

PREPARATION AND EVALUATION OF FLOATING MICROSPHERES OF OMEPRAZOLE MICROSPHERES BY SOLVENT EVAPORATION METHOD

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ABSTRACT

The main aim of the present investigation is to formulate Omeprazole loaded Floating microspheres by solvent evaporation technique. Total ten formulations were prepared by altering the concentration of drug to polymer concentrations. Process parameters such as stirring speed, stirring time and organic to aqueous phase ratio were optimized. Trials were made at 1:5 and 1:10 organic to aqueous phase ratio by altering drug to polymer concentration. Floating Microspheres were prepared by non-effervescent system. The obtained formulations were evaluated for drug content, entrapment efficiency, Buoyancy time and In vitro dissolution studies. The entrapment efficiency was found to be increased by increasing the concentration of the polymer. In vitro dissolution studies were conducted for a period of 12 hours. The drug release was continued up to 12 hrs with 99% drug release. From the study it was concluded that Formulation which has been prepared at 1:5 organic to aqueous phase ratio at 1:30 drug to polymer concentration was yielding the best floating microspheres which were floating for a period of 24 hrs.

Keywords: *Floating Microspheres, Omeprazole, Solvent Evaporation Technique*

INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems (Arora, 2005). The floating drug delivery system was first described by Davis (1968). Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems. FDDS are known as Hydro dynamically balanced systems or low density system that has been made developed in order to increase the gastric transit time of drug. These microspheres are characteristically free flowing powders consisting of natural or synthetic polymers and ideally having a particle size less than 200 μ m. Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug (Roy and Shahiwala, 2009; Nayak *et al.*, 2010).

Microspheres are one of the multiparticulate delivery system and are prepared to obtain controlled release from the dosage form to improve bioavailability, reduce the adverse effect and prolong the action of drug, reduce absorption difference in patients, reduce the dosing frequency and adverse effects during prolong treatment. It is needed to formulate in long acting dosage form, reaching to effective biological site rapidly.

Omeprazole is usually administered as conventional tablet form with the dose 15 mg, omeprazole is proton pump inhibitor which prevents stomach from producing gastric acid. The biological half life of omeprazole is 1 to 1.2hr (Patel *et al.*, 2012).

Mechanism

Mechanism of flotation of microspheres: When microspheres come in contact with gastric fluid, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped

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by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content is needed to allow proper achievement of buoyancy (Banarjee *et al.*, 201 and Yie, 1992).

Advantages of Floating Microspheres:-

- (1) It enhance the bioavailability
- (2) It sustains the drug delivery and reduces the frequency of dosing.
- (3) It is targeted therapy for local ailment in the upper gastro-intestinal tract.
- (4) Reduce fluctuation of drug.
- (5) Minimize adverse activity at the colon.
- (6) Reduce the gastric irritation caused by acidic drug.
- (7) When vigorous intestinal movement occurs in diarrhea, the biological half-life of the drug get decreased. In that condition the floating microspheres float in the gastric content and enhance the absorption (Narang, 2011; Roop and Khar (No date)).

Limitations of Floating Drug Delivery Systems

1. A high level of fluid in the stomach is required for drug delivery to float and work efficiently.
2. Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of system.
3. Drugs such as Nifedipine, which under goes first pass metabolism may not be desirable for the preparation of these types of systems (Arunachalam, 2011).

MATERIALS AND METHODS

Materials and Methodology

Omeprazole was obtained as gift sample from NATCO labs, hyd. Ethyl cellulose, Eudragit S100, DCM, PVA, was obtained from Fine Chemicals Pvt Ltd Mumbai.

Preparation of Omeprazole Floating Microspheres

The floating micro spheres were prepared by solvent evaporation method. 0.75g of polyvinyl alcohol was dissolved in 100 ml of distilled water. Different quantities of Ethyl cellulose and Eudragit S 100 were dissolved in dichloromethane by magnetic stirrer. A known quantity of Omeprazole was dissolved in above polymer solution along with surfactant (span 80). The resulting solution was added drop wise into the aqueous phase containing polyvinyl alcohol with continuous stirring at 700 rpm using mechanical stirrer.

The stirring was continued for 3 hrs to complete evaporation of solvent. Microspheres were separated and dried at room temperature (Sunil, 2014).

Characterization of Microspheres

The prepared floating microspheres were evaluated for product yield, drug content, entrapment efficiency and drug release studies. Buoyancy time and percentage of buoyancy was determined.

