosan in comparison with those prepared using conventional starch paste as binding agent

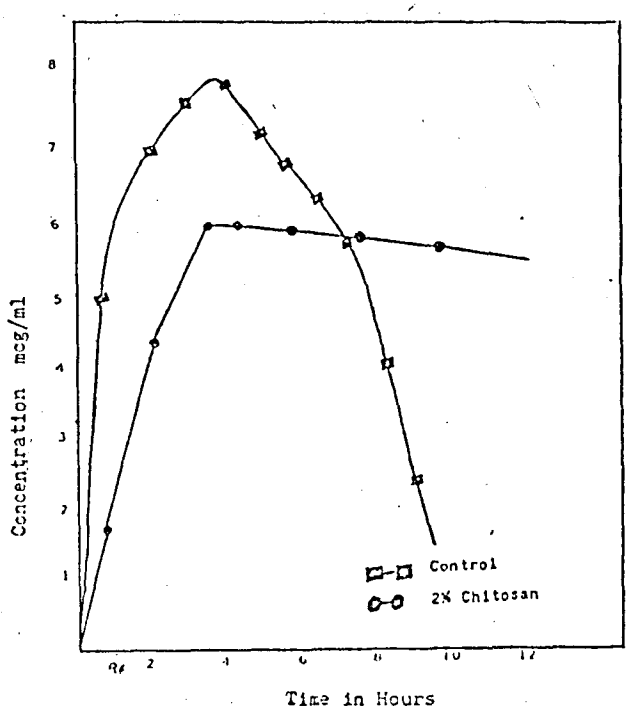

Fig. 2: *In vivo* release studies of Sulphamethoxazole Tablets prepared using 2% concentration of chitosan in comparison with starch paste as binding agent in male beagle dogs

Table 3 : Pharmacokinetic Parameters* of sulphamethozaxazole tablets

Formulation	Lag time	Absorption half life h	Elimination half life h	Ka	Auc mcg/h/ml O-T 0-∝	Mean Residence Time T-∝ O-∝	C MAX mcg	T MAX h
Conventional SMX Tablet	--	1.58	4.10	0.44	50.750 26.645 77.395	7.48	8.0	3.5
2% Chitosan based SMX Tablet	1.36	0.38	11.97	1.82	32.397 94.485 130.882	19.78	6.7	5.0

* Each value is the mean of Eight determinations

of 1.4 h. Parameters such as absorption rate half life, elimination half life, absorption rate constant, area under the curve,mean resident time, Cmax and Tmax were appreciably different for the above two sulphamethoxazole tablet dosage forms.

In conclusion, tablets prepared using chitosan as a granulating agent exhibited retarded release of sulphamethoxazole appreciably. Therefore, tablets with chitosan as a binding agent need to be

formulated for sustained release and further studies with these formulations are to be carried out.

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