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Formulation and Evaluation of Mupirocin Encapsulated Sodium Alginate Microspheres for Controlled Release Drug Delivery

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ABSTRACT

The primary objective of the present study formulates and evaluates a controlled drug delivery system by release the drug with predetermined lag time. The basic design of the Mupirocin encapsulated formulation provides time controlled release to treat the antibiotic and skin infections. In the present study we are selected natural polymer like (sodium alginate) for improving the solubility and time controlled release of Mupirocin. Microspheres (prescribed extensively in solid dosage forms) in a controlled release form to overcome drug resistance, and dosing non-compliance in patients. Mupirocin is used as a topical antibiotic ointment belonging to treat bacterial skin infections. The objective of this work is to develop biodegradable microspheres for controlled release topical drug delivery using mupirocin as a model drug, sodium alginate as a carrier polymer, sunflower oil as oil phase, span80 and tween80 act as a emulsifying agents, calcium chloride as a cross linking agent. The controlled release microspheres are to be prepared using different combinations of oil, emulsifiers, co-surfactant, stirring speed, and drug polymer ratio. The optimized formulation is subjected for evaluation of the *in-vitro* drug release of F20 formulation 83.07% shows better drug release for 8 hrs. The controlled release microspheres, a conclusion can be drawn on its quality and performance for stability studies.

Keywords: Mupirocin, Sodium alginate, *In vitro* drug release, Microspheres.

INTRODUCTION

Novel drug delivery systems evolved over a period of time to improve the patient compliance and perfect the therapeutic efficacy. These foundation were laid in 1952, with the introduction of first sustained release capsule of dextrin (Chess R, 1998). Micro indicates particle size from 1µm to 1000µm, spheres means spherical particles. Controlled drug delivery system is able to control the drug concentration within the target tissues, it deliver a drug in target site in specified time period in other words says therapeutic control of active medicament temporal nature or special nature. The goal in designing controlled release delivery system is to reduce the frequency of dosing and to increase effectiveness of the drug by assuming uniform delivery at the specific site of action. Ideal controlled delivery formulation should obtain these two ideal characteristics these are Single dose for entire treatment, it should deliver a medicament at the site of action (Theodore J, 1997).

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system (Bhatt Preeti and Gnanaranjan G, 2013). The topical drug delivery system such as microspheres (O/W emulsion) generally used where the other systems of drug administration fails to directly treat cutaneous disorders such as fungal infections, acne, psoriasis etc. Since the mid 1980's, these emulsion have been of growing importance in the field of pharmaceutical semisolid dosage forms. Skin is one of the most readily accessible parts of human body for topical administration and molecules penetrate in the skin mainly by three routes through intact stratum corneum, through sweat ducts, and through the sebaceous follicle. In cosmetics, such as hydrophilic systems have already been known for a longer period and their wide utilization as pharmaceutical dosage form comes from the wide utilization as pharmaceutical dosage form comes from wide utilization of emulsions systems particularly for dermatological formulae (Amsden B, 1999).

Microspheres are defined as small spherical particles, with diameter ranges from 1µm to 1000µm (1 mm). It is a monolithic spherical structure with drugs or

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active principle ingredient distributed throughout the matrix either as molecular dispersion or as dispersion of particles. Microsphere are characteristically free flowing powders consisting of protein or synthetic polymer, which are biodegradable in nature and ideally having a particle size less than 200µm. This is the important approach in delivering therapeutic substances to the target site in sustained and controlled release (Lachman *et al*., 1991).

Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hallow microspheres vary widely in density and, therefore, are used for different applications. Hallow microspheres are typically used as additives to lower the density of a material (Sankar V *et al*., 2012).

MATERIALS AND METHODS

Materials

Mupirocin was obtained as a gift sample, Sodium Alginate were supplied by Himedia, Sun Flower, Tween-80, Span-80, Methanol, N-Hexane, Acetone, 2-Propanol, Hydrochloric Acid, Potassium Di Hydrogen Phosphate, Sodium Hydrogen, Di Sodium Hydrogen Phosphate. All solvents used were of analytical grades and were used as obtained.