Process parameters such as stirring time, stirring speed and organic to aqueous phase ratio were optimized. Floating microspheres were prepared at 1:2, 1:5 and 1:10 organic to aqueous phase ratio. There was no formation of microspheres at 1:2 organic to aqueous phase ratio. Microsphere formation was observed at 1:5 and 1:10 organic to aqueous phase ratio. Total five formulations were prepared by altering drug to polymer ratio to study the effect of polymer concentration upon evaluation parameters such as product yield, drug content, entrapment efficiency, in vitro drug release and percentage of buoyancy.

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

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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

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 *et al.*, 2012)

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

4) In vitro Buoyancy Studies

The microspheres weighed about 0.3g were taken in the USP dissolution apparatus II which was filled with 900ml of phosphate buffer containing 0.02% of tween20. The medium was agitated with paddle rotating at 100 rpm for 12hrs. The floating and settled portions were taken separately dried and weighed. Buoyancy percentage was calculated by using the formula (Sunil, 2014)

$$\% \text{ Buoyancy} = \frac{\text{weight of floating microspheres}}{\text{initial weight of microspheres}} \times 100$$

5) Invitro Drug Release Study of Microsphere Formulations in Phosphate Buffer pH 7.2

The dissolution rate testing apparatus was employed to study the release of omeprazole floating using phosphate buffer pH 1.2 as a dissolution medium. 50mg equivalent of omeprazole containing ethyl cellulose microspheres was taken and dissolution test was being carried out at 50rpm maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. 5ml of sample were withdrawn at specific time interval for 24 hours. The sample volume was replaced by an equal volume of fresh medium. The concentration was determined spectrophotometrically at the same procedure was repeated for other formulations also (Prakash, 2012).

6) Particle Size Analysis and Zeta Potential Measurement

The average particle size and size distribution of Ibuprofen 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.

7) 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.

RESULTS AND DISCUSSION

Results of Omeprazole Floating Microspheres Formulated at 1:5 Organic to Aqueous Phase Ratio

The prepared five formulations of 1:5 organic to aqueous phase ratio were evaluated for product yield.

Different Formulations of Omeprazole Microspheres at 1:5 Organic to Aqueous Phase Ratio

Table 1: Omeprazole floating microspheres at 1:5 organic to aqueous phase ratio

code	Ratio	Practical yield	Drug content	Entrapment efficiency	%drug release	%Buoyancy
F1	1:15	75.9%	50%	94.1%	67.2%	74.8%
F2	1:20	78.5%	52.8%	94.3%	66%	76.1%
F3	1:25	80.1%	53.8%	87.5%	63.2%	70.9%
F4	1:30	79.1%	53.3%	93.2%	58.4%	76.3%
F5	1:35	86.4%	93.9%	98%	62.9%	72.8%

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Practical Yield: Practical yield of all the formulations was evaluated.

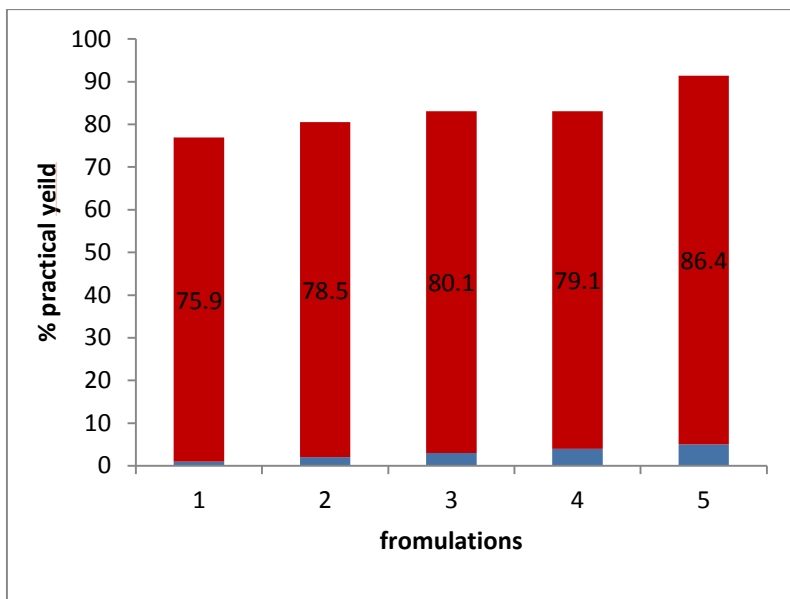


Figure 1: Comparison of product yield among the five formulations of Omeprazole Floating microspheres

The product yield of F1, F2, F3, F4 and F5 was found to be 75.9%, 78.5%, 80.1 %, 79.1% and 86.4% respectively. On comparison F5 formulation was showing highest yield.

