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Original Research Article

PREPARATION AND OPTIMIZATION OF MUCOADHESIVE MICROSPHERE OF OMEPRAZOLE IN THE TREATMENT OF PEPTIC ULCER

[1]Ravindra Balmiki*, [2]Shubham Patel, [2]Chhaya Chadar, [2]Reshu Jain, [3]Harshna Vishwakarma, [1]Yuvrajsingh Dangi, [4]Asmita Gajbhiye and [2]Shailendra Patil

[1]Sagar Institute of Pharmaceutical Science [SIPS] Sagar, Madhya Pradesh, 470228
[2]SVN institute of pharmaceutical Sciences, Swami Vivekananda University Sagar, Madhya Pradesh, 470228
[3]ADINA College of Pharmacy, Sagar, Madhya Pradesh, 470001
[4]Department of Pharmaceutical Sciences, Dr. H.S. Gour University, Sagar, Madhya Pradesh, 470003

***Correspondence Info:**
Ravindra Balmiki
Sagar Institute of Pharmaceutical Science [SIPS] Sagar, Madhya Pradesh
Email:
ravindrabalmiki9@gmail.com

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ABSTRACT

Gastroesophageal reflux disease (GERD) refers to mucosal damage caused by the abnormal reflux of gastric contents into the oesophagus or beyond, into the oral cavity (including larynx) or lungs. A common condition seen in both, primary care and gastroenterology clinics, the prevalence of GERD (defined by at least weekly heartburn and/or acid regurgitation) has been reported to be 10%–20% in the Western world and <5% in Asia. In a prospective, multi-center study carried out by the Indian Society of Gastroenterology Task Force (n=3,224), 7.6% of Indian subjects were found to have significant GERD symptoms. Omeprazole is soluble in organic solvent such a ethanol and diamethylformamide (DMF). The solubility of omeprazole in ethanol is approximately 30mg\ml DMF and DMSO Microspheres mostly improve the bioavailability of the conventional drug. Microspheres are also called as micro particles. Microspheres are improving quality and particle distribution. Microspheres mostly improve the availability of drug. Microbeads & beads are used alternatively for microspheres.

Keywords: Microspheres, HPMC, Omeprazole, sustain release, peptic ulcer treated.

INTRODUCTION

Microspheres mostly improve the bioavailability of the conventional drug. Microspheres are also called as micro particles. Microspheres are improving quality and particle distribution. Microspheres mostly improve the availability of drug. Microbeads & beads are used alternatively for microspheres. Microspheres are classified into two types such as microcapsules &micrometrics. The spherical shell of microspheres is usually made up of polymers which are having a diameter a micrometre or nanometer range. Microspheres can be used

for the controlled release of drugs, vaccines antibiotics & hormones (Dutta *et al.,* 2011). Microsphere may be defined as small spherical particles with diameter 1 µm to 1000µm. Microspheres are free flowing powder consisting of proteins & synthetic polymers. Microspheres are made up of Polymeric waxy or other protective materials. Drug absorption & its side effects due to the irritating drug against the irritating drug against the gastrointestinal mucosa is improved because of small size of microspheres which get widely distributed through the gastrointestinal tract. Microsphere consists of core of material and polymer matrix. Some materials are coated that is the core of materials (Mukund *et al.,* 2012). Morphology of microspheres is observed by a scanning electron microscopy. It should provide opportunity for protection & masking. In case of microencapsulation is used to modify & retard drug release. Their small particle sizes are widely distributed throughout the gastrointestinal tract which improves drug absorption & reduces side effects due to localized build-up of irritating drug against the gastrointestinal mucosa (Kawatra *et al.,* 2012).

Advantages of microspheres:

1. Particle size reduction for enhancing solubility of the poorly soluble drug (Ramteke *et al.,* 2012).
2. Provide constant and prolonged therapeutic effect.
3. Provide constant drug concentration in blood there by increasing patent compliance,
4. Decrease dose and toxicity.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.

Omeprazole

Omeprazole is a proton pump inhibitor used to treat GERD associated conditions such as heartburn and gastric acid hypersecretion, and to promote healing of tissue damage and ulcers caused by gastric acid and *H. pylori* infection.

