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EVALUATION OF THE EFFECT OF HYDROPHILIC POLYMER BLEND TO EXTEND THE RELEASE OF CLARITHROMYCIN FROM PREPARED MICROCAPSULES

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Abstract:
Whether the control of oral absorption is desired or the delivery of genes to the interior of specific cellsis sought the drug delivery macromolecule has emerged the most ubiquitous entity. In the current volume, macromolecules and their "younger (and sometimes smaller) cousins," dendrimers, are presented as components extraordinaire of a variety of drug delivery systems. The therapeutic effect of drugs that have a short biological half-life may be enhanced by formulating them as extended- or sustained-release dosage forms. Extended- and sustained-release dosage forms prolong the time that systemic drug levels are within the therapeutic range and, thus, reduce the number of doses the patient must take to maintain a therapeutic effect, thereby increasing compliance.Here in y research work the different polymer blend of sodium alginate ,methyl cellulose and hydroxypropyl methylcellulose has been used for preparation of the clarithromycin microcapsules.

Key Words: *Hydrophilic polyer, Clarithromycin, Microcapsulation, Extended release etc.*

1. INTRODUCTION:

The science of drug delivery may be described as the application of chemical and biological principles to control the *in vivo* temporal and spatial location of drug molecules for clinical benefit. When drugs are administered, only a very small fraction of the dose actually hits the relevant receptors or sites of action, and most of the dose is actually wasted either by being taken up into the "wrong" tissue, removed from the "right" tissue too quickly, or destroyed en route before arrival. Scientists researching drug delivery seek to address these issues in order to maximize drug activity and minimize side effects . Drug delivery[1] is becoming an extremely demanding science. The reasons are essentially threefold: (a) the emergence of the more challenging low-molecular-weight molecules and biomacromolecules[13] with either poor aqueous solubility, poor tissue permeation, or both, (b) the increased use of biological materials with poorly understood physical properties or questionable shelf life issues, and (c) the realization that if the portion of the dose responsible for adverse events could be directed away from sites where they originate, toxic side effects would become less frequent, thus benefiting the therapeutic index.

Today's world requires that drug delivery systems be precise in their control of drug distribution and, preferably, respond directly to the local environment of the pathology in order to achieve a dynamic and beneficial interaction with the host pathology or physiology.

1.1 POLYMERS IN DRUG DELIVERY

Whether the control of oral absorption is desired or the delivery of genes to the interior of specific cells is sought the drug delivery macromolecule has emerged the most ubiquitous entity. In the current volume, macromolecules and their "younger (and sometimes smaller) cousins," dendrimers[12,14], are presented as components extraordinaire of a variety of drug delivery systems[10,11]. Scientific reports are peppered with polymer- or dendrimer-containing systems that:

1. Prolong drug action by entrapping the drug within matrices
2. Shift drug distribution in the direction of tumors
3. Shunt therapeutic genes or oligonucleotides into cells

1.2 MODIFIED-RELEASE DOSAGE FORMS

It is now generally accepted that, for many therapeutic agents, drug delivery using immediate release dosage forms results in suboptimal therapy and/or systemic side effects. Pharmaceutical scientists have attempted to overcome the limitations of conventional oral dosage forms by developing modified-release dosage forms. With regard to oral drug delivery, modified release can be described as an alteration in the site or timing of drug release within the gastrointestinal tract, and can be further divided into extended release and delayed release.

