CIBTech Journal of Pharmaceutical Sciences ISSN: 2319–3891 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/cjps.htm
2016 Vol.5 (2) April-June, pp.17-30/Krishna Sailaja and Ramaya Shivani
Research Article

FORMULATION AND EVALUATION OF OMEPRAZOLE MAGNESIUM LOADED ETHYL CELLULOSE MICROSPHERES BY SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT
Omeprazole is a proton pump inhibitor used to treat infections like peptic ulcers, gastro esophageal disorders and Zollinger Ellison syndrome. It comes under BCS class II drug with low solubility and high permeability having half life of 0.5-1hrs. In this study, attempts have been made to formulate and prepare Omeprazole magnesium microspheres using emulsion solvent evaporation method by using ethyl cellulose (EC) polymer to obtain sustained release formulation, to minimize dosing frequency, to improve bioavailability and to reduce the adverse actions. Process parameters such as stirring speed, stirring time and organic to aqueous phase ratio were optimized. Five formulations were prepared at 1:5 and 1:10 organic to aqueous phase ratios by varying the polymer concentrations. The obtained microspheres were characterized for surface morphology and evaluated for practical yield, drug content, entrapment efficiency and *in vitro* drug release. Comparative study was performed between the best formulations formulated at 1:5 (F4) and 1:10 (F9) organic to aqueous phase ratios. F4 formulation was found to be the best for preparing the Omeprazole magnesium microspheres with good drug content 91.8%, entrapment efficiency of 97.4%, practical yield of 87.9% and drug release was sustained for 12 hours with 81.8% drug release rate. According to the kinetics plots the drug release followed first order kinetics by non fickian diffusion mechanism.

Keywords: *Omeprazole Magnesium Microspheres*

INTRODUCTION
The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration. Drugs that are easily absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation.
In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect, adverse effects decreases by lowering peak plasma concentration. The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time (Jain, 2001).
A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug.
One such in Microspheres became an approach of controlled release dosage form in novel drug delivery system.
Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as micro particles. Microspheres can be manufactured from various natural and synthetic materials such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and poly glycolic acid.
The solvent selection mainly depends on the polymer solubility and drug stability, process safety and economic considerations (Wade and Weller, 1994).
Microspheres for oral use have been employed to sustain the drug release and to reduce the irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This

results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms (Sudhamani *et al.*, 2010).

Advantages of Microspheres

1. Taste and odor masking of drug
2. Protection of drug against the environment (moisture, light, heat and oxidation)
3. To improve the bioavailability
4. To decrease the side effects
5. To reduce the dose frequency
6. To relative stability
7. To increase the patient compliance
8. To have better therapeutic efficacy
9. To reduce the fluctuation in plasma drug concentration
10. Safe handling of toxic substances

Criteria for Preparation of Microspheres

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability.
6. Susceptibility to chemical modification.

MATERIALS AND METHODS

Omeprazole Mg received from NATCO Labs, Ethyl cellulose; PVA, DCM, Ethanol and other materials are received from Sd fine-chem limited, Mumbai.

Preparation of Microspheres

Accurate quantity of ethyl cellulose was dissolved in DCM using magnetic stirrer. Omeprazole Mg was dissolved in ethanol. This drug solution was added to above polymeric solution. PVA (0.75%) was dissolved in 100 ml of distilled water.

Now, the organic phase is added drop wise to the aqueous phase under continuous stirring at 900 RPM. The agitation was continued until all the organic solvent gets evaporated. The microspheres were dried and collected (Sailaja and Sree Lola, 2014).

Characterization of Microspheres

The prepared microspheres were evaluated for product yield, drug content, entrapment efficiency, FTIR, SEM, ZETA POTENTIAL and Invitro drug release studies (Sailaja *et al.*, 2015).

1) Percentage Yield:

The dried floating microspheres of Omeprazole were weighed and percentage yield of the prepared microspheres was calculated by using the following formula (Prakash *et al.*, 2007).

Percentage Yield = {the weight of microspheres / the weight of polymer + drug}*100

2) Drug Content:

The various batches of the dried floating microspheres of Omeprazole microspheres were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of phosphate buffer PH 7.2 in two necked round bottomed Flask. With the help of mechanical stirrer the dispersion was stirred for 3 hours and filtered.

The UV absorbance of the filtrate was measured using a UV spectrometer at 221nm (Shekhar and Nagamadhu, 2010).

3) Entrapment Efficiency:

The prepared Omeprazole floating microspheres were examined for entrapment efficiency. 40mg of the prepared formulation was taken in equivalent quantity of 7.2 phosphate buffer. The suspension is ultra-centrifuged at 17240rpm for 40 minutes. The free concentration of the drug in the supernatant was

measured spectrophotometrically. Entrapment efficiency is calculated by the following equation (Rakesh Bagul *et al*., 2012).

$$\% \text{ Entrapment Efficiency} = \frac{W-w}{w} \times 100$$

4) Particle Size Analysis and Zeta Potential Measurement

The average particle size and size distribution of omeprazole magnesium loaded microspheres was determined by dynamic light scattering (DLS), using Malvern Zeta Sizer. The Zeta potential (Surface Charge) which indicates the stability of the microspheres can be defined as electro kinetic potential that is determined by electrophoretic mobility.

Sample was prepared by diluting with doubled distilled water and corresponding zeta potential measured using Malvern Zeta Sizer.

5) Determining the Size and Surface Morphology of the Microspheres:

Suspension was made to obtain Photomicrographs of the ibuprofen loaded microspheres using the SEM Scanning Electron Microscopy is used to determine the shape, size and surface morphology of the microspheres.