Drug Content: Drug content of all the formulations was evaluated

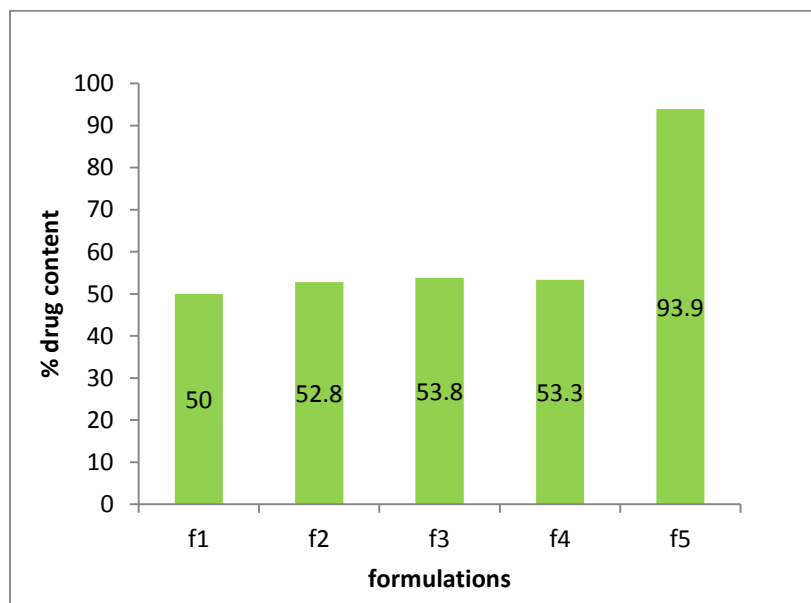


Figure 2: Comparison of Drug content among the five formulations of Omeprazole Floating microspheres

The drug content of F1, F2, F3, F4 and F5 formulations was found to be 50%, 52.8%, 53.8 %, 53.3% and 93.9% respectively. On comparison F5 formulation was showing highest drug content.

Entrapment Efficiency: Entrapment efficiency of all the formulations was evaluated

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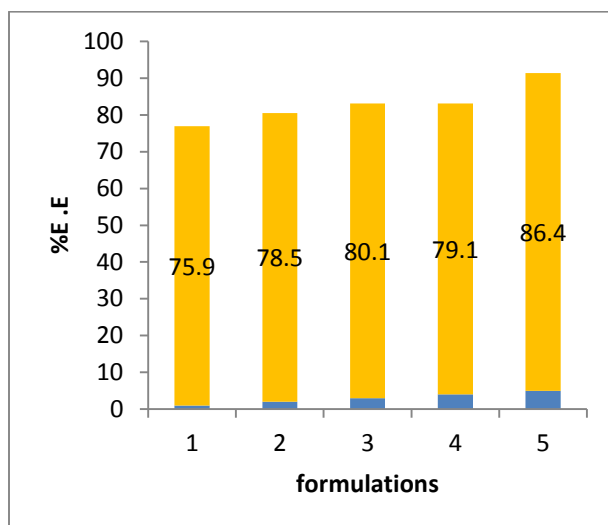


Figure 3: Comparison of entrapment efficiency among the five formulations of Omeprazole Floating microspheres

The entrapment efficiency of F1, F2, F3, F4 and F5 formulations was found to be 75.9%, 78.5%, 80.1 %, 79.1% and 86.4 % respectively. On comparison F5 formulation was showing highest entrapment efficiency.

Invitro Drug Release

Different Formulations of Omeprazole Microspheres at 1:5 Organic to Aqueous Phase Ratio:

In vitro data of prepared Omeprazole magnesium loaded with ethyl cellulose microspheres at 1:5 organic to aqueous phase ratio.