Preparation of Mupirocin microspheres

Preparation of microspheres by emulsification method

The required amount of drug and polymer were weighed accurately and dissolved in 25ml of water: ethanol (3:1). The surfactant (span80-1%) was added to the 200ml of oil (external phase) at 60^0c.the aqueous phase was emulsified into oil phase by stirring the system the system in a 500ml beaker at 200rpm using mechanical stirrer for 2hrs.until the aqueous phase was completely removed and evaporation, The light oil was decanted and collected microspheres were washed three times with 100ml liquid of n-hexane. Filtered through what man filter paper. Dried in an oven at 50^0c. For 2hrs and stored at a room temperature. (5% cross linking agent 10ml calcium chloride ($cacl_2$)).

A solution of calcium chloride ($cacl_2$) 5% w/v in IPA) was added drop wise to the emulsion to rigidize the formed microspheres and stirring was continued for another 20mins. To ensure efficient cross linking. (Note: petroleum ether can be used for washing).

Characterization of microspheres

Drug –Excipient compatibility studies by FTIR

The Excipients play an important role in the stability of formulation. FT-IR spectra determine the positions relative sizes of all the absorptions, or peaks, in the IR region. This is used to access the possible chemical interactions between the drug and other Excipients in the formulation.

Method: Compatibility study was performed by preparing compatibility blends at difference ratios of different Excipients with the drug, based on tentative average weight. In the present study, the potassium bromide disc (pellet) method was employed. Chemical stability was confirmed by IR spectrometry. The Excipients compatibility of Mupirocin was checked with Excipients like Sodium alginate and calcium chloride.

Particle size analysis (Patel Samirkumar *et al*., 2013)

It is performed by using ordinary microscope. The microscope is first calibrated with a stage micrometer. Then the microspheres were mounted on a slide using glycerine and the average particle size is determined by using eye piece micrometer. Then the average particle size is obtained by multiplying the obtained value with calibration factor. From that the average size frequency distributed curve is drawn by plotting the range on X-axis and number of particles on Y-axis.

***In vitro* drug release study** (Bunty Chanu Irom *et al*., 2012)

In-vitro release profile of Mupirocin from the microspheres was examined in 0.1N Hcl (pH 1.2) using USP (XXI) six stage dissolution rate test apparatus (Electro lab TDT-08L). Microspheres equivalent to 100 mg of drug packed in filter paper and was suspended in dissolution medium at 50 rpm and 37 ± 0.5°C. An aliquot of 1 ml was withdrawn periodically at intervals of one hour and same volume of fresh medium was replaced. The samples were filtered through what man filter paper and analyzed spectrophotometrically at 220 nm for amount of drug released.

% Drug release:

$$\frac{\text{Cummulative drug dissolved}}{\text{Total amount of drug present in the microspheres}} \times 100$$

Scanning electron microscopy

Scanning electron microscopy is an excellent tool for physical observation of morphological features of microspheres. It is helpful to examine the shapes. The microspheres were sprinkled on to one side of adhesive stub. The stub was then coated with conductive gold with JOEL-JFC 1600 AUTO COATER and was examined under JOEL-JFC 6360 scanning electron microscope for qualitative assessment of morphology of microscope.

Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. The principles of accelerated stability studies are adopted.

ICH specifies the length of study and storage conditions.

Long Term Testing: 25^0 C ± 2^0 C / 60% RH ± 5% for 12 months

Accelerated Testing: 40^0 C ± 2^0 C / 75% RH ± 5% for 6 months

Stability studies were carried out at 40^0 C ± 2^0 C / 75% RH ± 5% for all the formulations for a period of 3 months.