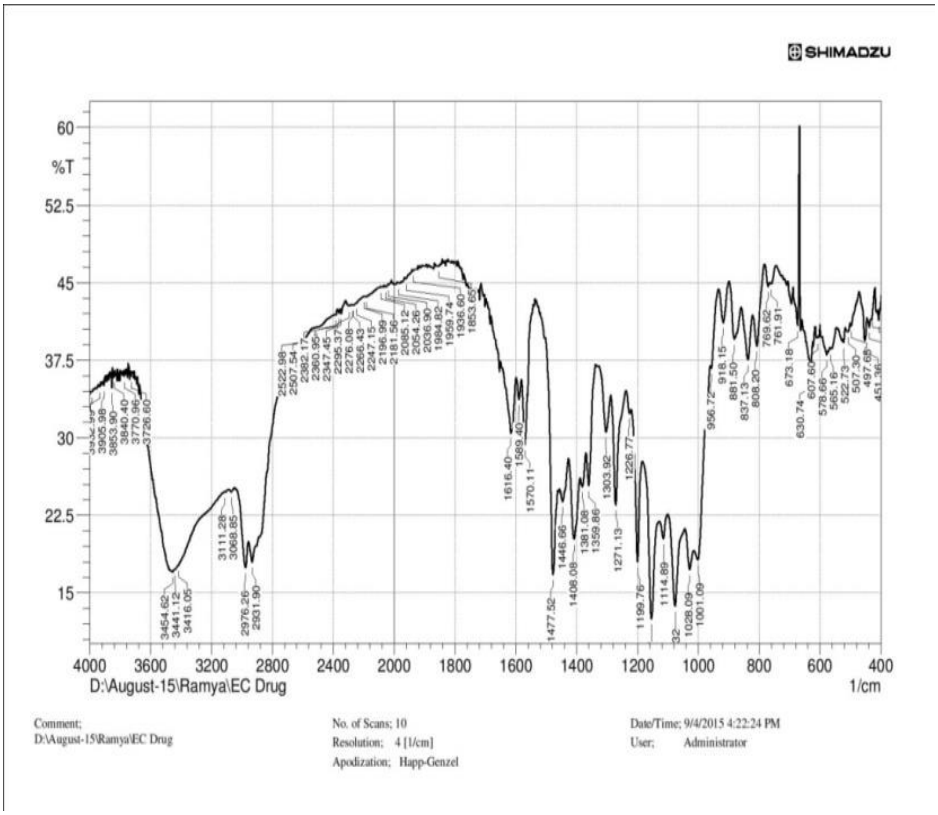
6) In Vitro Dissolution Studies:

In vitro dissolution studies Omeprazole Mg loaded microspheres were performed using USP paddle type apparatus. 900 ml of buffer is used as dissolution medium .the medium was maintained at 37+0.5°c at a speed of 100 rpm (Junyaprasert and Pornsuwannapha, 2008).

RESULTS AND DISCUSSION

Results and Discussion of Omeprazole Magnesium Loaded Ethyl Cellulose Microspheres at 1:5 Organic to Aqueous Phase Ratio

FTIR:



Drug Excipient Compatibility Studies were Performed by Means of FTIR

Figure 1: FTIR Spectrum of Omeprazole mg Loaded Ethyl Cellulose Microspheres

ZETA POTENTAIAL:

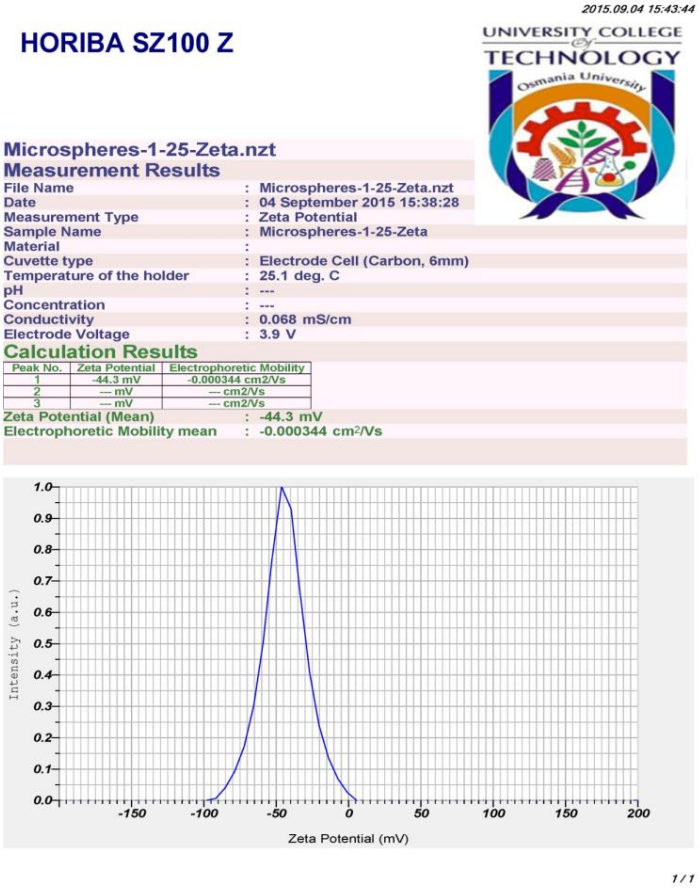


Figure 2: Zeta Potential Report of Best Formulation F4 of Omeprazole Mg Microspheres

From the above zeta potential report value of the best formulation F4 was found to be -44.3mV showing good stability.

SEM:

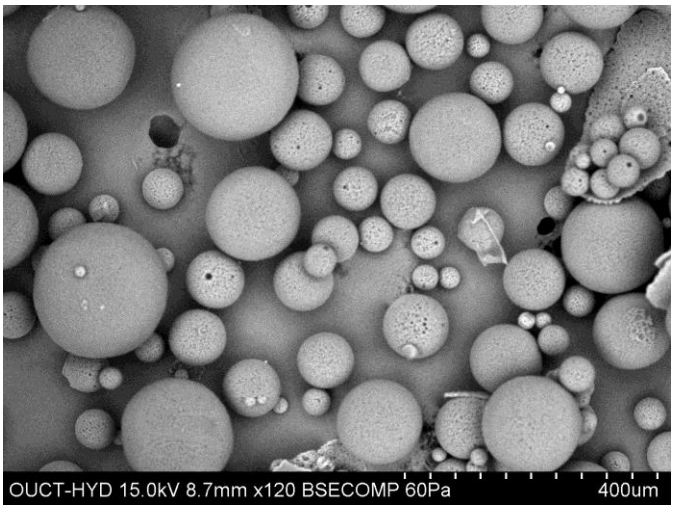


Figure 3: SEM Image of Prepared Omeprazole Magnesium Loaded Ethyl Cellulose Microspheres at 1:5