Table 2: Invitro data of prepared Omeprazole Floating microspheres at 1:5 organic to aqueous phase ratio

TIME	F1	F2	F3	F4	F5
30mins	5.5%	4.2%	9.5%	5.2%	4.5%
1hr	8.4%	8.4%	18.2%	6%	7.2%
2hr	11.9%	12.6%	20%	8.4%	12.3%
3hr	14.1%	14.2%	24.3%	13.2%	14.5%
4hr	17.9%	18.3%	26.4%	14.1%	17.2%
5hr	21.6%	19.9%	28.5%	16.6%	18.9%
6hr	26.5%	22.5%	31.7%	18.9%	21.5%
7hr	30.6%	25%	35%	21.5%	32.1%
8hr	33.2%	27.3%	39.6%	24%	37.6%
9hr	38.4%	32.3%	42.2%	27.1%	39.9%
10hrs	40.7%	39.4%	44%	27.8%	48.2%
11hrs	51%	42.5%	48%	32.5%	49%
12hrs	67.2%	66%	63.2%	58.4%	62.9%

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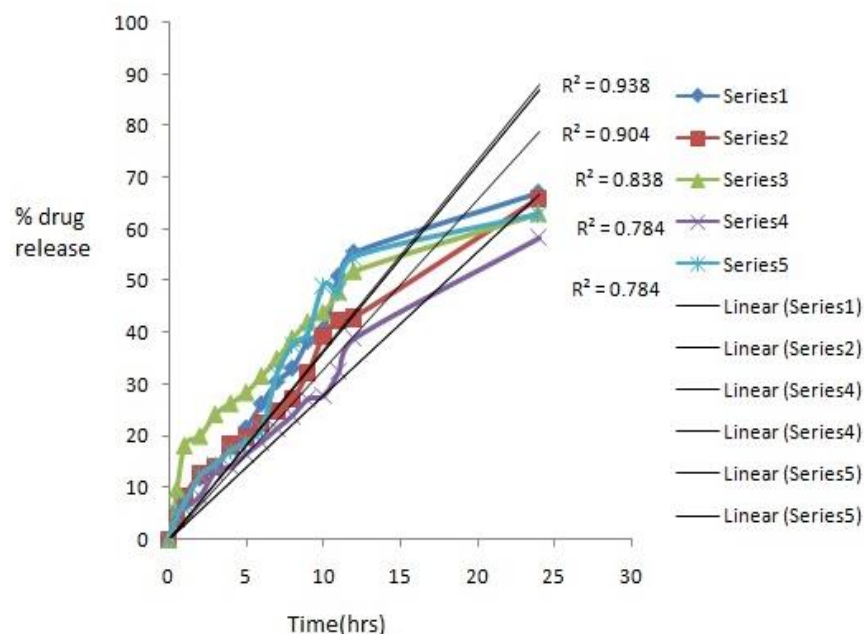


Figure 4: *In vitro* data of prepared Omeprazole floating microspheres at 1:5 organic to aqueous phase ratio

Results and Discussion of Omeprazole Floating Microspheres at 1:10 Organic to Aqueous Phase Ratio

Product Yield: - Product yield of all the formulations was evaluated

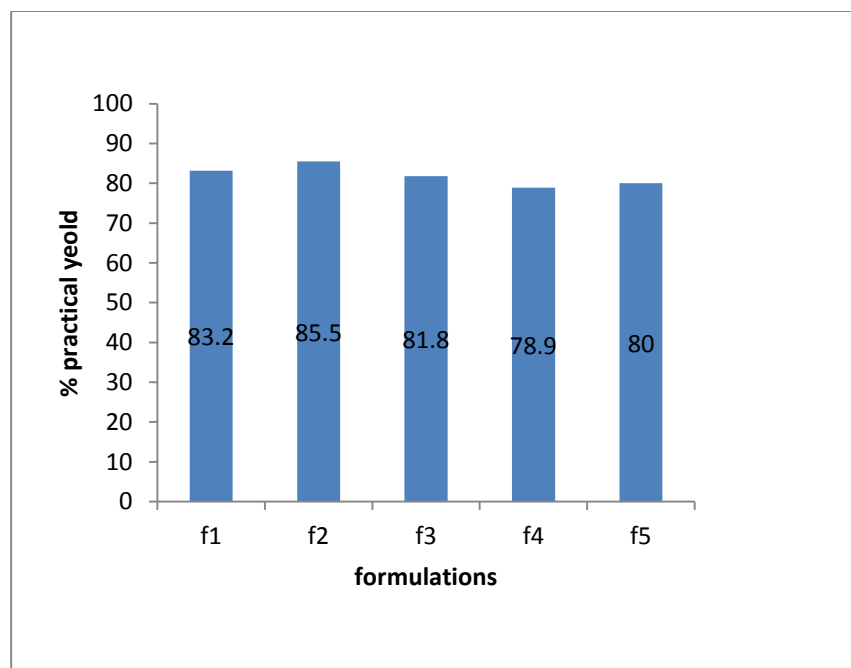


Figure 5: Comparison of product yield among the five formulations of Omeprazole Floating microspheres

The product yield of F1, F2, F3, F4 and F5 was found to be 83.2%, 85.5%, 81.8 %, 78.9% and 80% respectively. On comparison F5 formulation was showing highest yield.