The selected formulations were closely packed in amber colour bottles and then stored at 40^0 C ± 2^0 C / 75% RH ± 5% in stability chamber for 3 months and evaluated for their physical appearance, % Entrapment efficiency, drug release, particle size at intervals of 3 months. The shelf life period of the prepared microspheres is determined by using similarity factor.

Table.1 Formulation of microspheres

Formulation	Drug	Polymer	External phase	Internal phase	Speed (RPM)	Time (hrs)
1	-	1	200ml	25ml	2000	1
2	-	2	200ml	25ml	2000	1
3	-	4	200ml	25ml	2000	1
4	-	5	200ml	25ml	2000	1
5	-	10	200ml	25ml	2000	1
6	1	4	25ml	3.1ml	2000	1
7	1	4	50ml	6.2ml	2000	1
8	1	4	75ml	9.3ml	2000	1
9	1	4	100ml	12.4ml	2000	1
10	1	4	125ml	15.5ml	2000	1
11	1	4	100ml	12.4ml	1000	1
12	1	4	100ml	12.4ml	2000	1
13	**1**	4	100ml	12.4ml	3000	1
14	1	4	100ml	12.4ml	4000	1
15	1	4	100ml	12.4ml	5000	1
16	1	4	100ml	12.4ml	3000	1
17	1	4	100ml	12.4ml	3000	2
18	**1**	4	100ml	12.4ml	3000	3
19	1	4	100ml	12.4ml	3000	4
20	1	4	100ml	12.4ml	3000	5

RESULTS AND DISCUSSION

Table.2 Particle size

Formulations	Particle size	Shape	Remarks
F1	85-400 µm	Irregular	Irregular in shape
F2	80-370µm	Needle shape	Agglomeration
F3	90-480 µm	Round shape	Uniform size and shape
F4	95-560 µm	Not even in shape	Not even in size and shape
F5	110-625 µm		gel formation was observed during washing

Table.3 *In vitro* release studies in p^H 6.8

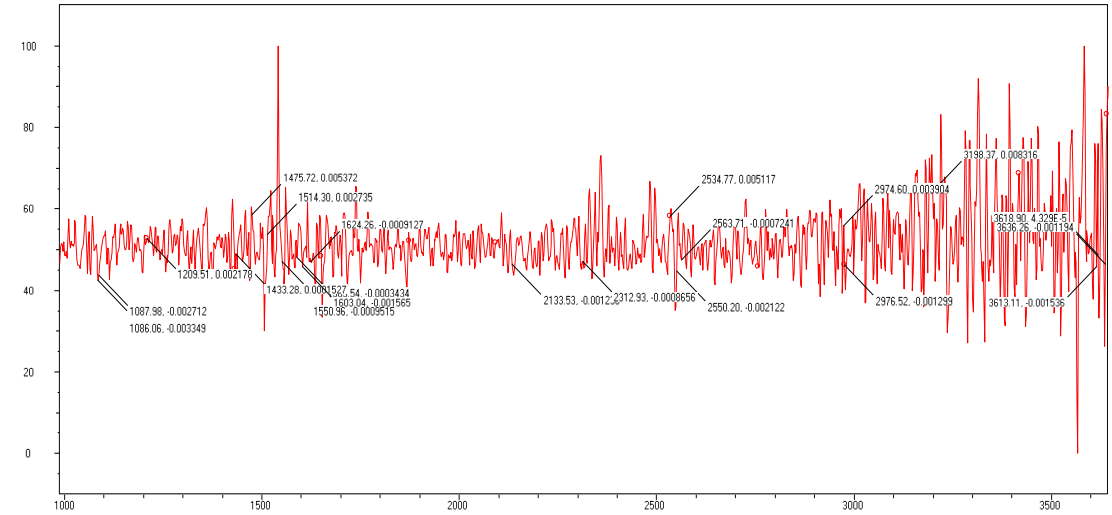
Time (hrs)	% cumulative amount of drug released from formulations				
	F16	F17	F18	F19	F20
0	0	0	0	0	0
30min	10.23±2.65	10.96±2.92	11.98±3.98	9.98±3.76	11.34±2.30
1	22.05±1.90	24.80±3.40	23.72±3.11	18.84±2.02	19.61±2.42
2	41.09±4.98	38.84±4.20	34.02±1.98	25.38±5.21	31.73±2.48
3	58.07±3.21	57.69±1.99	58.52±5.32	32.05±3.92	40.76±4.02
4	77.69±4.90	76.53±4.87	73.92±2.90	38.07±4.76	52.30±3.54
5	86.15±5.28	83.07±2.67	84.08±3.47	43.26±2.67	55.96±4.08
6				55.57±5.09	63.26±2.45
7				64.42±4.53	76.53±3.76
8				76.53±3.89	83.07±5.02