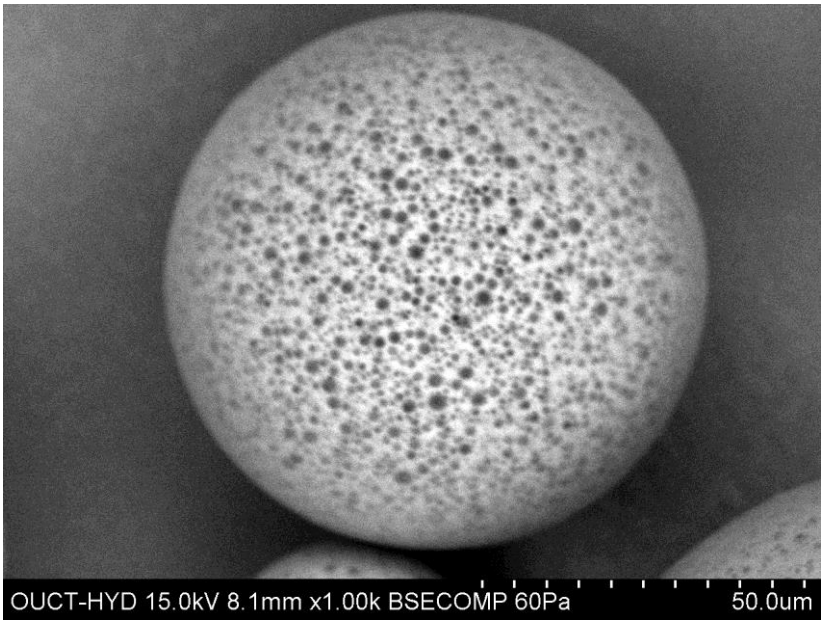


Figure 4: SEM Images of F4 Formulation of Omeprazole Magnesium Loaded with Ethyl Cellulose Microspheres

From the SEM images it was found that all the images showed spherical particles in micron Range.

Practical Yield:

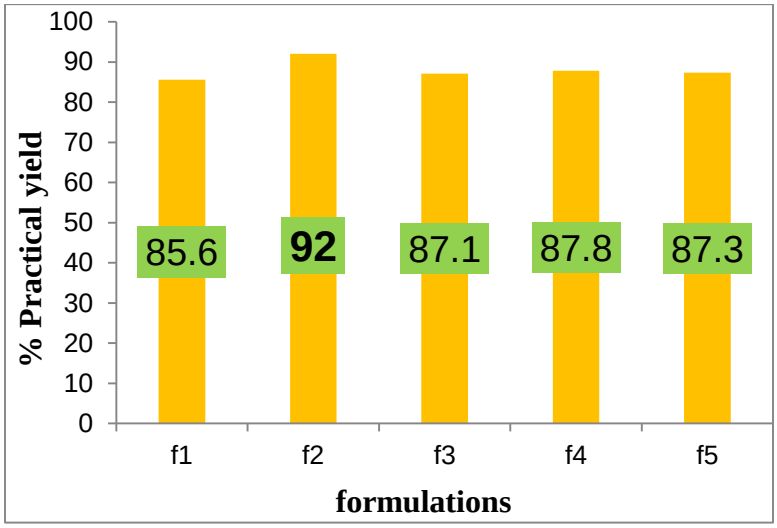


Figure 5: Comparison of Product Yield among the Five Formulations of Omeprazole Magnesium Microspheres

The product yield of prepared five formulations F1, F2, F3, F4 and F5 was found to be 85.6%, 92%, 87.1%, 87.8 % & 87.3% respectively. Out of the five formulations the higher product yield was observed for F2 formulation.

Drug Content:

The drug content of prepared five formulations F1, F2, F3, F4 and F5 was found to be 90.1%, 91.1%, 91.4%, 91.8 % & 90.3% respectively. Out of the five formulations the highest drug content was observed for F4 formulation.

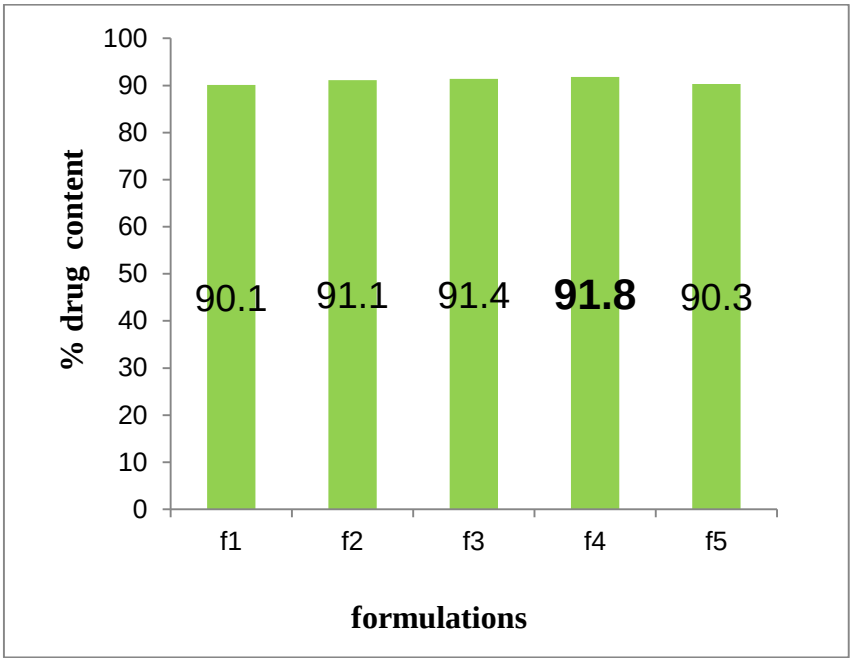


Figure 6: Comparison of Drug Content among the Five Formulations of Omeprazole Magnesium Loaded with Ethyl Cellulose Microspheres

Entrapment Efficiency:
The prepared five formulations were evaluated for entrapment efficiency.