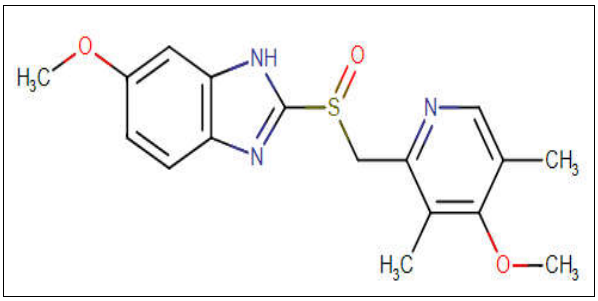

Figure 1: Structure of Omeprazole

MATERIALS AND METHODS

Preformulation study

1. Physical Appearance:

The drug Ascorbic acid was found as white or slightly yellow crystal powder.

2. Melting Point:

The Melting point of Omeprazole was determined with the help of Melting Point apparatus and was found to be 155-160°C.

3. Solubility:

The solubility is the maximum quantity of a solute that can be dissolved in certain quantity of solvent at a specified temperature. Excess amount of solute was suspended in 9 mL each of different solvents at room temperature in tightly closed test tubes and shaken on a wrist action shaker for 24 h. The solubility profiles of omeprazole in various solvents.

4. Partition coefficient:

The partition coefficient of the drug was measured by taking 10 mg of drug in 10 mL of each ethanol and water/PBS (pH 7.4). The drug in the mixture of phases was shaken on a

wrist action shaker for 24 h. Both the phase were separated using separating funnel and aqueous phase analyzed for the amount of drug after suitable dilution using UV visible spectrophotometer (cintra-10 GBC, Japan). The concentration in organic phase was determined by difference in initial concentration and concentration in aqueous phase. This was used to calculate the partition coefficient of the drug in two selected phases using the formula:

$$P_{o/w} = C_{octanol}/C_{water/PBS\ (pH\ 7.4)}$$

5. FTIR Spectroscopy:

The FTIR spectra of Omeprazole & its physical mixture with Ethyl Cellulose & HPMC. The FTIR spectra of physical mixture did not show any significant difference from those for the pure drug. These results indicate that there was no positive evidence for the interaction between Omeprazole & polymer material. These results clearly indicate the usefulness of the utilized polymer for the preparation of Microspheres of Omeprazole. In physical mixture of drug and polymer, there was neither masking of single characteristic peak nor existence of additional peak in the spectra. So, we conclude that drug and polymers are compatible with each other.

6. UV Spectroscopy:

Stock solutions (100ml) of drug sample (Omeprazole) was prepared by dissolving accurately weighed 10 mg of drug sample in Methanol till drug dissolved completely. Then volume was made upto 100 ml. Then 0.1,0.2,0.3,0.4,0.5,0.6,0.8,1.0 ml of stock solution were transferred to a 10.0 ml volumetric flask and volume made up with respective solvents to get the standard solutions of concentration 1-10 µg/ml. The absorbance of the resulting solutions were measured spectrophotometrically at respective wavelengths of maximum absorbance using corresponding solvent as blank. Calibration curve was plotted. The maximum absorption value of pure drug Omeprazole was found at 306 nm wavelength.

PREPARATION OF MICROSPHERE:

1. Solvent evaporation technique:

Development of floating microspheres by solvent evaporation method has been applied extensively in pharmaceutical industries for various purposes such as controlled drug delivery, masking the taste and odour of drugs, protection of drug degradation (Bayomi *et al.,* 1998).

This method involves the emulsificationof an organic solvent containing dissolved polymer and dissolved dispersed drug in an excess amount of continuous phase, with the help of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape (Sinha *et al.,* 2004). When the desired droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is realized under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric micro particles entrapping the drug. The solid micro particles are recovered from the suspension by filtration, centrifugation, or lyophilisation. In solvent evaporation technique, there are basically two systems which include single and multiple emulsion solvent evaporation technique.

a. Single emulsion solvent evaporation technique:

In case of single emulsion solvent evaporation technique, there are also two systems such as oil-in-water (o/w) and water in oil (w/o). For insoluble or poorly water-soluble drugs, the oil-inwater (o/w) method is frequently used. This method is the simplest and effective method for the preparation of floating microspheres.

