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Formulation and Evaluation of Mucoadhesive Microcapsules Of Rifampicin

Gottapu Prashanti[1]
(A.U. College of Pharmaceutical Sciences, Visakhapatnam, Andhra Pradesh-530003)[1]

Abstract: *Mucoadhesive microcapsules of rifampicin were prepared by orifice ionic gelation technique for a novel controlled release product. Sodium alginate, sodium carboxy methyl cellulose and chitosan were used as coating polymers in different ratios to obtain elegant microcapsules. The formulations were characterized for encapsulation efficiency, SEM analysis and invitro release studies. The microcapsules were discrete, large almost spherical and free flowing with encapsulation efficiency in the range 75 to 88% and size ranging from 780 to 882nm. Rifampicin release from these microcapsules was slow and extended over longer periods of time depending on polymer coat. Drug release was diffusion controlled and followed first order kinetics. The formulation F11 with coating ratio1:2:2 of sodium alginate and chitosan was found to be suitable for oral controlled release.*

Keywords: *Rifampicin, tuberculosis, sodium alginate, sodium carboxy methyl cellulose, chitosan.*

I. INTRODUCTION

Microcapsules are one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability, stability and target drug to specific sites. These can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing the dosing frequency and improving patient compliance.

Tuberculosis is a chronic communicable disease caused by the bacterium Mycobacterium tuberculosis that infects over 1.8 billion people worldwide and is responsible for 1.5 million deaths annually. Rifampicin is a first-line drug for being used in the therapy of tuberculosis and is included in the list of recommended drug regimens for the treatment of latent M. tuberculosis infection in adults.

Rifampicin is the semi-synthetic hydrazine derivative of Rifampicin B. In the last several years, many different types of rifampicin controlled release formulations have been developed to improve clinical efficacy of drug and patient compliance.

II. MATERIALS AND METHOD OF PREPARATION

Rifampicin drug was a gift sample from Lupin laboratories,. All other chemicals and solvents used were of analytical grade. Paddle stirrer, dissolution apparatus, and UV-visible spectrophotometer, were the equipments used in this study. Microcapsules of rifampicin were prepared by using ionotropic gelation technique employing sodium alginate/sodium cmc/chitosan as coat material. Three sets of microcapsules were prepared. In the first set microcapsules of rifampicin were prepared using only sodium alginate in different ratios(1:1), (1:2),(1:3). In the second set, microcapsules of the drug were prepared using sodium alginate and sodium carboxymethyl cellulose polymers in different ratios(1:1:1),(1:1:2),(1:2:1),(1:2:2) and in the third set microcapsules of the drug were prepared in combination of polymers like sodium alginate and chitosan (1:1:1),(1:1:2),(1:2:1),(1:2:2).

III. CHARACTERISTICS OF THE PREPARED MICROCAPSULES

3.1 Size And Shape Of Microcapsules

Size of the rifampicin microcapsules was determined by sieve analysis. The microcapsules were separated in to different size fractions by sieving using standard sieves. The particle size distributions of the microcapsules were determined to know the mean particle size of microcapsules. All readings are average of three trials ±SD.

The shape and surface morphology of the rifampicin microcapsules were investigated using a Hitachi-S5-20, scanning electron microscope at room temperature using the required magnification. The sample was deposited on aluminium stubs and coated with gold in HUS-5GB vacuum evaporator, to render it electrically conductive. Encapsulation efficiency was calculated using the formula, Encapsulation efficiency= (estimated percent drug content/theoretical percent drug content)×100.

3.2 Estimation Of Rifampicin

Rifampicin content in the microcapsules was estimated by using UV spectrophotometer method. A quantity of microcapsules equivalent to 100 mg were powdered and transferred into a 100 ml volumetric flask, sufficient amount of methanol was added to produce 100 ml, shaken for 20 min and filtered. Two milliliters of the filtrate was diluted to 100 ml with phosphate buffer (pH 7.4) and HCl buffer (pH 1.2) containing ascorbic acid (200 µg/ml) and the drug content was analyzed at 475 nm. Three determinations were carried out for each fraction.