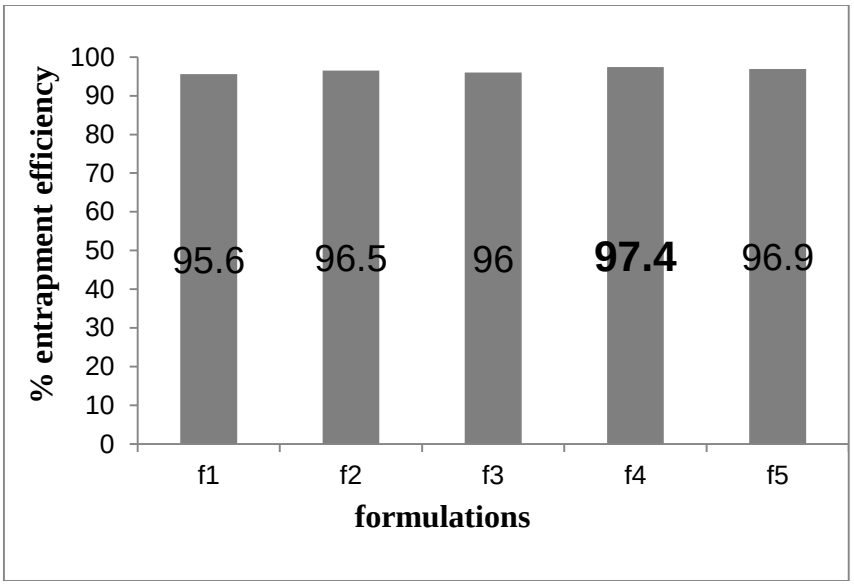


Figure 7: Comparison of Entrapment Efficiency among the Five Formulations of Omeprazole Magnesium Loaded with Ethyl Cellulose Microspheres

The entrapment efficiency of prepared five formulations F1, F2, F3, F4 and F5 was found to be 95.6%, 96.5%, 96%, 97.4 % & 96.9% respectively. Out of the five formulations the highest entrapment efficiency was observed for F4 formulation.

Invitro Drug Release:
The prepared 5 formulations were subjected to invitro dissolution studies by using USP II apparatus.

Table 1:???

Time	F1	F2	F3	F4	F5
30mins	4.3	14.2	17	11.2	13.5
1hr	18	16.8	21.8	17.4	22.3
2hr	22.6	21.2	26.9	24.8	29.5
3hr	43.2	25.6	30.5	29	31.4
4hr	46.8	31.3	31.5	35.2	32.7
5hr	54.7	38.6	38.6	42	36.9
6hr	60	45.8	50.6	47.8	45
7hr	65.2	53	52.7	52.6	51.5
8hr	72.2	61.5	60.1	59.9	57.2
9hr	77.1	68.7	66	62.8	60.2
10hrs	81.2	73.1	68.4	69.5	69.5
11hrs	83.9	77.4	72	74.6	74.4
12hrs	87.3	85.8	82.1	81.8	78.9

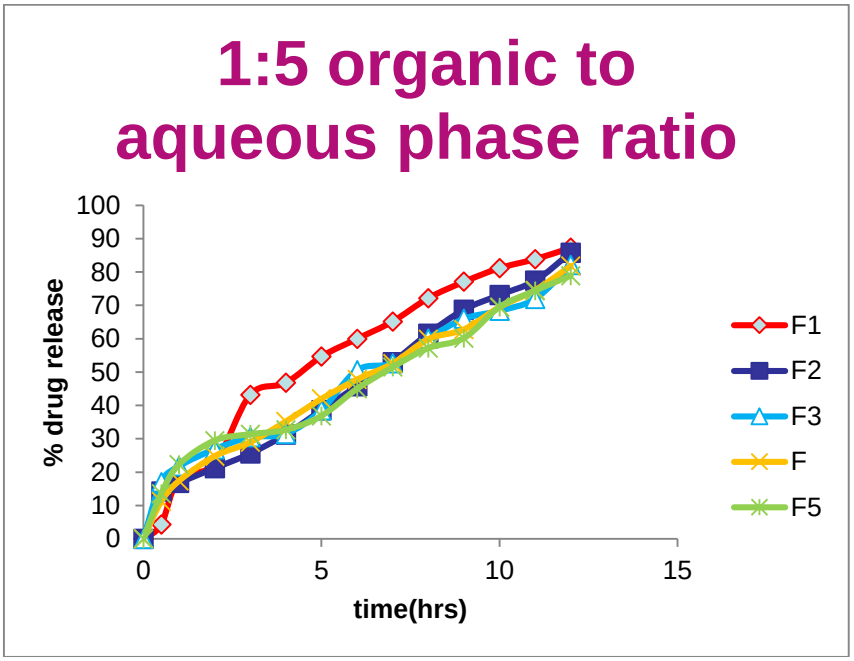


Figure 8: Comparative Invitro Drug Release Profiles of Omeprazole Magnesium Loaded with Ethyl Cellulose Microspheres

In all the formulations the drug release was sustained for 12 hrs. From F1, F2, F3, F4, F5 formulations the percentage of drug release was found to be 87.3%, 85.8%, 82.1%, 81.8%, and 78.8% in a time period of 12 hrs.