1.3 EXTENDED RELEASE DOSAGE FORMS

The therapeutic effect of drugs that have a short biological half-life may be enhanced by formulating them as extended- or sustained-release dosage forms. Extended- and sustained-release [18,19]dosage forms prolong the time that systemic drug levels are within the therapeutic range and, thus, reduce the number of doses the patient must take to maintain a therapeutic effect, thereby increasing compliance. Drugs with a narrow therapeutic index are also suitable for incorporation into an extended release dosage form, where the peaks associated with Cmax can often be dampened, reducing the possibility of systemic side effects occurring when drug levels in blood exceed the minimum toxic concentration. Unlike an immediate-release dosage form, where disintegration and drug release occurs rapidly in the stomach, extended-release formulations release the drug gradually as the dosage moves along the gastrointestinal tract. Extended-release dosage forms are commonly proposed as a formulation tool for achieving zero-order drug release; however, zero order release *in Vitro* rarely translates to constant drug absorbance and drug blood levels *in vivo* because of the heterogeneous composition of, and transit rate through, the gastrointestinal tract Single-unit hydrophilic matrix tablets composed of high-viscosity HPMC have also been proposed as extended-release formulations; these tablets are capable of swelling upon contact with the gastrointestinal fluid and releasing the drug over a prolonged period of time. This concept has been extended and applied to the versatile Geomatrix tablet.

1.4 Micro-encapsulation: is a process in which tiny particles or droplets are surrounded by a coating to give small capsules many useful properties. In a relatively simplistic form, a microcapsule[2,3,4] is a small sphere with a uniform wall around it. The material inside the microcapsule[5;6] is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters.

2. Materials and method of preparation :

2.1 Materials : Clarithromycin was supplied as a gift sample (sun Pharma advanced Research centre (Vadadora) Sodium Alginate, Procured from Central drug house, New Delhi, Methyl cellulose, Procured from Central drug house, New Delhi, Hydroxy propyl methyl cellulose, Procured from Central drug house, New Delhi.

2.2 Method of preparation of microcapsules and tabletted microcapsules:

2.2.1. Method of preparation of Microcapsules:

Method of preparation:

The alginate microcapsules[12,14] were prepared by employing the sodium alginate in combination with the two hydrophilic, polymers-methyl cellulose and hydroxypropyl methyl cellulose. These polymers are suitable for taste masking as a coat materials, that is used for the preparation of the alginate microcapsules. (Chowdary et al., 2003.)

In this method sodium alginate and the other polymers like methyl cellulose & hydroxylpropylmethyl cellulose in 3%,4%,5% & 6% solution is prepared by dissolving the to weighed polymer in 45 ml of purified water and the viscous solution is prepared the separate 300mg clarithromycin is dissolved in 5ml of purified water and dispersed and add few drops of glacial acetic acid for preparation of clear dissolved drug solution. This drug added to the above polymer solution

and mixed well. The resulting dispersion of drug-polymer solution was added manually drop wise into the 6% (w/v) calcium chloride solution through a syringe with a needle of size of 26. The added droplets were retained in the calcium chloride solution for 20 minute to complete curing reaction and after completion of rigidition the spherical rigid microcapsule obtained. Microcapsules[7,8,9] were separated or decanted and washed with the n-hexane repeatedly and then dried at 40°C for 12hrs. The microcapsules along with their composition, is listed in Table 1,2 and 3.

2.2.2 Particle Size Measurement:

The microcapsules size was measured by optical microscopy. The eye piece micrometer and stage micrometer were calibrated and the microcapsules of different formulation were evaluated. The determination was done for at least 300 microcapsules.

2.2. 3. Drug Incorporation Efficiency:

The drug loaded microcapsules (100 mg) were washed with phosphate buffer and then microcapsules were kept into the phosphate buffer (pH-7.4) (100 ml.) for 24 hours and sonicate for 1hrs. at room temperature to break the microcapsule completely and also to facilitate the drug extraction. The solution was centrifuged at 1000 g for 10 minutes to remove the polymeric debris. The clear supernatant solute-ion was analyzed for the clarithromycin content at the λ max value of 203 nm. The % in corporation efficiency were calculated as follows.

$$\% \text{ Incorporation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretic drug content}} \times 100$$

2.2.4. Identification By F.T.I.R.:

FTIR spectrophotometry of drug was done and the spectral assignment confirm that the drug was clarithromycin. So the FTIR spectra were done by FTIR spectrop-hotometry.