3.3 *INVITRO* STUDIES

3.3.1 MUCOADHESIVE STUDY OF MICROCAPSULES

The mucoadhesive property of the microcapsules was evaluated by an *in vitro* adhesion testing method known as the wash-off method. Freshly excised pieces of intestinal mucosa (2 × 2 cm) from sheep were mounted onto glass slides (3 × 1inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread onto each wet rinsed tissue specimen, and immediately thereafter the support was hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given a slow, regular up-and-down movement in the test fluid at 37°C contained in a 1 L vessel of the machine. At the end of 30 minutes, at the end of 1 hour, and at hourly intervals up to 12 hours, the machine was stopped and the number of microcapsules still adhering to the tissue was counted. The test was performed at both gastric pH (0.1N HCl, pH 1.2) and intestinal pH (phosphate buffer, pH 7.4).

3.3.2 DISSOLUTION STUDIES

Dissolution studies were carried out using USP XXIII rotating basket method. The stirring rate was 75 rpm. 900 ml of pH 7.4 phosphate buffer having ascorbic acid (200 µg/ml) was used as dissolution medium and maintained at 37±1°. Samples of 5 ml each were withdrawn at regular time intervals, filtered, diluted suitably, analyzed using double beam UV spectrophotometer at 475 nm and an equal volume of fresh medium was immediately added to maintain the dissolution volume. Dissolution studies were carried out up to 100% release of the drug. The drug release experiments were conducted in triplicate.

IR studies (not shown) indicated that the qualitative composition of the drug formulation and verified the identity of each of the components. No drug interaction or complexation occurred during the manufacturing process.

IV. RESULTS AND DISCUSSION

A standard calibration curve for the drug was obtained by measuring absorbance at 475nm, and by plotting the graph of absorbance V/s concentration in triplicate pH 1.2, pH 7.4 between 2 to 10 µg/ml concentrations. Estimation of drug content and *in-vitro* drug release studies are based on this standard curve.

The particle size distribution of all the formulations were determined and the Mean average particle size of rifampicin mucoadhesive microcapsules as showm in table no.1 was found to be in the range of 780 to 882µm.

Table no.1 Average particle size of microcapsules

Sl no.	FORMULATIONS	Mean particle size(µm)
1	F1	792
2	F2	780
3	F3	840
4	F4	832
5	F5	840
6	F6	865
7	F7	882
8	F8	810
9	F9	800
10	F10	840
11	F11	825

The drug entrapment efficiency of all the formulations were in the range between 75% to 88%. Drug entrapment efficiency of microparticles increases with increase in concentration of Sodium cmc and chitosan.

The percentage encapsulation yield of the formulations are given in table no.2 shows percentage yield from 67 to 72%.

Table no.2 Encapsulation yield of all formulations

Formulations	% percentage yield
F1	67±0.65
F2	68.5±0.79
F3	69.4±0.87
F4	70.11±1.01
F5	72.3±0.45
F6	73.2±0.73
F7	71±0.91
F8	72.09±0.82
F9	71.43±1.1
F10	70.64±0.71
F11	71.92±0.96

The swelling ratio of microcapsules were determined was higher in pH 7.4 than pH 1.2. among the all formulations, the chitosan alginate microcapsules are having the low swelling indices.

In vitro wash –off test was conducted to assess mucoadhesive properties of prepared microcapsules. Mucoadhesion test was carried out with everted sheep intestinal sac in the presence of pH 1.2 and pH 7.4. The wash–off was faster at intestinal pH than at gastric pH. The rapid wash-off observed at intestinal pH was due to ionization of carboxyl and other functional groups in the polymers at this pH. The results of the wash-off test indicated that the microcapsules had fairly good mucoadhesive property.

4.1 *INVITRO* DISSOLUTION STUDIES

Dissolution studies of all the formulations were carried out using dissolution tester USP XXIII.The dissolution studies were conducted by using two different dissolution medias, pH 1.2 & pH 7.4.
Formulations F1, F2, F3 containing drug and sodium alginate polymer in different ratios i.e, 1:1, 1:2, 1:3 have shown drug release of 100%, 99.99% &100% in 25, 26 & 27hrs respectively as shown in fig no.1. This shows that more sustained release was observed with increase in percentage of sodium alginate.