Results and Discussion of Omeprazole Magnesium Loaded Ethyl Cellulose Microspheres at 1:10 Organic to Aqueous Phase Ratio

Five formulations were prepared by altering the drug to polymer ratio. The effect of polymer concentration up on practical yield, drug content, entrapment efficiency and drug release was studied**.**

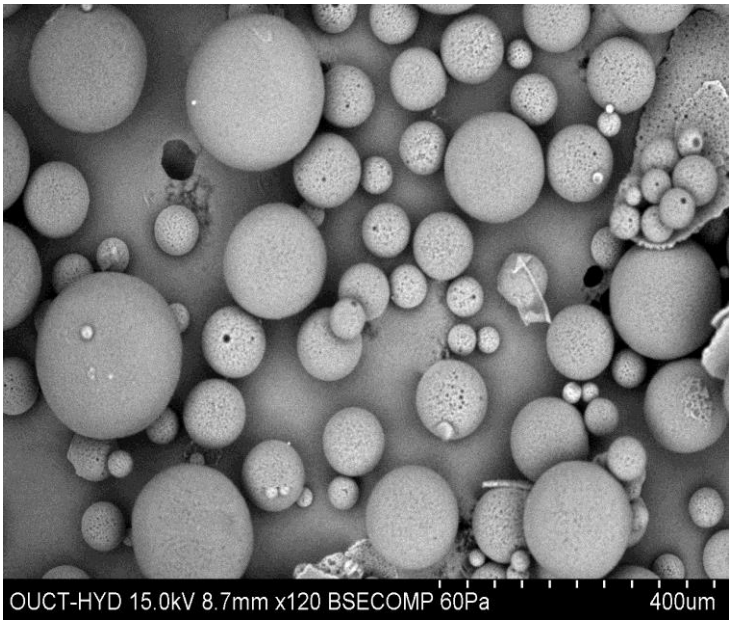


Figure 9: SEM Image of Prepared at 1:10 Omeprazole Magnesium Loaded Ethyl Cellulose Microspheres

Practical Yield:

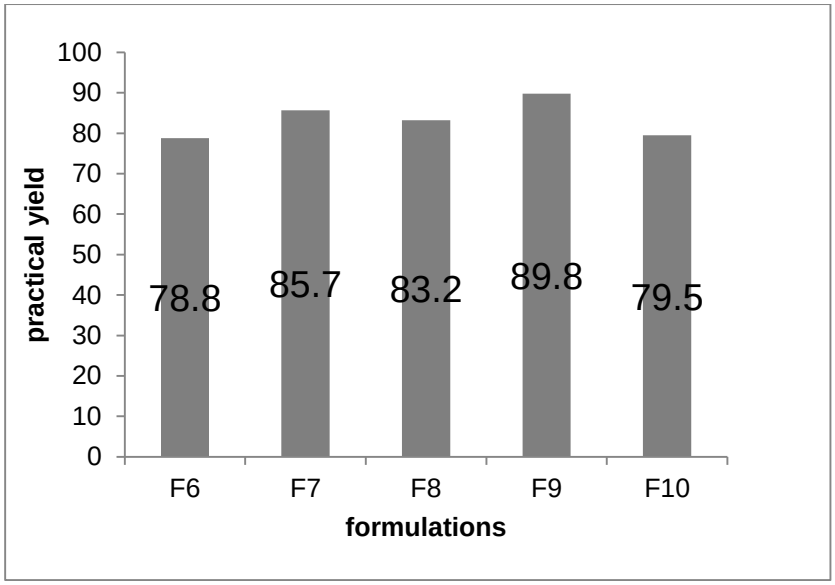


Figure 10: Comparison of Product Yield among the Five Formulations of Omeprazole Magnesium Microspheres

The product yield of prepared five formulations F6, F7, F8, F9 and F10 was found to be 78.8%,85.7%, 83.2%, 89.8 % & 79.5% respectively. Out of the five formulations the highest practical yield was observed for F9 formulation.

Drug Content:

The prepared formulations were evaluated for drug content.

The drug content of prepared five formulations F6, F7, F8, F9 and F10 was found to be 76%, 77.8%, 83%, 81.5 % & 79.8% respectively. Out of the five formulations the highest drug content was observed for F8 formulation.

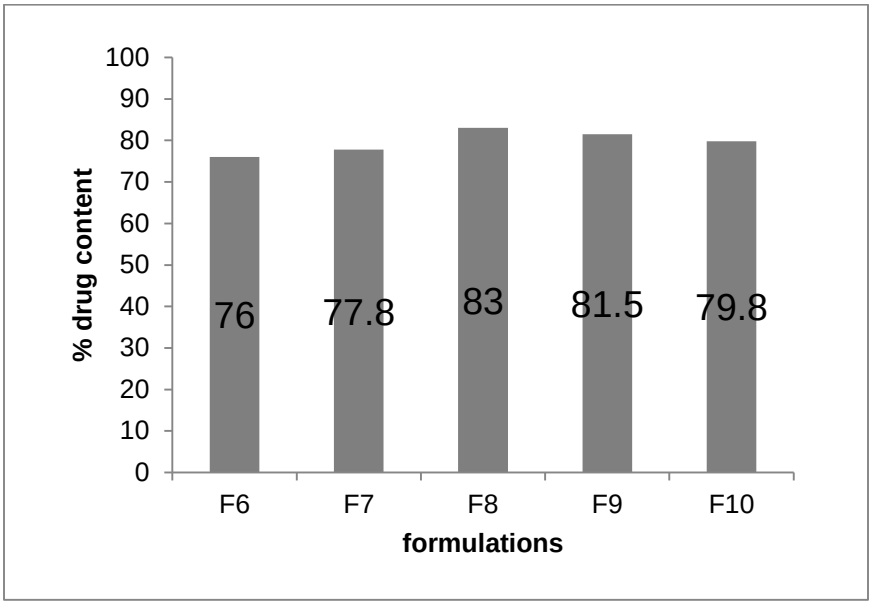


Figure 11: Comparison of Drug Content among the Five Formulations of Omeprazole Magnesium Loaded with Ethyl Cellulose Microspheres

Entrapment Efficiency:
The prepared 5 formulations were subjected to entrapment efficiency.