2.2.5. SEM test: SEM photograph were obtained to examines shape and surface morphology of microcapsules. The microcapsules were dusted onto double sided tape on an copper stub, which were coated with gold by a sputter coated. Then the sample were imaged.

Table. 1 Composition of formulations MCF1 to MCF4

Microcapsules formulations code No.	Polymer Blend solution used (% w/v)	Polymer Blend Composition	
		Sodium alginate (mg)	Methyl cellulose (mg.)
MCF1	3%	1050	450
MCF2	4%	1400	600
MCF3	5%	1750	750
MCF4	6%	2100	900

Table: 2. Composition of formulations MCF5 to MCF8

Microcapsules formulations code No.	Polymer Blend solution used (% w/v)	Polymer Blend Composition	
		Sodium alginate (mg)	Hydroxy propyl Methyl cellulose (mg.)
MCF5	3%	1050	450
MCF6	4%	1400	600
MCF7	5%	1750	750
MCF8	6%	2100	900

Table :3 Composition of formulations MCF9 to MCF12

Micro capsules formulations code No.	Polymer Blend solution used (% w/v)	Polymer Blend Composition		
		Sodium alginate (mg)	Methyl cellulose (mg.)	Hydroxy propyl Methyl cellulose (mg.)
MCF9	3%	1050	225	225
MCF10	4%	1400	300	300
MCF11	5%	1750	375	375
MCF12	6%	2100	450	450

2.2.6.*In-Vitro* drug release of Microcapsules:

Procedure of *In-Vitro* release of Microcapsules:

Dissolution experiments were performed using a dissolution appa-ratus (USP II) with 75 rpm maintained paddle rotational speed was used in studies. The temperature was maintained at constant temperature 37°C. Drug release studies for microcapsules were performed in 900 ml. of simulated gastric fluid

Table 4 : Characterization of Formulation & Evaluation:
Result of % incorporation efficiency and mean size of microca-psules:

Formulation Code	Polymer Concentration (% w/v)	% incorporation efficiency (% ± S.D)	Mean particle Size µm ± S.D	Cross linking agent (%w/v)	Time for cross linking (minutes)	% yield (%) ± S.D.
MCF1	3%	61.95 ± 1.59	307.23 ± 4.2	6%	20	97.77 ± 0.35
MCF2	4%	62.81 ± 2.00	428.26 ± 1.6	6%	20	95.65 ± 1.5
MCF3	5%	61.48 ± 2.311	506.73 ± 4.2	6%	20	91.07 ± 2.0
MCF4	6%	68.425 ± 2.7	601.16 ± 2.6	6%	20	90.15 ± 1.5
MCF5	3%	61.78 ± 1.49	295.26 ± 5.6	6%	20	91.66 ± 2.1
MCF6	4%	59.51 ± 2.05	428.26 ± 1.6	6%	20	98.26 ± 2.55
MCF7	5%	65.09 ± 2.44	516.04 ± 3.6	6%	20	96.42 ± 1.03
MCF8	6%	63.36 ± 2.76	610.47 ± 4.2	6%	20	92.42 ± 0.44
MCF9	3%	65.52 ± 1.58	316.54 ± 5.2	6%	20	97.22 ± 1.33
MCF10	4%	67.4 ± 1.98	426.93 ± 4.2	6%	20	95.21 ± 0.68
MCF11	5%	67.94 ± 2.45	508.06 ± 3.6	6%	20	96.21 ± 1.58
MCF12	6%	68.94 ± 3.26	599.83 ± 4.2	6%	20	95.45 ± 2.13

(pH:1.2) initially for two hours and followed by 900ml. of pH 7.4 phosphate buffer solution. These two dissolution media were used for dissolution studies. First SGF (pH-1.2) used for 2 hrs. and phosphate buffer solution (pH 7.4) is replaced with SGF and dissolution is performed for remaining 8 hours. The 5 ml of sample is withdrawn from the dissolution bowl and replaced with 5ml of fresh dissolution media to maintain the sink condition at interval of one hours. It is performed for the10 hours. The withdrawl sample is analyzed for the clarithromycin concentration spectrophotometrically by U.V., at 213 nm, λ_{max}. In the case of microcapsules[15,16,17] evaluation, first microcapsules (100mg.) is taken in muslin cloth and tied with thread and is hang with paddle and placed in dissolution bowl and performed for 10hrs. These studied were performed in triplicate for each sample and average values were considered for data analysis.