In this method, the polymer is dissolved in organic solvents such as dichloromethane, chloroform or ethyl acetate, either alone or in combination in which had been used by various scientific investigators in their study. The drug is either dissolved or dispersed in polymer solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in water emulsion by using a surfactant or an emulsifying agent.

b. Multiple emulsion technique:

Multiple emulsion or double emulsion technique is appropriate for the efficient incorporation of water soluble peptides, proteins and other macromolecules. In this process the polymers are dissolved in an organic solvent and emulsified into an aqueous drug solution to form an emulsion. The primary emulsion is reemulsified into an aqueous solution containing an emulsifier to produce multiple w/o/w dispersion.

The organic phase acts as a barrier between the two aqueous phases, preventing the diffusion of the active material toward the external aqueous phase. Microspheres developed by w/o/w method exhibit various characteristics such as porous or nonporous external shell layer enclosing hollow, macroporous, or microporous internal structures depending on different parameters. These methods utilize high-speed homogenization or ultra sonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure.

2. Procedure:

1. Firsty issues all glassware clean and dried.
2. The polymer hpmc are weight and dissolved in the acetone to the form of homogeneous solution.
3. The drug omeprazole is dissolved or dispersed in polymer solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in water emulsion by using a surfactant or an emulsifying agent.
4. These was added 50ml of aqueous phase solution being stir 800rpm to emulsified the added fine droplets.
5. After the formation of stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring.
6. Solvent removal from embryonic microspheres determines the size and morphology of the microspheres.
7. It has been reported that the rapid removal of solvent from the embryonic microspheres leads to polymer precipitation at the o/w interface.
8. Drug and polymers are dissolved at room temperature into polar solvents such with vigorous agitation to form uniform drug–polymer dispersion.
9. The produce microspheres was examined by the microscopy.

Table 1: Composition of microspheres

Ingredients	F1	F2	F3	F4	F5
Drug	20mg	20mg	20mg	20mg	20mg
HPMC	5%	20%	10%	10%	15%
PVP	0.5%	1.5%	1%	0.5%	1%
EC	0.5%	1.5%	1%	0.5%	1%
PVA	1%	2%	0.5%	1%	0.5%
HEC	0.5%	1.5%	1%	0.5%	1%

Characterization of Microspheres:

The prepared microspheres were evaluated for product yield, drug content, entrapment efficiency, and *in vitro* drug release studies.

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 (Patil *et al.,* 2003).

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 (Chinna *et al.,* 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 17240 rpm for 40 minutes. The free concentration of the drug in the supernatant measured spectrophotometrically (Jayvaden *et al.,* 2010). Entrapment efficiency is calculated by the following equation:

% Entrapment Efficiency= W-w X 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 (Basul and Adhiyanam, 2008).

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.

RESULTS AND DISCUSSION

The FTIR spectra of Omeprazole & its physical mixture with ethyl cellulose & HPMC. The FTIR spectra of physical mixture did not show any significant difference from those for the pure drug. These results indicate that there was no positive evidence for the interaction between Omeprazole & polymer material.

The absorbance of the resulting solutions were measured spectrophotometrically at respective wavelengths of maximum absorbance using corresponding solvent as blank. Calibration curve was plotted. The maximum absorption value of pure drug Omeprazole was found at 306 nm wavelength.
The product yield of prepared five formulations F1, F2, F3, F4 and F5 was found to be 86.92%, 92.16%, 87.08%, 88.32 % & 89.04% respectively. Out of the five formulations the higher product yield was observed for F2 (92.16%) formulation.
The drug content of prepared five formulations F1, F2, F3, F4 and F5 was found to be 23.2%, 28.5%, 13.1%, 18.4% & 21.8% respectively. Out of the five formulations the highest drug content was observed for F2 (28.5%) formulation.
The entrapment efficiency of prepared five formulations F1, F2, F3, F4 and F5 was found to be 65.7%, 76.6%, 69.6%, 60.4% & 65.8% respectively. Out of the five formulations the highest entrapment efficiency was observed for F2 (76.6%) formulation.
In all above the formulations the drug release was sustained for 7 hrs. From F1, F2, F3, F4, F5 formulations the percentage of drug release was found to be 72.4%, 80.2%, 42.2%, 78.2%, and 43.2% in a time period of 7 hrs. Out of the five formulations the higher drug release was observed for F2 (80.2) formulation.
Drug content in F1, F2, F3, F4,and F5 Formulation were estimated by UV Spectrophotometric method.
Percent loading efficiency were found in the range of 93.64 to 58.66%. Formulation F2 containing HPMC (20%), Poly vinyl pyrrolidine (1.5%), ethyl cellulose (1.5),poly vinyl alcohol (2%), and hydroxy ethyl cellulose (1.5%) showed maximum percent loading of drug up to 93.64%.
Formulation F2 containing percentage yield (92.16 to 0.043), drug content (28.5 to 0.59), entrapment efficiency (76.6 to 0.94), particle size (205.1 to 0.42) and drug release (93.64 to 3.05) of drug. Above the formulation f1 f2 f3 f4 and f5 the highest range found to f2 formulation.

