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Effect of different Co-polymers on Sodium Alginate Microcapsules Containing Isoniazid

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Abstract: The present investigation was designed to develop, characterize and evaluate mucoadhesive microcapsules of isoniazid employing various mucoadhesive polymers for prolonged gastric intestinal absorption. Sodium alginate is an anionic polymer which can be easily cross-linked with calcium chloride. This is because the calcium ions are bound to carboxylate residues of both mannuronic acid and glucournic acid which are components of sodium alginate. The complexation between calcium ions and sodium alginate leads to controlled release of drugs. Three different formulations were prepared with core: coat ratio 1:2 and by using three different co-polymers in the ratio of 5:1(polymer: co-polymer) by employing orifice ionic gelation method. The method produced discrete, free flowing and spherical microcapsules ratios. The prepared microcapsules were evaluated for SEM analysis, sieve analysis, drug content, encapsulation efficiency, swelling studies and compared with pure drug. The microcapsules obtained were spherical, discrete and free flowing. The release depended on the type of copolymer and size of microcapsules. *In-vitro* release studies were carried out in pH 7.4 and 20.83%, 32.40% and 51.54% of the drug was released from F1 (sodium alginate+methyl cellulose), F2 (sodium alginate+Hydroxy propyl methyl cellulose) and F3 (sodium alginate+sodium carboxy methyl cellulose) respectively upto 12 hrs. Drug release was found to be diffusion controlled and followed first order kinetics. The prepared microcapsules showed sustained release over a period of 12 hrs.
Key words: Isoniazid, microcapsules, sustained release, methyl cellulose, sodium CMC and HPMC.

INTRODUCTION

Sustained release (SR) dosage forms are gaining increased acceptance over conventional dosage forms in the treatment of several acute and chronic conditions. So, SR dosage forms are designed to achieve a prolonged therapeutic action by continuously releasing medication over an extended period of time after the administration of a single dose. In addition to better patient compliance they reduce the incidence and severity of side effects(1). They have proved particularly valuable in ensuring continuous therapeutic effect in conditions such as arthritis, angina pectoris and asthma.

Micro encapsulation is a process for coating small particles of solids/droplets of liquids and dispersion using polymeric material to produce small particles of 1-5000µm in size. It is a rapidly expanding technology for achieving sustained release dosage form. Micro encapsulation is used to modify and retard drug release. Microencapsulation is receiving considerable attention fundamentally, developmentally and commercially (2).

The controlled delivery of antimycobacterial agents may be accomplished by employing various polymeric drug carriers (3). (sodium alginate, chitosan, CMC, HPMC, MC, etc.,) . Sodium alginate is an anionic polymer which can be easily cross-linked with calcium chloride. This is because that the calcium ions are bound to carboxylate residues of both mannuronic acid and glucournic acid which are components of sodium alginate (Figure 1). Here it is the interaction of calcium ions with guluronic acid that contributes to the complexation mechanism (Figure 2).This complexation between calcium ions and sodium alginate leads to controlled release of drugs.

Isoniazid has been selected as a model drug because it exhibits all the pharmacokinetic and physico-chemical properties required for sustained release. It has broader antimicrobial activity and has profound application in the treatment of number of different bacterial infections (4) (mainly used in the treatment of tuberculosis). Isoniazid is well absorbed from GIT after oral administration. It is not bound to proteins. It has a short biological half life of 3.1 ± 1.1hours and its urinary excretion is 29±5% (5) . It is usually administrated as a tablet containing 100-300mg. The effect of the drug lasts for a few hours and it needs to be administrated daily once in the treatment of tuberculosis for a six months period. Hence to improve therapeutic efficacy and patient compliance and to reduce adverse effects, fluctuations in plasma concentration and to decrease the dose and dosing frequency controlled release preparations of isoniazide are essential.

MATERIALS AND METHODS

Isoniazid was a gift sample from Alkem Laboraties limited, Mumbai), sodium alginate and HPMC (Alkem laboraties limited, Mumbai), methyl cellulose, (Karnataka fine chem., Banglore), sodium CMC (Universal laboratories, Mumbai), calcium chloride (Sd fine chem. Limited, Mumbai). All other chemicals and solvents used were of analytical grade. Paddle stirrer (Remi motors), dissolution apparatus (Campbell electronics, Mumbai) and UV-visible spectrophotometer (Systronics) were the equipments used in this study.