3. Result and discussion:

3.1: Characterization of microcapsules: The present study deals with the production of microcapsules by orifice-ionic-gelation technique by cross linking with the $CaCl_2$ solution. Microcapsules of clarithromycin with a coat consisting of sodium alginate and some other hydrophilic polymers such as methylcellulose, and hydroxypropyl methyl cellulose in different concentration were prepared. The microcapsules were found to be discreate, spherical, free flowing and the monolithic matrix type. The microcapsules were uniform in size with mean size ranging from the 295.26 µm to 610.47 µm of all the four different polymer concentration formulations.

3.2 : Spectral Studies: In FTIR study of clarithromycin C=O (ketone carbonyl) stretching is at 1691 cm-1, lactone carbonyl at 1733 cm^{-1} , N-CH3 at 1460 cm-1, C-O-C stretching at 1051 cm-1, and CH2 group at 1379 cm-1.In case of clarithromycin ,S.A., M.C., H.P.M.C. mixture study FTIR shows C-O stretching at 1107 cm-1, CH3-O-CH3 bending at 2877 cm-1, C-C stretching at 1051 cm-1, lactone carbonyl at 1733 cm-1, N-CH3 stretching at 1458 cm-1, aromatic C-OH stretching at 3450 cm-1, and C-O-C stretching at 1170 cm-1 is there.

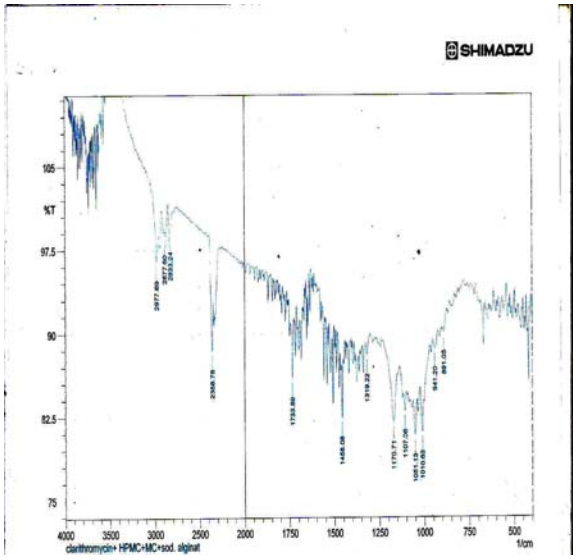

Fig. 1 FTIR Spectra of Clarithromycin, HPMC, MC and sodium alginate

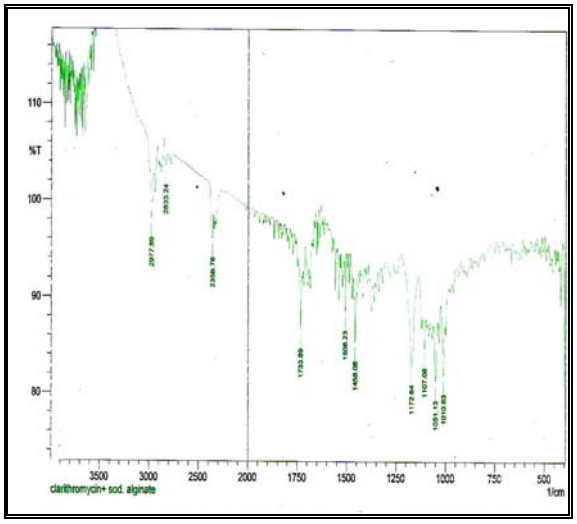

Fig: 2. FTIR Spectra of Clarithromycin and Sodium alginate.