Table.4 Physical stability characterization of selected formulations

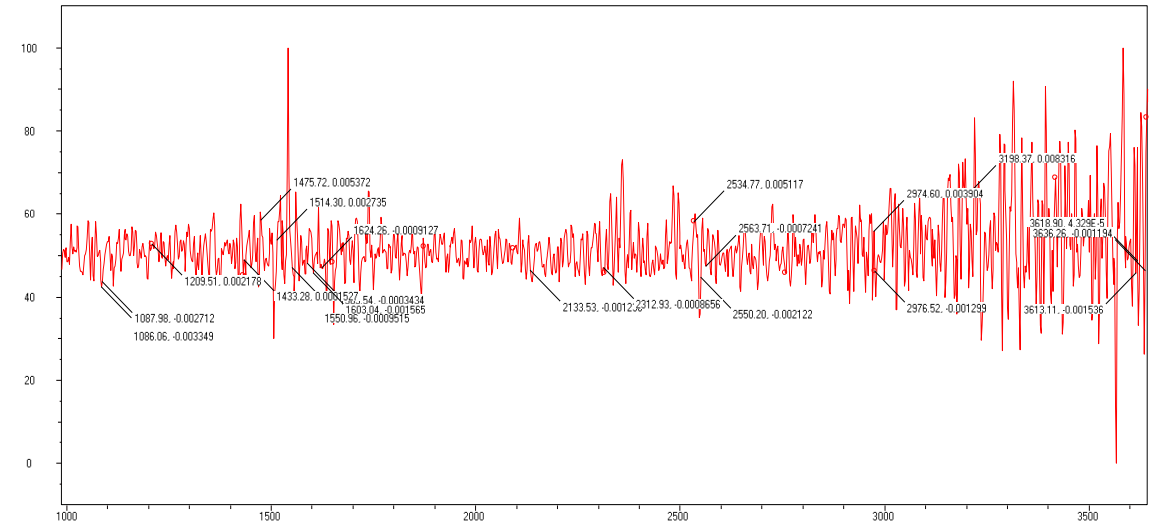
Evaluation parameter	Formulation code	1^{th} month	2^{th} month	3^{th} month
Entrapment efficiency (%)	F3	86.09 ± 0.98	85.72 ± 0.56	85.75 ± 0.67
	F9	73.12 ± 1.23	72.08 ± 1.24	72.20 ± 1.34
	F20	83.86 ± 2.32	83.82 ± 2.09	83.54 ± 1.98

Drug release	F3	74.98 ± 0.96	74.95 ± 0.69	74.59 ± 0.69
	F9	86.02 ± 1.23	86.12 ± 0.32	85.98 ± 1.23
	F20	83.08 ± 3.05	83.08 ± 0.75	83.17 ± 0.57
Particle size (µm)	F3	470 ± 0.22	469 ± 0.94	469 ± 0.89
	F9	215 ± 0.42	215 ± 0.91	214 ± 0.67
	F20	293 ± 0.09	293 ± 0.01	292 ± 0.08