PREPARATION OF MICROCAPSULES

Microcapsules containing isoniazid were prepared by using sodium alginate in combination with sodiumcarboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose as coat material employing orifice ionic gelation method. The required quantities of sodium alginate (500mg) and mucoadhesive copolymer (100mg) were soaked separately in purified water (9.5ml) and mixed properly to obtain homogenous polymer solution. The active ingredient, isoniazide (300mg) was added to the polymer solution then mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually drop wise into calcium chloride (10% w/v) solution (100ml) through a syringe with a needle of size no.24. The added droplets were retained in calcium chloride solution for 15 minutes to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 45^0c for 12hrs.

CHARACTERIZATION OF MICROCAPSULES

The microcapsules were found to be discrete and free flowing. The prepared microcapsules were evaluated for SEM analysis, size analysis, drug content, encapsulation efficiency, swelling studies and in-vitro release studies.

SEM ANALYSIS

The particle size, shape and surface morphology of microcapsules were examined by scanning electron microscopy. Microcapsules were fixed on aluminum studs and coated with gold using a sputter coater SC 502, under Vacuum [0.1mm Hg] the micro capsules were then analyzed by SEM [model LEICA S-430, London,U.K. (6).

SIEVE ANALYSIS

Particle size analysis was carried out using a standard sieve set (7).

ESTIMATION OF DRUG CONTENT IN MICROCAPSULES

Microcapsules (50mg) were powdered and transferred into a 50ml volumetric flask. The volume was made up to the mark with phosphate buffer 7.4 and kept for 12 hours with occasional shaking and filtered. Then the drug content was analyzed spectrophotmetrically at 263 nm using a single beam U.V./Visible spectrophotometer.

The encapsulation efficiency was calculated using the formula (8)

$$\%\text{Encapsulation Efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

SWELLING STUDIES (9)

A known weight (50mg) of microcapsules were placed in a glass vial containing 10ml hydrochloric acid buffer pH 1.2 and phosphate buffer pH 7.4 at 37± 0.5˚C with occasional shaking. The microcapsules were periodically removed, weighed and again allowed for swelling until equilibrium weight was attained. Finally, the weight of swollen microcapsules was recorded after a time period of 4 hours and the swelling ration (SR) was then calculated from the formula.

$$\text{Swelling Ratio (SR)} = \frac{We - Wo}{Wo}$$

Where

Wo=initial weight of the dry microcapsules.

We =weight of the swollen microcapsules at equilibrium Swelling in the media.

IN VITRO DISSOLUTION STUDIES

The release of Isoniazide from microcapsules was investigated in phosphate buffer of pH 7.4 as a dissolution medium (900ml) using

the rotating basket method specified in USPXXIV (model TDT6P-Electro lab). Sample of 100mg microcapsules was taken in the basket. A speed of 75 rpm and temperature 37 ± 0.5˚C was maintained through out the experiment. At fixed intervals, aliquots (5ml) were with drawn and replaced with same amount of fresh dissolution media. The concentration of drug released at different time intervals was then determined by measuring the absorbance using UV visible spectrophotometer at 263nm against blank. The studies were carried out in triplicate. The percent of drug released at various time intervals was calculated and plotted against time. The release of pure drug was also determined in the same way.

RESULTS AND DISSCUSSION

. Isoniazid microcapsules containing three different formulations were prepared with core:coat ratio 1:2 and by using three different co-polymers in the ratio of 5:1(polymer :co-polymer) by employing orifice ionic gelation method. The method produced discrete, free flowing and spherical microcapsules.

SCANNING ELECTON MICROSCOPY

Scanning electron microscopy was used to investigate the morphology of microcapsule. The microphotographs indicate that the microcapsules were almost spherical, discrete and covered continuously and completely with sodium alginate-methyl cellulose coat material (Figures 3 and 4).The orifice ionic gelation method was found to be suitable for the preparation of uniform microcapsules of a sodium alginate with methyl cellulose.

SIEVE ANALYSIS

Particle size analysis was carried out using standard sieve set. The microcapsules were uniform in size with a mean size of 920 µm in the mesh size -18+20.

DRUG CONTENT AND MICROENCAPSULATION EFFICIENCY

Drug content of microcapsules determines the amount of drug entrapped in the microcapsule. The drug content estimated in each 50mg of various microcapsules were found in the range of 8.71-15.07 mg as shown in Table 1.