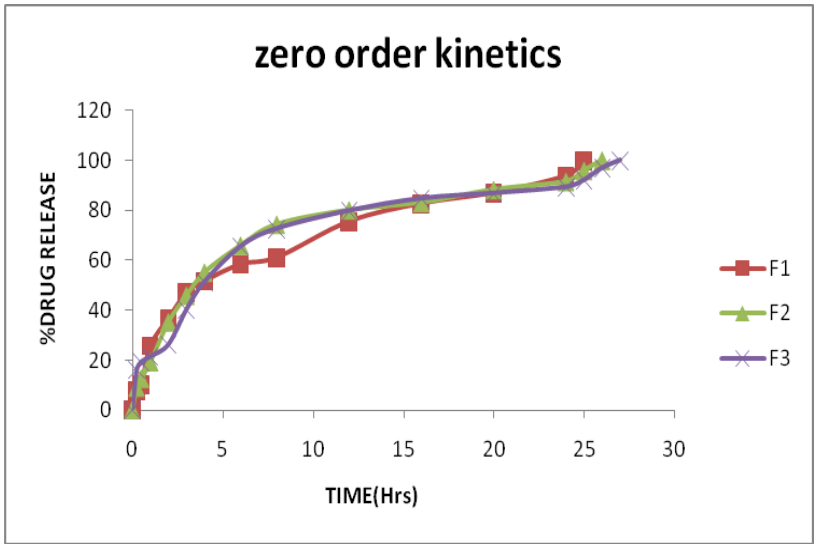

Fig no.1 Zero order kinetics for F1,F2,F3

In formulations F4, F5, F6, F7 containing sodium alginate and sodium cmc in ratios 1:1:1, 1:1:2, 1:2:1, 1:2:2 the drug released completely in 26, 28, 28,30hrs of time period shown in fig no.2. This shows that the release rate is retarted.

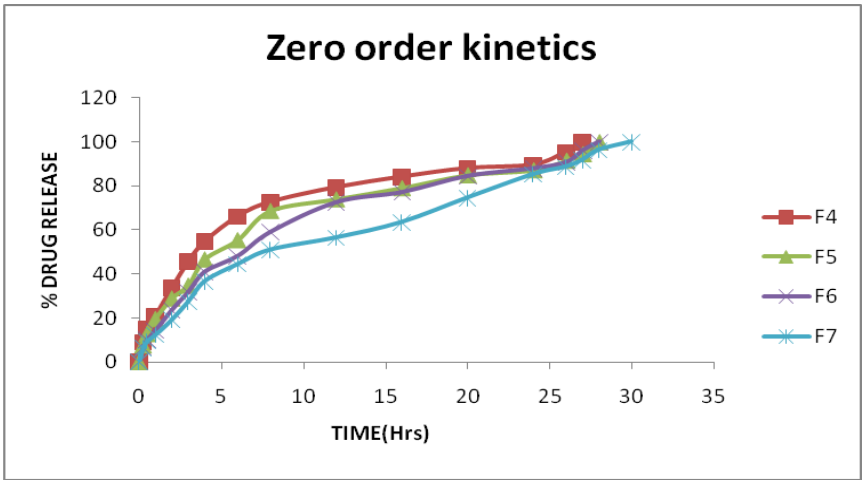

Fig no.2 Zero order kinetics for F4,F5,F6,F7

Similarly the time period was further increased when chitosan was replaced to sodium cmc following same ratios. For formulation F11 it took 46hrs for complete release of the drug and for F10, F9, F8 the time period was 44, 43&41 hrs as shown in fig no.3. This indicates that the release rate time period was further increased with the addition and increase in concentration of chitosan because of strong bonds between chitosan and sodium alginate.