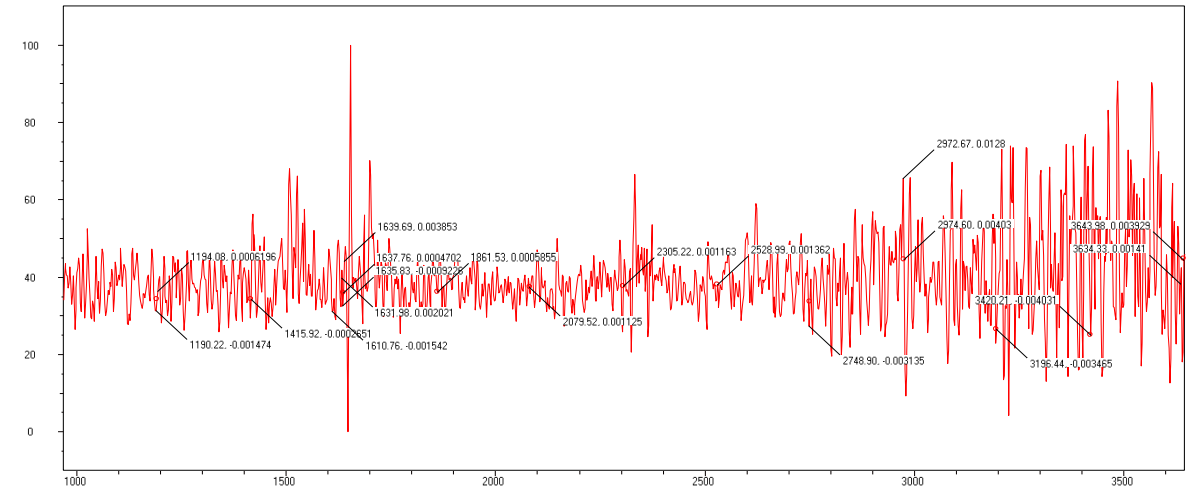
Graph.1 FT-IR Spectrum of Mupirocin



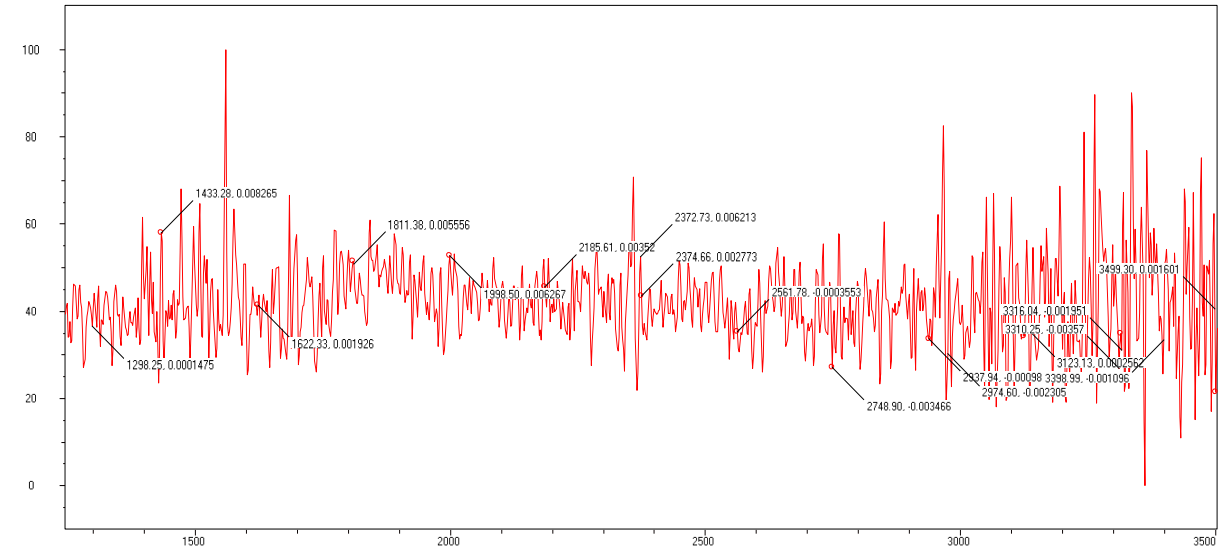
Graph.2 FT-IR Spectrum of sodium alginate