The encapsulation efficiency represents the percentage of encapsulated drug with respect to the total drug introduced into the polymer solution. The encapsulation efficiency ranged from 54-82%. The encapsulation efficiency was increased with decrease in solubility of co-polymer. The microencapsulation efficiency of F1, F2, F3, was found 82%, 60% and 54 % respectively as shown in Table 1.

Table 1 : Isoniazid drug content and microencapsulation efficiency of sodium alginate microcapsules

FORMULATIONCODE.	DRUG CONTENT (MG)		ENCAPSULATION EFFICIENCY (%)
	THEORITICAL	PRACTICAL	
F1	18.38	15.07	82
F2	19.52	11.71	60
F3	16.13	8.71	**54**

Table 2:Kinetic values obtained for sodium alginate- methyl cellulose microcapsules in ph 7.4.

Formulation	Type of equation	Slope Values(n)	orrelation Coefficient(r) values
F1	Zero order	3.5060	0.9765
	First order	0.0191	0.9860
	Higuchi	13.0370	0.9812
	Korsemeyer	0.7332	1.0985

Drug release data were fitted into zero order equation, first order equation, Higuchi equation and Korsemeyer equation. Microcapsules (F1) were formulated using sodium alginate and methyl cellulose in the ratio of 5:1.

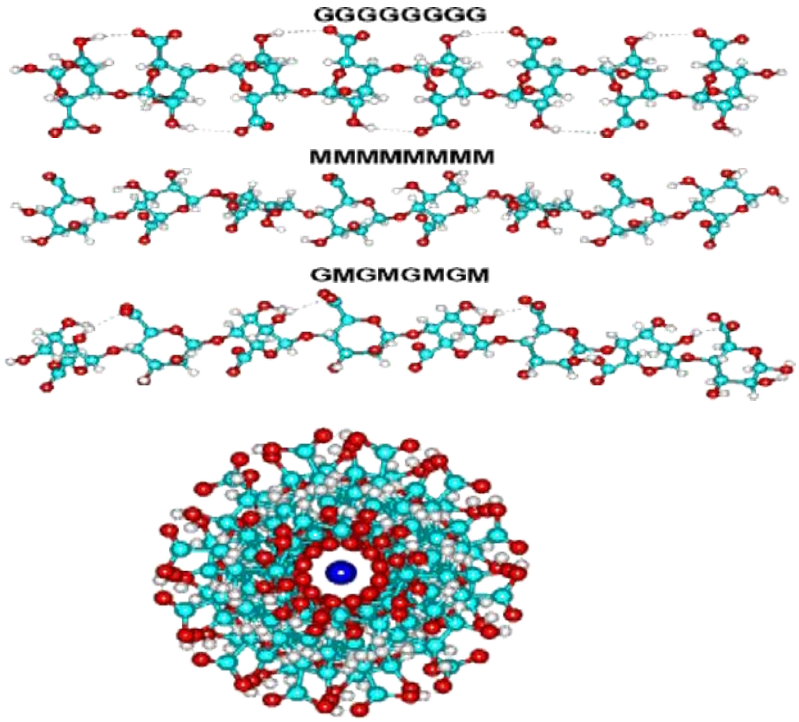

Figure 1.Calcium poly-αL-guluronate left-handed helix view down axis

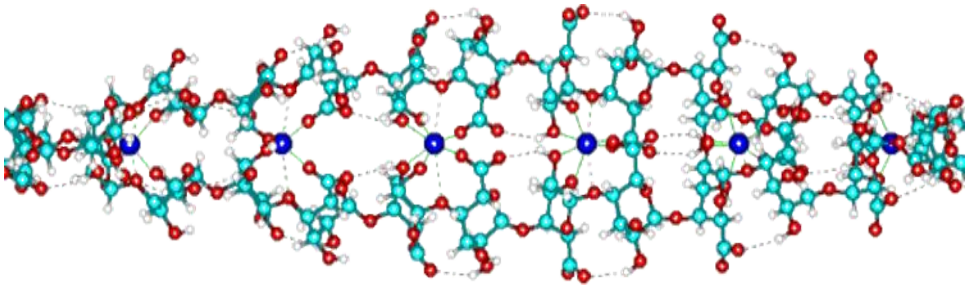

Figure 2: Showing the hydrogen bonding and calcium binding sites

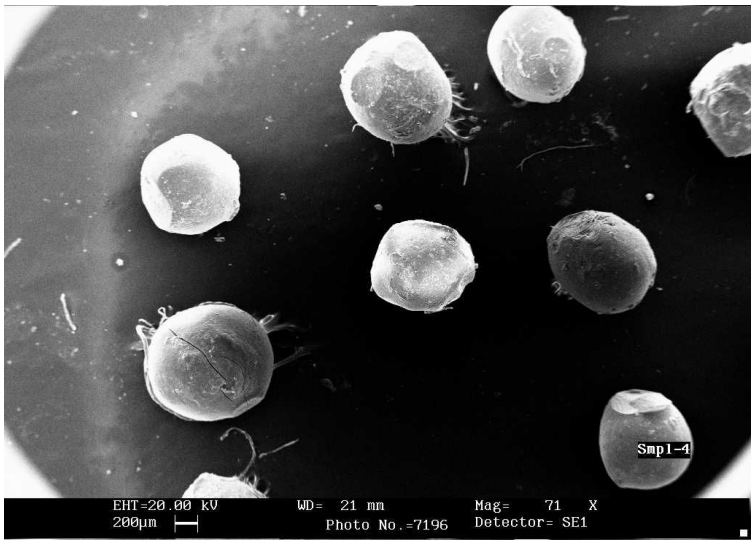

Figure 3:SEM photograph of sodium alginate-methyl cellulose microcapsules.

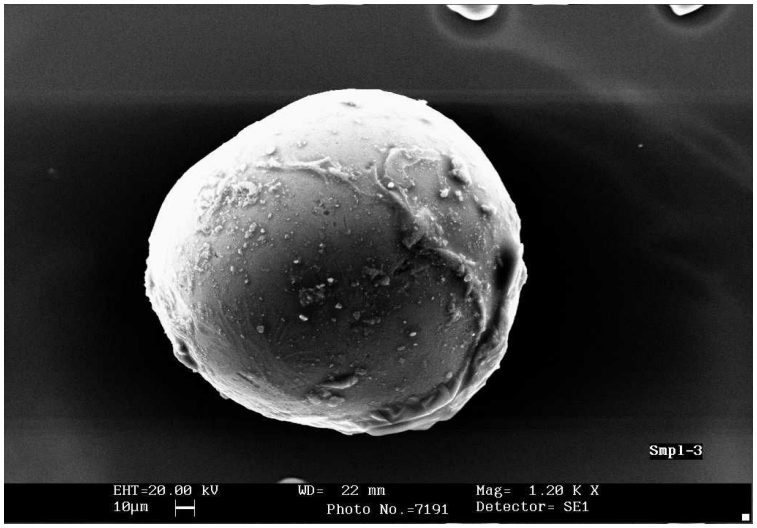

Figure 4: SEM photograph of a single sodium alginate-methyl cellulose microcapsule.

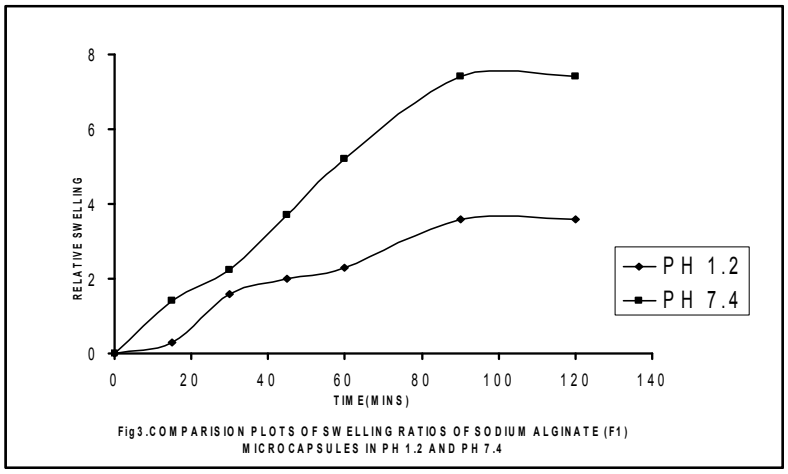

Figure 5: Comparison plots of swelling ratios of sodium alginate [F1] microcapsules in —♦— pH 1.2 and—■—pH 7.4.