Drug Content: Drug content of all the formulations was evaluated

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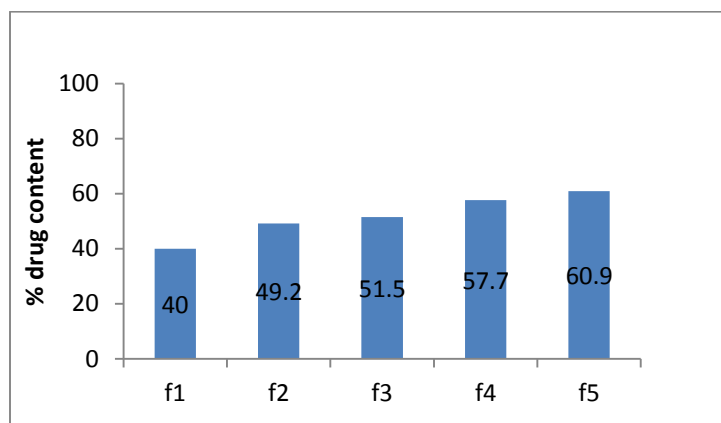


Figure 6: Comparison of drug content among the five formulations of Omeprazole microspheres

The drug content of F1, F2, F3, F4 and F5 formulations was found to be 40 %, 49.2%, 51.5 %, 57.7% and 60.9% respectively. On comparison F5 formulation was showing highest drug content.

Entrapment Efficiency: Entrapment efficiency of all the formulations was evaluated

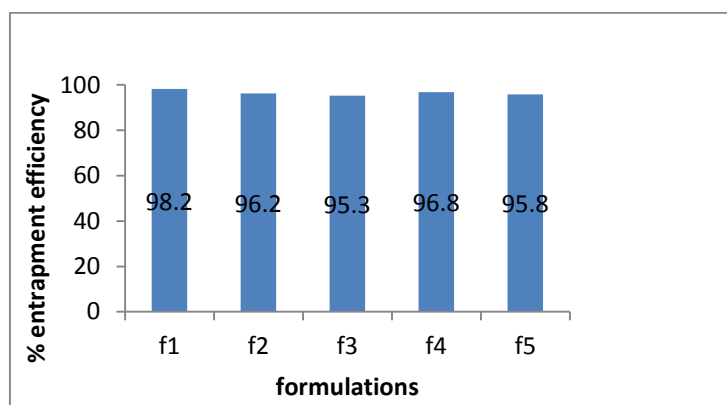


Figure 7: Comparison of entrapment efficiency among the five formulations of Omeprazole microspheres

The entrapment efficiency of F1, F2, F3, F4 and F5 formulations was found to be 98.2%, 96.2%, 95.3 %, 96.8% and 95.8 % respectively. On comparison F4 formulation was showing highest entrapment efficiency.

Different Formulations of Omeprazole Microspheres at 1:10 Organic to Aqueous Phase Ratio

In vitro Release Data:

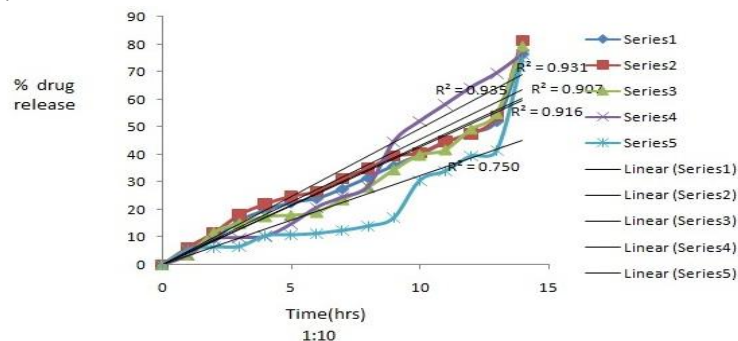


Figure 8: *In vitro* data of prepared Omeprazole microspheres at 1:10 organic to aqueous phase ratio

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Table 3: *In vitro* data of prepared Omeprazole magnesium floating microspheres at 1:10 organic to aqueous phase ratio