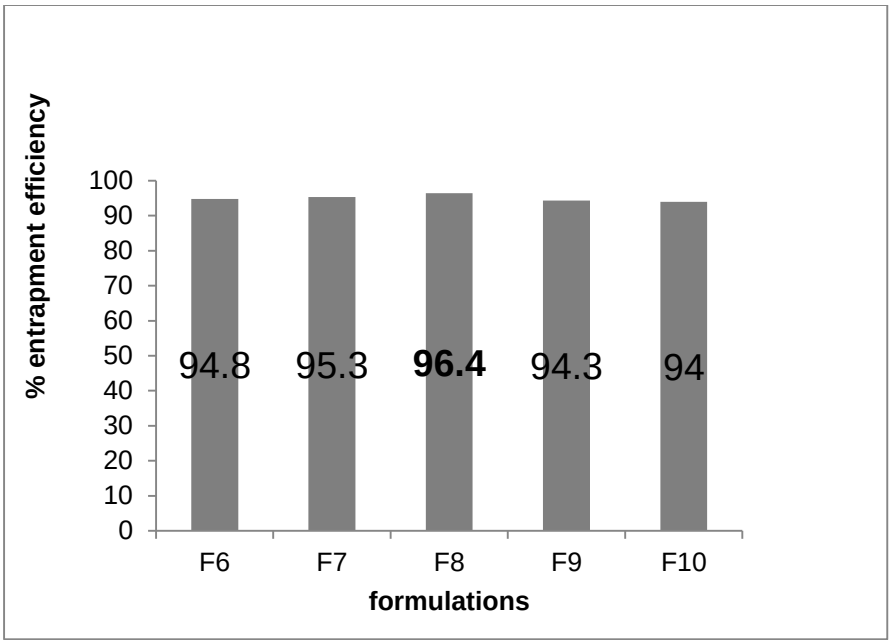


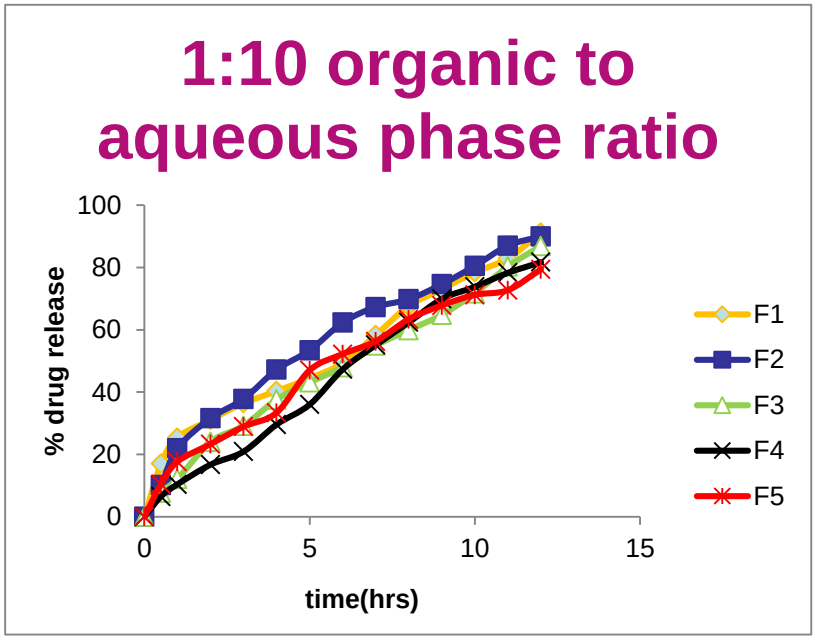
Figure 12: Comparison of Entrapment Efficiency among the Five Formulations of Omeprazole Magnesium Loaded with Ethyl Cellulose Microspheres

The entrapment efficiency of prepared five formulations F6, F7, F8, F9 and F10 was found to be 9.8%, 95.3%, 96.4%, 94.3%, 94 % respectively. Out of the five formulations the highest entrapment efficiency was observed for F8 formulation

Invitro Drug Release:
The prepared 5 formulations are subjected to invitro dissolution studies by using USP II apparatus.

Table 2: Invitro Data of Prepared Omeprazole Magnesium Loaded with Ethyl Cellulose Microspheres at 1:10 Organic to Aqueous Phase Ratio

Time	F6	F7	F8	F9	F10
30mins	17	10.2	7.7	6.5	10.5
1hr	25.4	22	12.1	10.4	17.7
2hr	31.1	31.6	24	16.7	23.3
3hr	36.4	37.8	29.2	20.9	28.9
4hr	40.3	47.2	37.6	29.6	33.4
5hr	44.4	53.4	43.1	36	47
6hr	49.3	62.3	48	47.3	52.2
7hr	58.3	67.3	54.9	55.1	56.3
8hr	67.6	69.8	59.9	62.4	63.4
9hr	73	74.6	64.8	69.9	67.8
10hrs	78.4	80.5	71.7	73.8	71.2
11hrs	82.9	87	80.3	78.3	72.7
12hrs	91.2	90	86.9	81.7	79.4



Among all prepared 5 formulations F10 showing sustained drug release.

Figure 13: Invitro Drug Dissolution Data of Prepared Omeprazole Magnesium Loaded Ethyl Cellulose Microspheres at 1:10 Organic to Aqueous Phase Ratio

In all the formulations the drug release was sustained for 12 hrs. From F6, F7, F8, F9, F10 formulations the percentage of drug release was found to be 91.2%, 90%, 86.9%, 81.7%, and 79.4%. in a time period of 12 hrs.

Comparison between the Best Formulations of Microspheres at 1:5 and 1:10 Organic to Aqueous Ratio

Best formulation F4 at 1:5 organic to aqueous phase ratio and F9 formulation at 1:10 organic to aqueous phase ratio were selected for comparative study.

Both the formulations were compared for all the evaluation parameters such as practical yield, drug content, entrapment efficiency and drug release.

Practical Yield:

Product yield of both the formulation was compared.