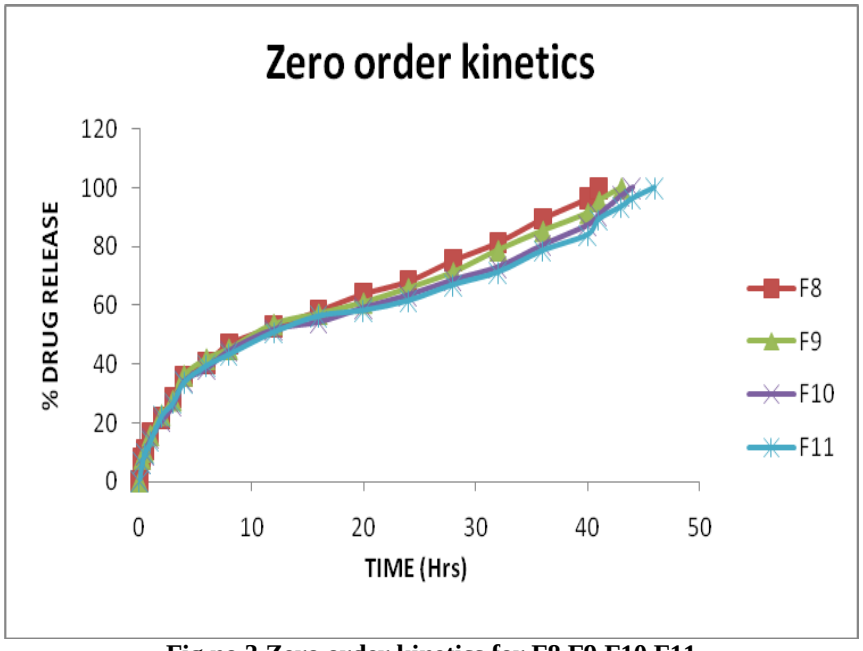

Fig no.3 Zero order kinetics for F8,F9,F10,F11

The highest time period taken by the optimized formulation F11 which is about 46 hrs for complete drug release.Further these drug releases were subjected for mathematical treatment to check whether it is following first order or zero order. Based on the co-efficient of correlation (r) values in table no.3 it was observed that the drug release is following zero order kinetics.

The plots of amount of drug released *vs* square root of time were found to be linear indicating that the drug release mechanism is **diffusion controlled**. In the present system, based on the calculated values rifampicin follows **non-fickian transport and zero order kinetics**.

Table no.3 Calculated values of various kinetic models

Formulations	Zero order	First order	Higuchi	Peppas
F1	**r=0.806**	**r=0.834**	**r=0.947**	**r=0.851 n=0.590**
F2	**r=0.834**	**r=0.843**	**r=0.954**	**r=0.862 n=0.653**
F3	**r=0.847**	**r=0.913**	**r=0.970**	**r=0.871 n=0.673**
F4	**r=0.865**	**r=0.853**	**r=0.947**	**r=0.860 n=0.599**
F5	**r=0.874**	**r=0.856**	**r=0.973**	**r=0.863 n=0.607**
F6	**r=0.909**	**r=0.858**	**r=0.989**	**r=0.872 n=0.635**
F7	**r=0.945**	**r=0.923**	**r=0.992**	**r=0.875 n=0.650**
F8	**r=0.935**	**r=0.920**	**r=0.983**	**r=0.870 n=0.600**
F9	**r=0.954**	**r=0.934**	**r=0.984**	**r=0.877 n=0.675**
F10	**r=0.968**	**r=0.930**	**r=0.987**	**r=0.878 n=0.690**
F11	**r=0.989**	**r=0.951**	**r=0.991**	**r=0.921 n=0.697**

V. CONCLUSION

Mucoadhesive microcapsules of rifampicin were formulated by ionotropic gelation technique using sodium alginate, sodium cmc & chitosan. The IR spectras revealed that, there was no interaction between polymers and drug. All the polymers used were compatible with the drug. From the study it is evident that a promising controlled release microcapsules drug delivery of rifampicin can be developed. Further *in-vivo* investigation required to establish efficacy of these formulations.The study also indicated that the time required for drug release increases with an increase in the polymer concentration.

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