TIME	F1	F2	F3	F4	F5
30mins	9.5%	10%	3.6%	3.5%	5.3%
1hr	16.3%	11.5	11.7%	9.1%	6.3%
2hr	19.7%	18.1	15%	9.9%	6.6%
3hr	22%	22	17%	10.3%	10.5%
4hr	24.1%	24.8	17.9%	14.7%	10.8%
5hr	27.5%	26.5%	19%	20.8%	11.3%
6hr	31.6%	31.3%	23.5%	24.5%	12.2%
7hr	35.9%	34.9%	28.1%	28.4%	14.6%
8hr	39.8%	39.4%	34.4%	44.2%	17.9%
9hr	44.3%	40.5%	39.7%	52%	29.8%
10hrs	47.8%	44.6%	41.6%	58.1%	34.3%
11hrs	52%	47.4%	49.1%	64.3%	39.8%
12hrs	76.7%	81.1%	79.1%	76.3%	74.4%

Comparative Study between the Best Formulations of Floating Microspheres at 1:5 and 1:10 Organic to Aqueous Phase Ratio

Comparative study was performed between the best formulations prepared at 1:5 and 1:10 organic to aqueous phase ratio. Both the formulations were compared for Product yield, Drug content, Entrapment efficiency and drug release profiles.

Product Yield: - The product yield of both the formulations was compared.

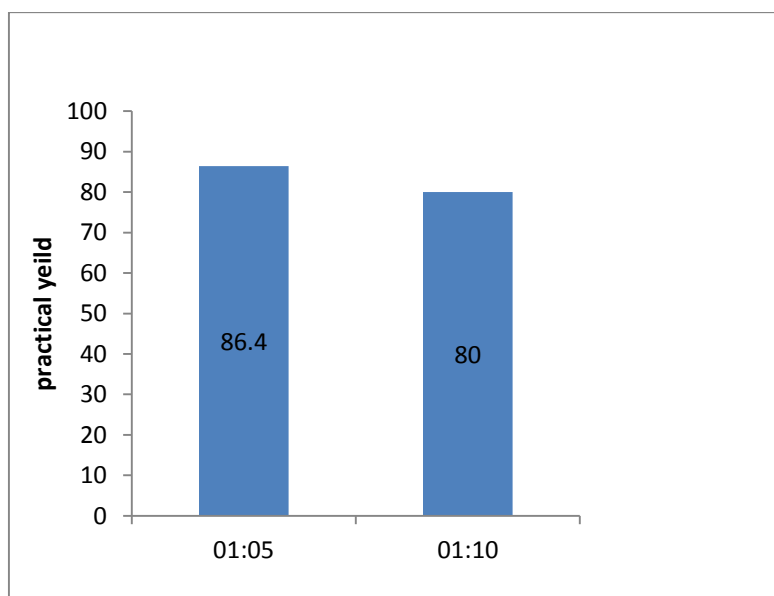


Figure 9: Comparison of product yield among the five formulations of Omeprazole microspheres

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The product yield of F5 formulation 1:5 organic to aqueous phase ratio and 1:10 organic to aqueous phase ratio was found to be 86.4 % and 80 % respectively. On comparison F5 formulation at 1:5 organic to aqueous phase ratio at was showing highest product yield.

Drug Content: - The drug content of both the formulations was compared.

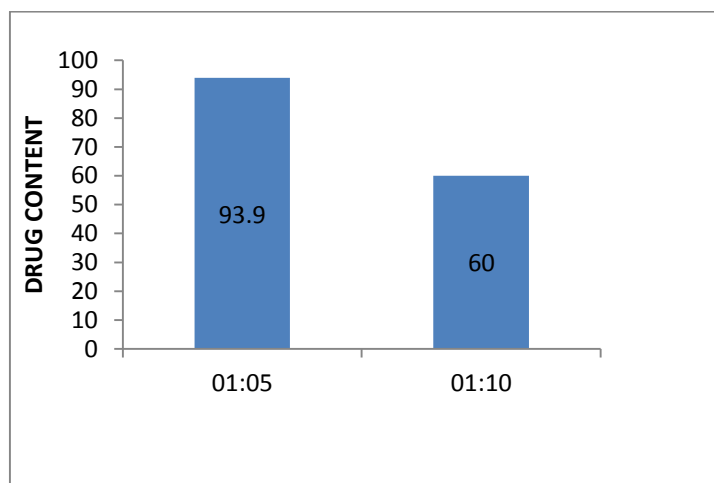


Figure 10: Comparison of drug content among the five formulations of Omeprazole microspheres

The drug content of F5 formulation at 1:5 organic to aqueous phase ratio and 1:10 organic to aqueous phase ratio was found to be 93.9 % and 60 % respectively. On comparison F5 formulation at 1:5 organic to aqueous phase ratio was showing highest drug content.