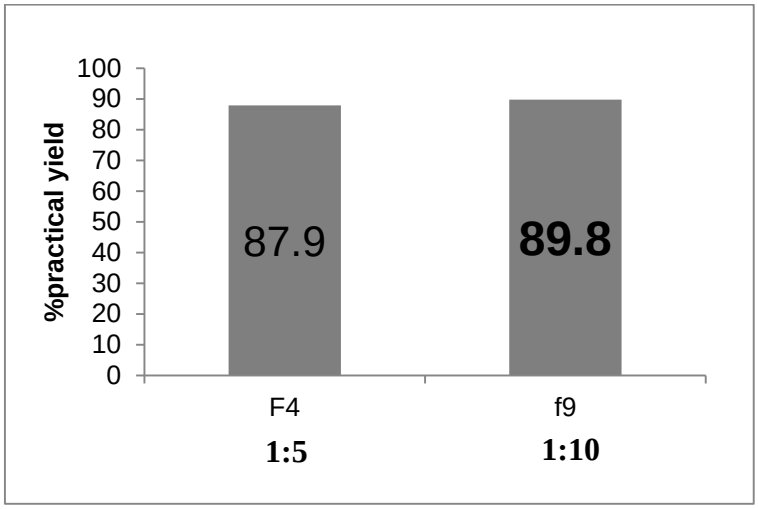


Figure 14: Comparative between F4 and F9 Formulation of Practical Yield

On comparison the product yield of F9 formulation prepared at 1:10 organic to aqueous phase ratio was found to be highest **89.8%.**

Drug Content

Drug content of both the formulation was compared.

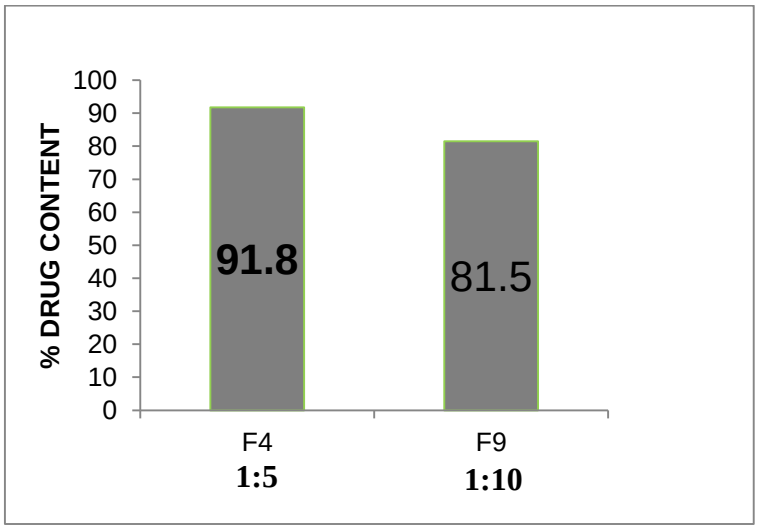


Figure 15: Comparative between F4 and F9 Formulation of %DC

On comparison the drug content of F4 formulation prepared at 1:5 organic to aqueous phase ratio was found to be highest **91.8%.**

Entrapment Efficiency

Entrapment efficiency of both the formulation was compared.

On comparison the entrapment efficiency of F4 formulation prepared at 1:5 organic to aqueous phase ratio was found to be highest **97.4%.**

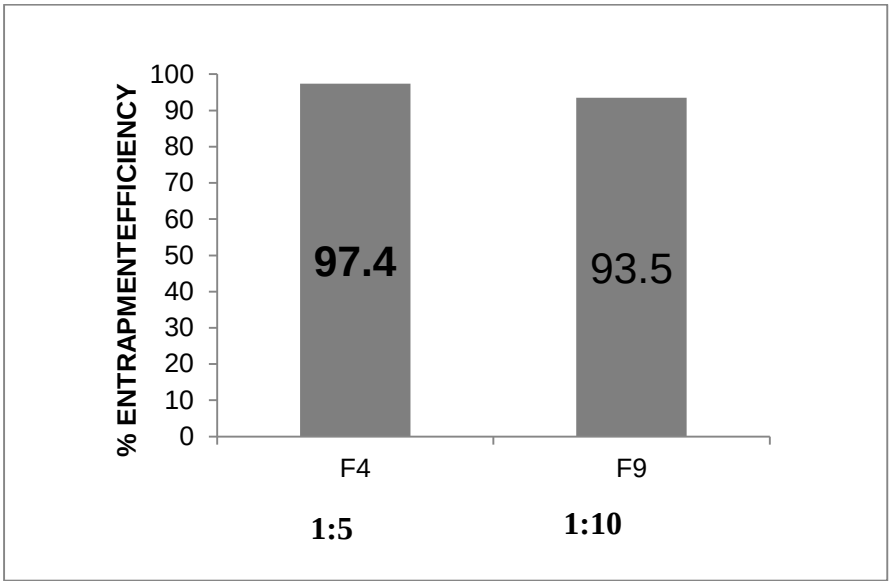


Figure 16: Comparative between F4 and F9 Formulation of %EE

Invitro Drug Release
The drug release profiles of both best formulations were compared.
Comparison between F4 and F9 formulations

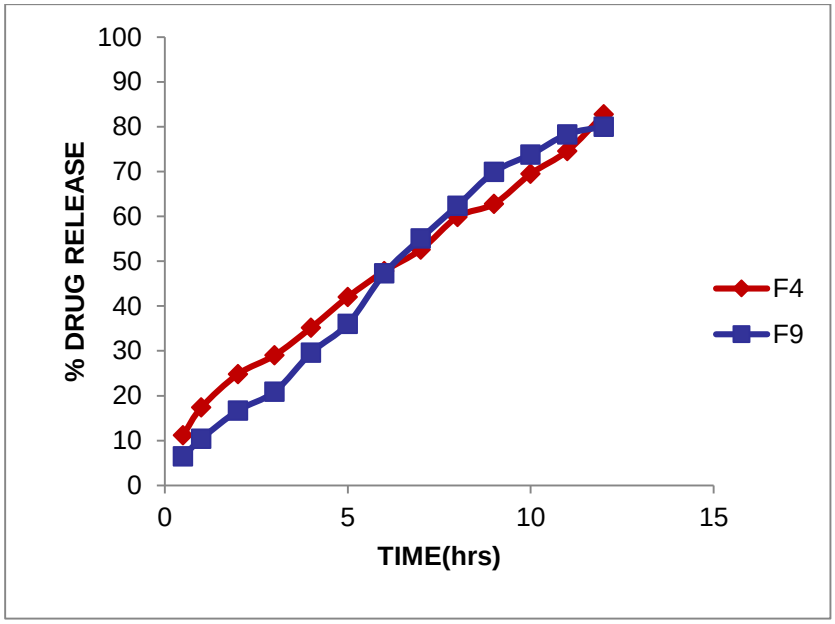


Figure 17: Comparative Study of Invitro Drug Release Profiles of F4 and F9 Formulations