Graph.3 FT-IR Spectrum of drug and polymer



Graph.4 FT-IR Spectrum of formulation



Graph.5 Maximum wavelength of Mupirocin 220nm

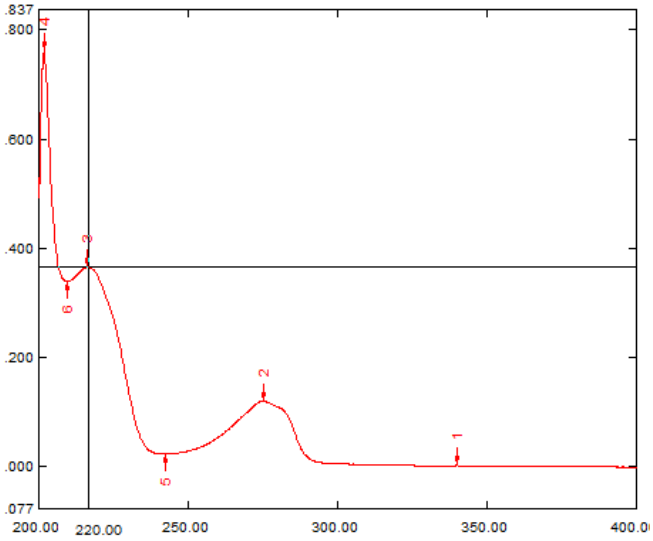


Fig.1 The SEM image of F20 formulation of Mupirocin microspheres