Entrapment Efficiency: - The entrapment efficiency of F5 and F10 formulations were compared.

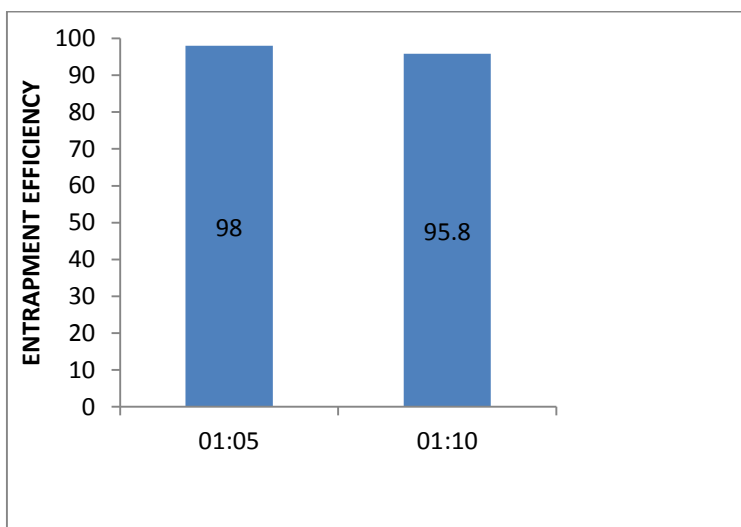


Figure 11: Comparison of entrapment efficiency among the five formulations of Omeprazole microspheres

On comparison F5 formulation at 1:5 organic to aqueous phase ratio was showing highest entrapment efficiency than F5 formulation at 1:10 organic to aqueous phase ratio.

Comparison of In Vitro Drug Dissolution Profiles

Dissolution studies were conducted for a period of 12 hours. Both the formulations were able to sustain the drug release up to 12 hours. In a time period of 12 hours 68.9 % of drug has been released from F5 formulation. Whereas from F10 formulation 70.3% of drug has been released.

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On comparison of all the evaluation parameters F5 at 1:5 organic to aqueous phase ratio was concluded as the best formulation because of highest product yield, more drug content, Highest entrapment efficiency and sustained drug release properties. The percentage of buoyancy was found to be 70.3% for F5 formulation. Several plots were drawn for F5 formulation to determine the order of kinetics and mode of drug release.

Kinetics Data for Best Formulation F5 Formulated at 1:5 Organic to Aqueous Phase Ratio

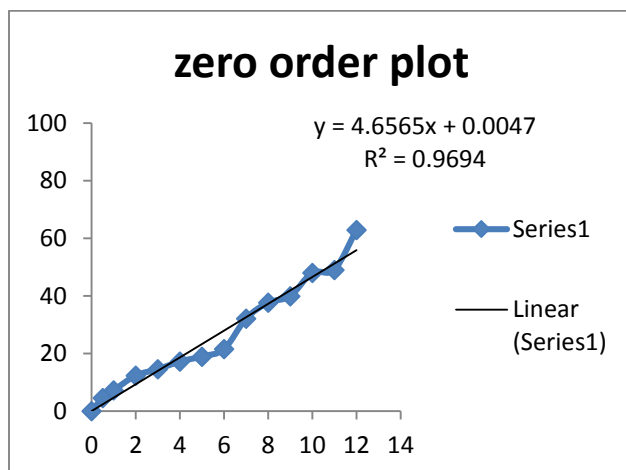


Figure 12: Zero order plot of F5 formulation at 1:5 organic to aqueous phase ratio

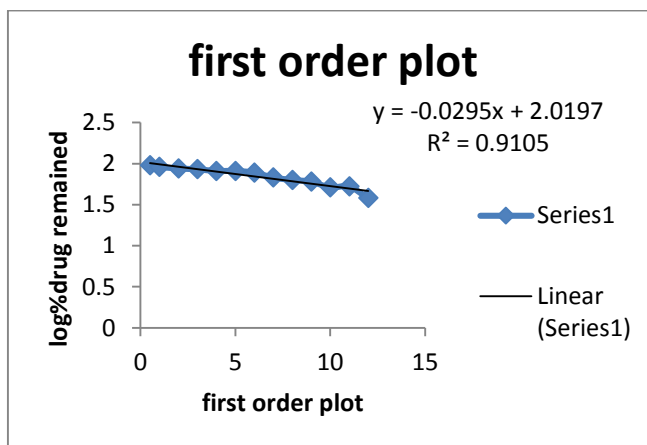


Figure 13: First order plot of F5 formulation at 1:5 organic to aqueous phase ratio