Both the formulations were able to sustain the drug release for period of 12hrs the % of drug release from F4 and F9 formulations was found to be 81.8% and 81% respectively in a time period of 12hrs.
From the results the F4 formulation was found to be best formulation because of high drug content, entrapment efficiency and better sustained release property. Kinetics plots were drawn for F4 formulation to determine the Oder of kinetics and mode of drug release.
Release Kinetics of Optimize Formulation:
Plots of best formulation of omeprazole magnesium loaded with ethyl cellulose microspheres**.**

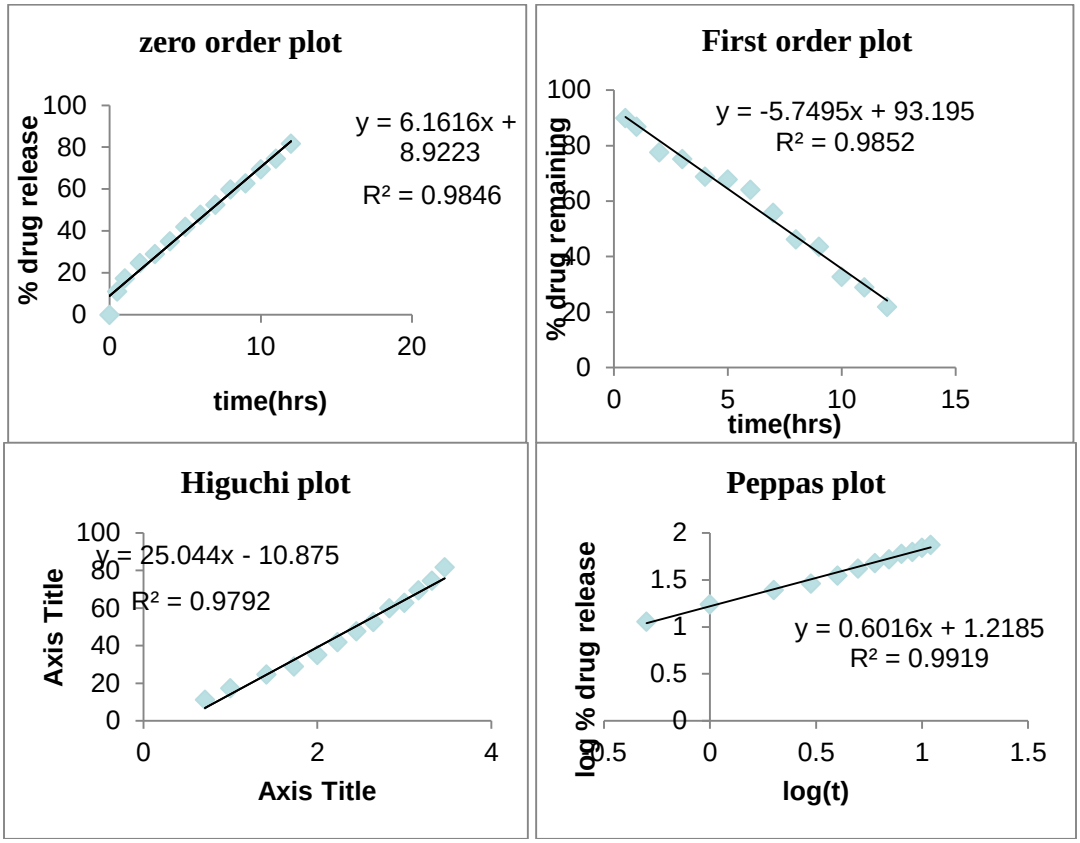


Figure: ???

Conclusion

In this study attempt have been made to prepare omeprazole magnesium microspheres by solvent evaporation method using ethyl cellulose as synthetic polymer. Process parameters such as stirring speed, stirring time were optimized. Formulations have been prepared at 1:2, 1:5 and 1:10 organic to aqueous phase ratio. 1:2 ratio there were no formation of microspheres. At 1:5 and 1:10 organic to aqueous phase ratio microspheres were observed. Further formulations were prepared at 1:5 and1:10 O/W ratio by altering the drug and polymer ratio. Five formulations were prepared at 1:5 and 1:10 organic to aqueous phase ratio by increasing the polymer concentration. The effect of polymer Concentration up on particle size, drug content, entrapment efficiency and drug release was studied.

Out of the 5 formulations prepared at 1:5 organic to aqueous phase ratio F4 formulation was showing better results the practical yield 87.9%, drug content 91.8%, entrapment efficiency 97.4% was found to be more than remaining formulations. F4 formulation was able to sustain the drug release up to 12hrs.

Out of the 5 formulations prepared at 1:10 organic to aqueous phase ratio F9 formulation was showing better results the practical yield 89.8%, drug content 81.5%, entrapment efficiency 93.5% was found to be more than remaining formulations. F9 formulation was able to sustain the drug release up to 12hrs.

F4 formulation at 1:5 organic to aqueous phase ratio and F9 formulation at 1:10 organic to aqueous phase ratio were selected for comparative study. Both the formulations were compared for all the evaluation parameters. On comparison F4 formulation was found to be better because of high practical yield, good drug content and high entrapment efficiency. F4 formulation was able to sustain drug release up to 12hrs.

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