3.3: Scanning electron microscopic studies:

Shape and surface characteristics of the microcapsules formula-tion coded as MCF1 to MCF4 (SA+MC) and MCF12 were characterized and SEM figure is given. Drug loaded alginate microcapsules are sphere-ical and no drug crystals were found on the surface. The microcapsules prepared containing higher amount of polymer concentration (6%) with respect to constant drug amount, exhibited smoother surface than those prepared by taking the lower amount of polymer concentrations.

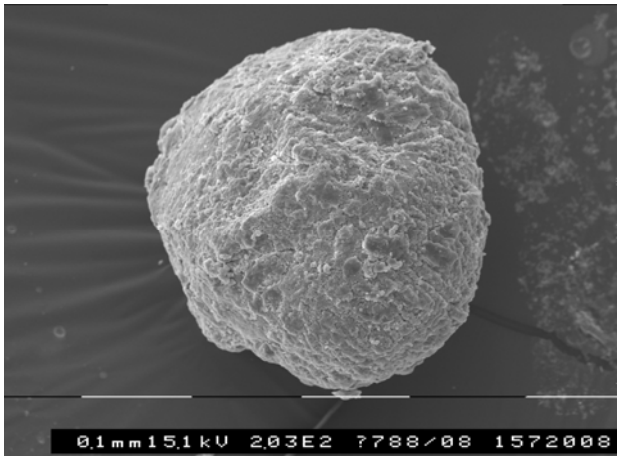

Fig. 3. SEM image of microcapsule (MCF1) shape & size (310.6 µm)

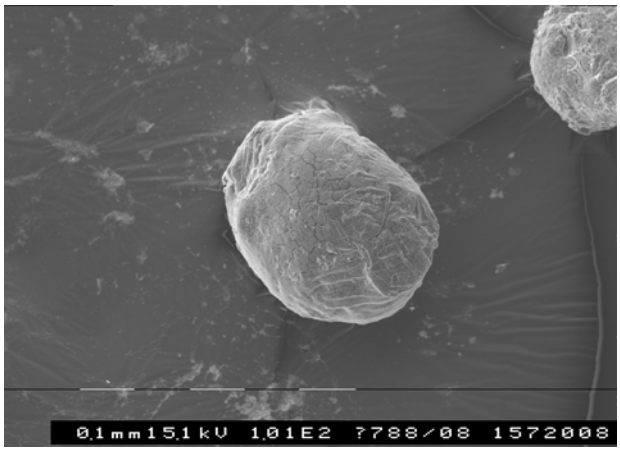

Fig. 4. SEM image of microcapsule (MCF2) shape & size (400 µm)

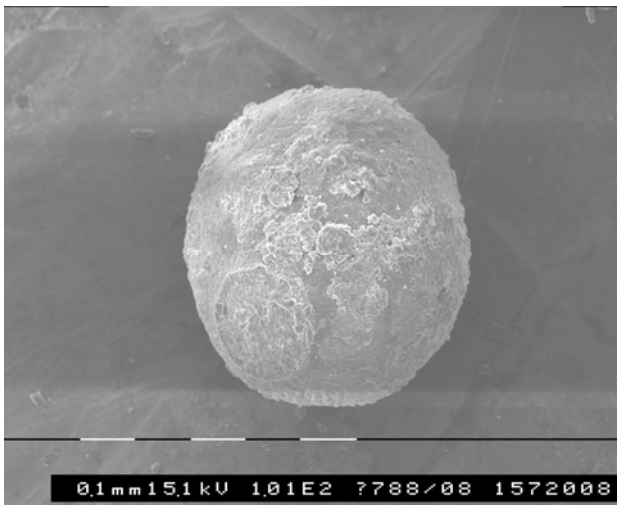

Fig. 5. SEM image of microcapsule (MCF3) shape & size (502 µm)