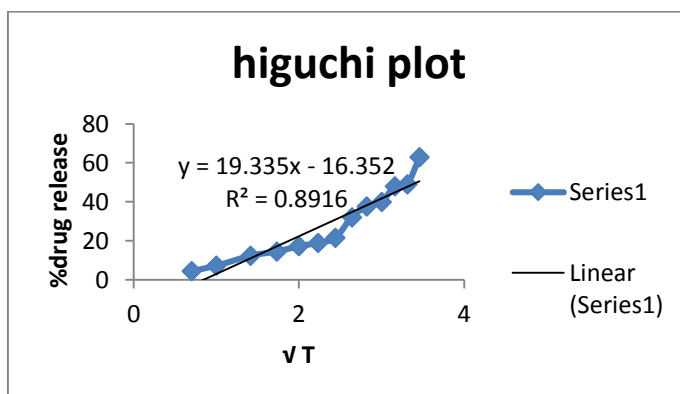


Figure 14: Higuchi plot of F5 formulation at 1:5 organic to aqueous phase ratio

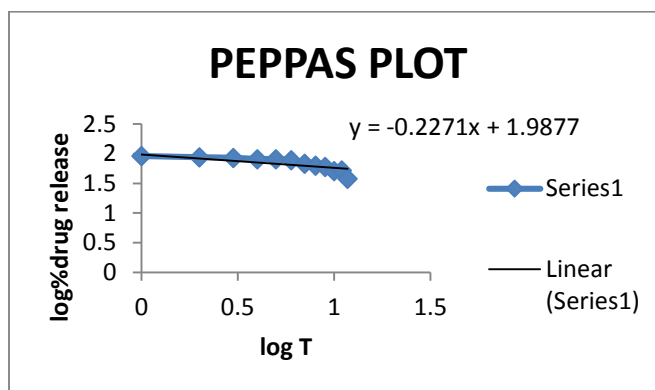


Figure 15: Peppas plot of F5 formulation at 1:5 organic to aqueous phase ratio

Kinetic data reveals that the formulation follows zero order kinetics with fickian diffusion mechanism.

Discussion

In the present investigation Omeprazole loaded Floating microspheres were prepared by solvent evaporation technique.

Process parameters such as stirring time, stirring speed and organic to aqueous phase ratio were optimized. Floating microspheres were prepared at 1:2, 1:5 and 1:10 organic to aqueous phase ratio. There was no formation of microspheres at 1:2 organic to aqueous phase ratio. Microsphere formation was observed at 1:5 and 1:10 organic to aqueous phase ratio. Total five formulations were prepared at each 1:5 and 1:10 organic to aqueous phase ratio by altering drug to polymer ratio to study the effect of polymer concentration upon evaluation parameters such as product yield, drug content, entrapment efficiency, in vitro drug release and percentage of buoyancy.

Out of five formulations prepared at 1:5 organic to aqueous phase ratio On F5 formulation was concluded as the best formulation because of highest product yield, more drug content, Highest entrapment efficiency and sustained drug release properties. The percentage of buoyancy was found to be 72.8% for F5 formulation.

Among the five formulations prepared at 1:10 organic to aqueous phase ratio F5 formulation was concluded as the best formulation because of highest product yield, more drug content, highest entrapment efficiency and sustained drug release properties. The percentage of buoyancy was found to be 70.3% for F5 formulation.

Then the F5 formulations prepared at 1:5 and 1:10 organic to aqueous phase ratio were compared for all the evaluation parameters such as product yield, drug content, entrapment efficiency, and Percentage of buoyancy. In vitro drug release profiles of both the formulations were compared. On comparison from F5 formulation prepared at 1:5 organic to aqueous phase ratio 68.9% of drug was released in a time period of 12 hours proving its sustain release property. Several plots were drawn for F5 formulation to determine the order of kinetics and mode of drug release. From the plots it was concluded that the formulation follows zero order kinetics with fickian diffusion mechanism.

Conclusions

From the results it was concluded that at 1:30 drug to polymer ratio at 1:5 organic to aqueous phase ratio omeprazole floating microspheres can be formulated with good entrapment efficiency, sustained release property and highest percentage of buoyancy.

Further Scope of the Work: Stability studies should be performed at 0.1N Hcl. According to the literature azoles exhibit poor stability in gastric environment. Measurements should be taken to improve the stability of omeprazole floating microspheres in the gastric environment.

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