Graph.6 % Cumulative Amount of Drug Released From Formulations F16-F20

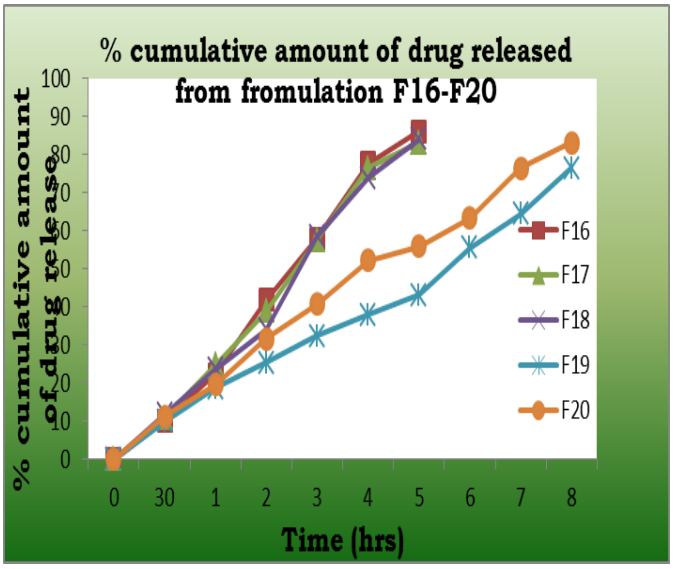
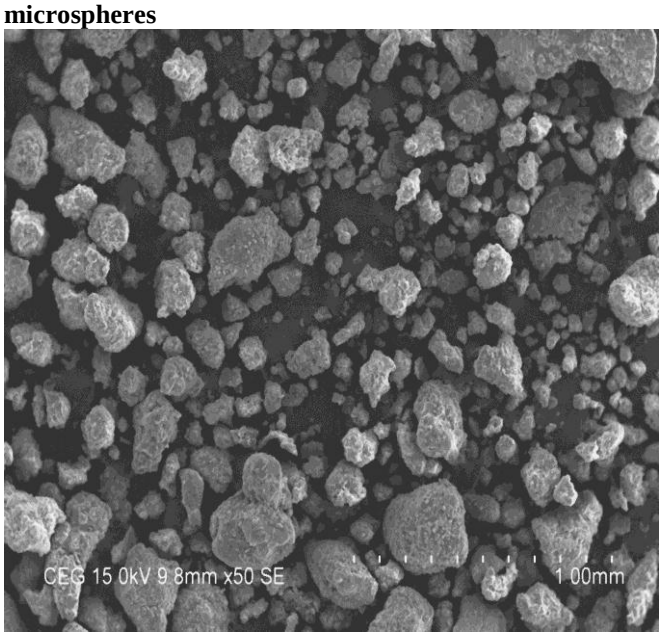
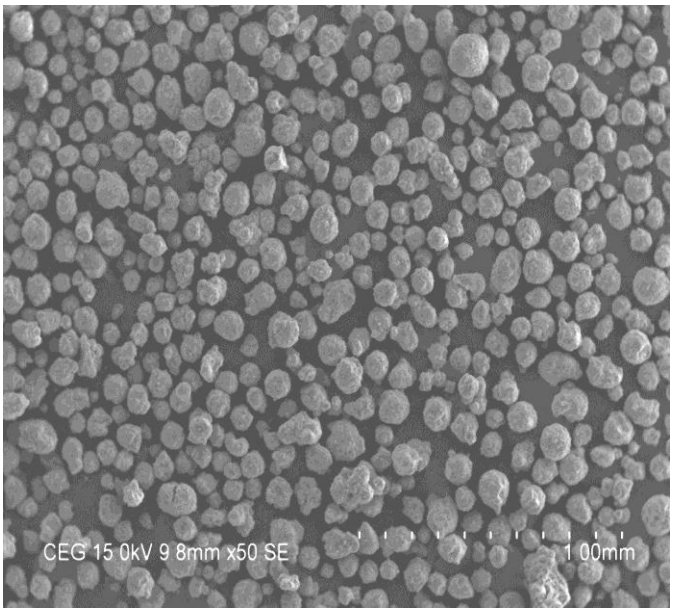
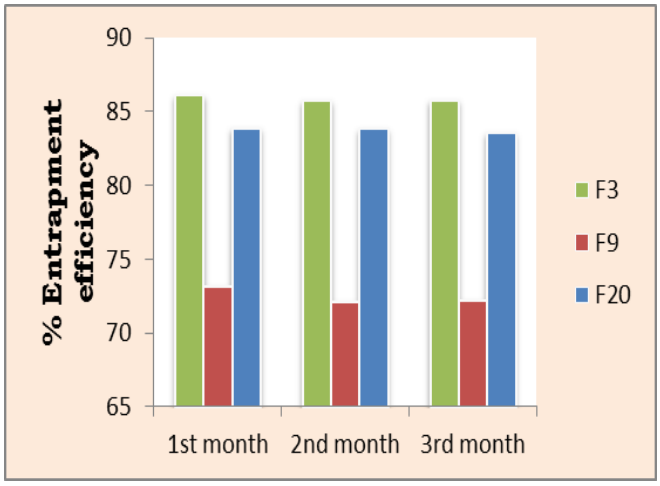