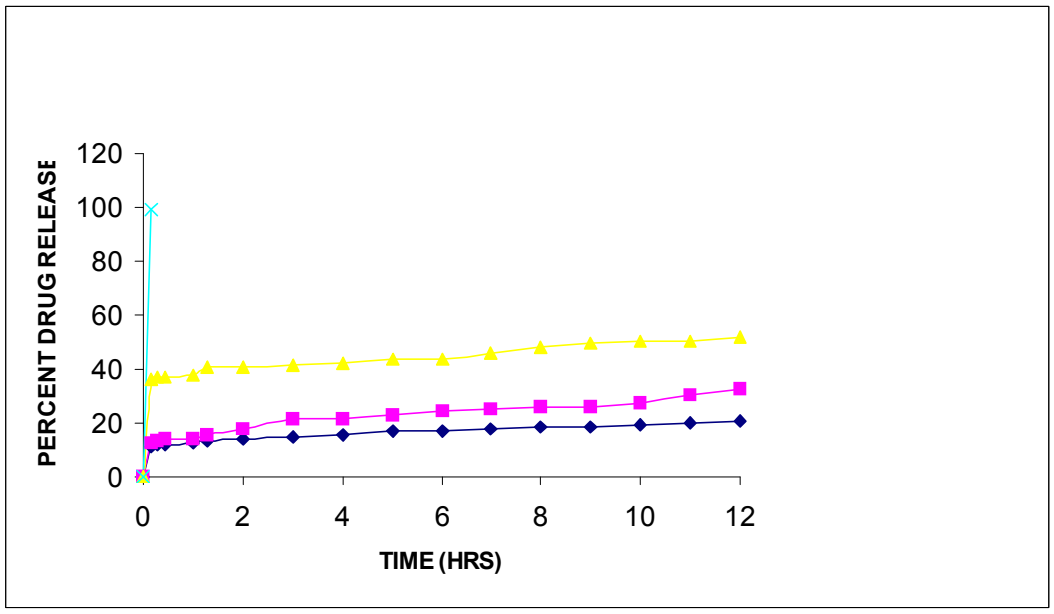

Figure 6: *In vitro* release studies of microcapsules F1—♦— , F2 —■— , F3 —▲— and pure drug —x— .

SWELLING STUDIES

In order to know the behaviour of sodium alginate microcapsule during gastro-intestinal passage, the swelling were done by incubating in pH 1.2 and pH 7.4 at 37˚C. Comparison plots of swelling ratios of sodium alginate-methyl cellulose microcapsules are shown in Figure 5. The sodium alginate microcapsules showed higher equilibrium swelling ratio value 7.4 at the end of 2 hrs in pH 7.4 medium and 3.6 at the end of 2 hrs in pH 1.2. The results showed that swelling ratio of sodium alginate was higher in pH 7.4 as compared to pH 1.2. This may be due to shrinkage of sodium alginate gel network in pH 1.2 and erosion in pH 7.4.

***In Vitro* Dissolution**

To assess the influence of co-polymer, three batches of microcapsules were prepared with core : coat ratio 1:2 & polymer : co-polymer ratio 5:1. *In vitro* release studies were performed in pH 7.4 and the microcapsules gave sustained release over a period of 12 hrs as shown in Figure 6.

Drug released in 12 hrs from the formulations F1, F2, F3 in pH 7.4 buffer was 20.83%, 32.40%, 51.54% respectively. This indicates that the increase in solubility of co-polymer resulted in increase in release of drug.

KINETICS OF DRUG RELEASE

In order to elucidate the release mechanism the data of F1 was fitted in to models representing Zero order, first order Higuchi (10) and Korseymeyer Equations (11) (Table 2).When the data was plotted according to the first order release kinetics, a fairly linear plot was obtained incase of F1 with their high regression coefficient value.0.9860 suggesting that the rate of release from microcapsules was followed as per first order kinetics.

The data fitted with Higuchis equation, F1 yielded a linear plot with their high correlation coefficient value 0.9812 indicating that mechanism of release from microcapsules was diffusion controlled. To know precisely whether Fickian or non-Fickian diffusion exists, the data was plotted according to Korsemeyer equation. The plot showed the slope value n=0.7332. These findings showed that the mechanism of release was Non Fickian diffusion.

CONCLUSION

The method of preparation of microcapsules of isoniazid was found to be simple and reproducible. The sustained release of isoniazid from microcapsules will help to improve the therapeutic efficiency and patient compliance by reducing the dose and dosing frequency of isoniazid. This study shows that sodium alginate –methyl cellulose microcapsules could be a carrier for isoniazid.

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