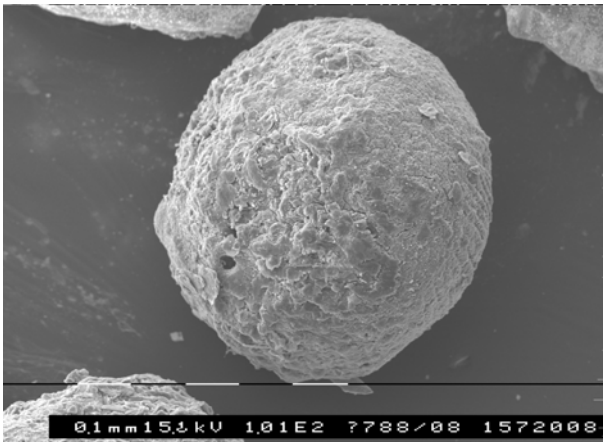

Fig. 6. SEM image of microcapsule (MCF4) shape & size (606 µm)

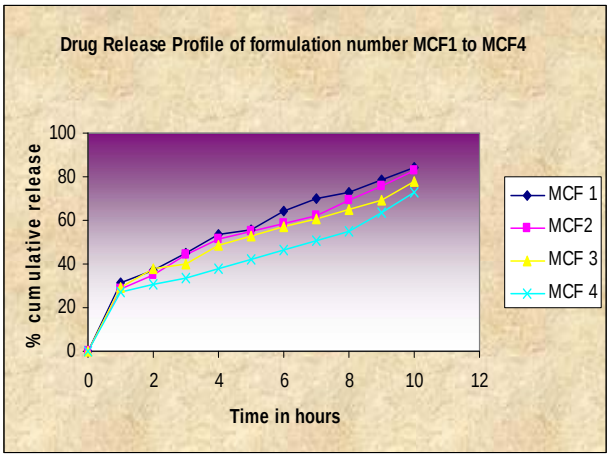

Fig.9. *In- vitro* Drug Release Profile of formulation number MCF1 to MCF4.

Fig. 7. SEM image of microcapsule (MCF12) shape & size (600 µm)