Fig.2 The SEM images of F13 formulation

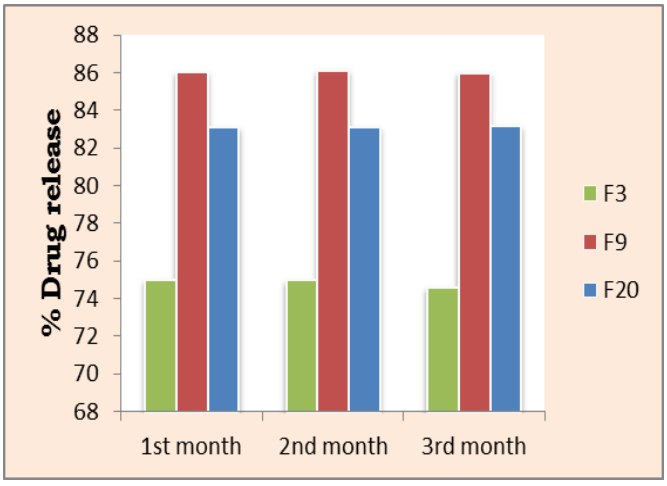




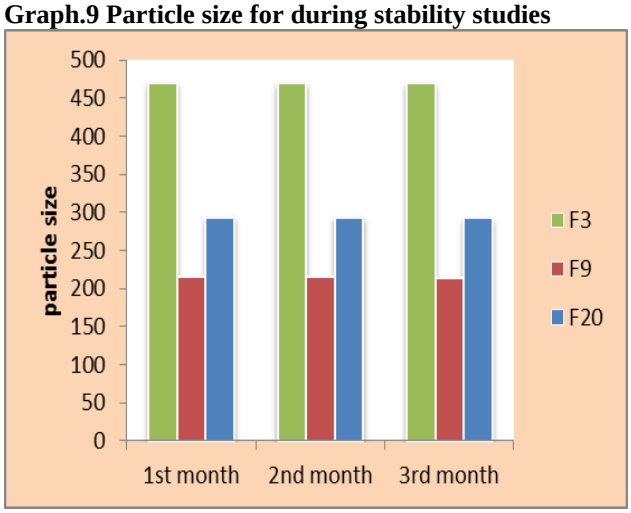
Graph.7 % Entrapment efficiency during stability studies



Graph.8 % Drug release during stability studies



Graph.9 Particle size for during stability studies



Drug and excipients compatibility studies

The IR spectrum of Mupirocin and polymer was compared with the IR spectrum of pure drug. The IR spectrums of the physical mixture were matching with the IR spectrum of pure Mupirocin. There was no appearance of any new characteristics peak. This shows that there was no interaction between the drug, and polymer used in the formulation with that of active ingredient.

Particle size analysis

Particle size analysis was done for F1-F5 formulations in that F3 formulation has shows better uniformity of size the particle size was 90-480 µm.

***In vitro* release studies**

In vitro release studies were performed for formulations F16-F20. The studies for Mupirocin microspheres were performed at p^H condition 6.8. Among all the formulations the optimized formulation of F20 has shown better *in vitro* drug release it shows maximum drug release was observed for a period of 8hours in p^H 6.8. In overall the results showed that the maximum release of Mupirocin 83% was obtained from F20 formulation.

Surface morphology

The surface morphology of the microspheres prepared by using sodium alginate and calcium chloride with different ratios are prepared for microspheres. These microspheres are then analysed for surface morphology using scanning electron microscope and found that they are spherical shape, with homogenous morphology.

Stability studies

The results of stability studies indicate that there was no influence on the chemical and physical stability of the formulations during test period and the results are mentioned.

Accelerated stability studies for the % entrapment efficiency, % drug release; particle size analysis shows that there was no change in results after 3 months study.

CONCLUSION

The Mupirocin microspheres were prepared by solvent evaporation technique using sodium alginate as polymer and calcium chloride as a cross linking agent for several trails were done by maintaining the speed, external phase concentration and time. All the formulations were evaluated for Particle size, surface morphology and *Invitro* drug release studies. Among the all formulations, F20 formulation has shown better *invitro* drug release was shown 83.07% for 8hrs. This project work contributes the idea to formulate the Mupirocin microspheres through effect of phase volume ratio on particle size and entrapment efficiency of drug, stirring time and speed on surface morphology and drug release mechanism etc., Using other variables in formulation may enlighten the research outcome which could be useful to develop the method for Mupirocin microspheres as effective drug delivery system.

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