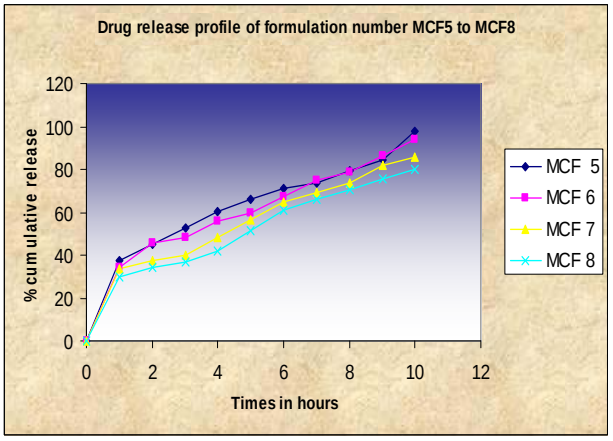

Fig: 10. *In-vitro* drug release profile of formulation number MCF5 to MCF8

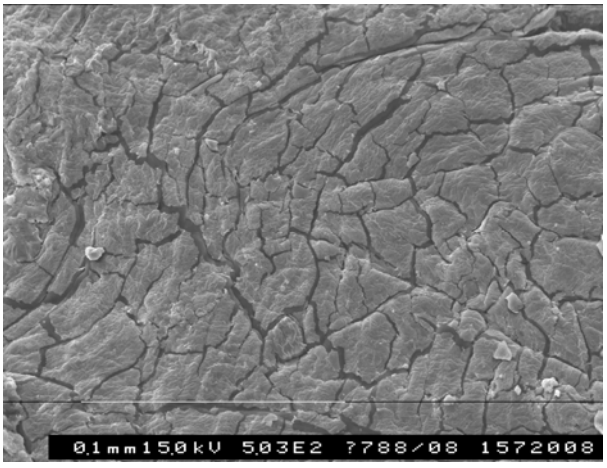

Fig. 8. SEM image of microcapsule (MCF4) surface characterization

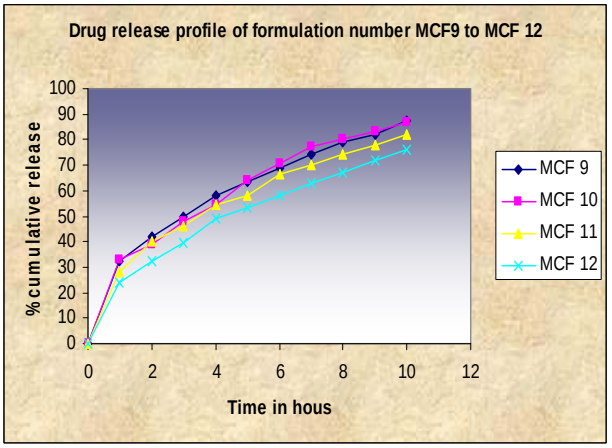

Fig.11. *In-vitro* drug release profile of formulation number MCF9 to MCF 12

3.4 : *In- vitro* release study: In all formulation MCF1to MCF12 of this study the release rates were extended and sustained release formulation were prepared. The dissolution test was performed for 10 hours. Drug release rate from different formulation were evaluated. The figure shows that, as the polymer ratio is increased %ge release rate of drug from microcapsules are decreased due to the decreased dissolution rate. If the dissolution is decreased, the release rate is also decreased. In my formulated microcapsules, MCF1 has only 3% W/V polymer blend used and drug was 300 mg, But when the polymer ratio is increased up to 4,5 & 6 % w/v the release rate of drug from formulated microcapsules was decreased corresponding to increasing polymer ratio from 3% to 6% in comparision to the pure powdered drug release. .Order with increasing release rates can be given as :

S.A.+M.C. < S.A.+M.C. +H.P.M.C. < S.A.+H.P.M.C.

The S.A. and M.C. polymer blend show reduced drug release in compare to other polymer blends.

4. SUMMARY & CONCLUSION

Polymer blend can be used effciently to extend the release of the drug fro the polymer matrx. Here in the research work the polymer blend of sodium alignate, hydroxy propyl methyl cellulose and methyl cellulose has been used to prepare the mcrocapsules of clarthromycn.Microencapsulation is the best technique to sustain the release of the drug. In this investigation the taste masking was done by microencapsulation technique and sustained release of the drug was also obtained. The orifice ionic gelation technique was used to prepare micro-capsules by using different polymer blend concentration. FTIR confirmed cross linking reaction. Clarithromycin was successfully entrapped into polymer matrix and was stable in matrix, developed without undergoing any chemical changes during microcapsules preparation. Microcapsules were spherical but there morphologies were affected by amount of polymers used in the formulation. The microcapsules were able to sustan the release of clarithromycin up to maximum, depending on the concentration of polymer blend used. In-vitro release test was also performed for determination of ability of different formulated microcapsules to extend the release of the clarthromycn. Evaluation studies indicated that, release of clarithromycin can be extended successfully by the microencapsulation method usng the dfferent polymer blend. The release of drug from microcapsules showed a dependence on the amount of polymer blend used, extent of cross linking of the matrix as well as amount of drug loading. Here the Order with increasing release rates can be given as :

S.A.+M.C.<S.A.+M.C.+H.P.M.C.< S.A.+H.P.M.C.

The S.A. and M.C. polymer blend show reduced drug release in comparsion to other polymer blend of H.P.M.C. ,M.C. and S.A. and S.A. and H.P.M.C.. So t is clear that the odiu alginate and methyl cellulose polyer blend successfully controlled and extended the release of carithromycin from microcapsules n comparison of the other polymer blend microcapsule formulations. Fnally t is clear that hydrophlc polymer blens shows a good result in controlling the release of the drug depending on the concentraton of the polymer used.

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