Table 2: Physical properties of Omeprazole

Physical properties	Observed
Appearance	White or slightly yellow
Odor	Characteristics

Table 3: Solubility profile of Omeprazole

Solvent	Solubility
Distilled water	Freely soluble
Alcohol	Soluble
Methanol	Freely soluble
Chloroform	Insoluble

Table 4: Partition coefficient of Omeprazole

Solvent	Partition coefficient
ethanol/water	0.950

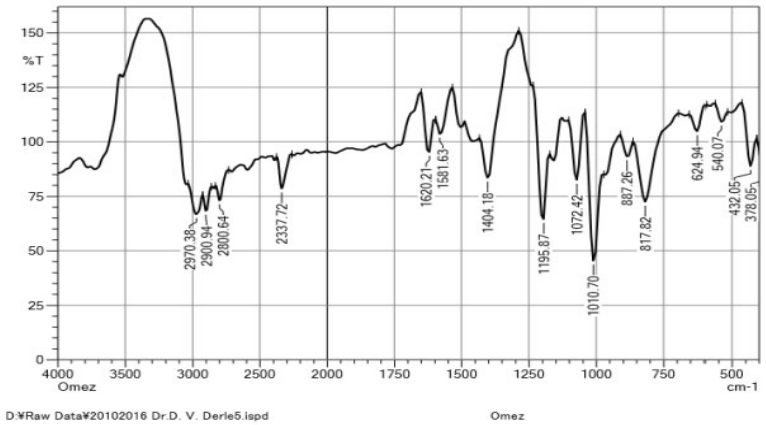

Figure 2: FTIR spectrum of omeprazole

Table 5: FT-IR Spectral Analysis of omeprazole

Observed band frequency (cm^{-1})	Functional group
3711,3626	N-H stretching
2978	C-Hstretching
1728	C=C stretching
1627	C-C ring stretching
1581	S=O bending
1458	C-N stretching
1195	C-O stretching

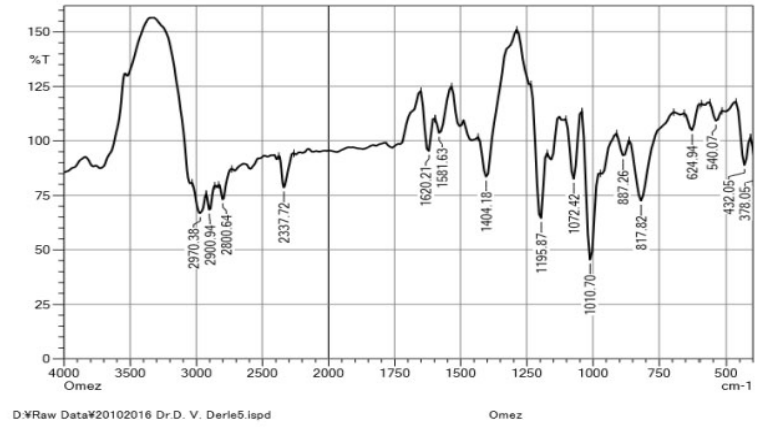

Figure 3: FTIR Spectrum of Physical mixture of Omeprazole

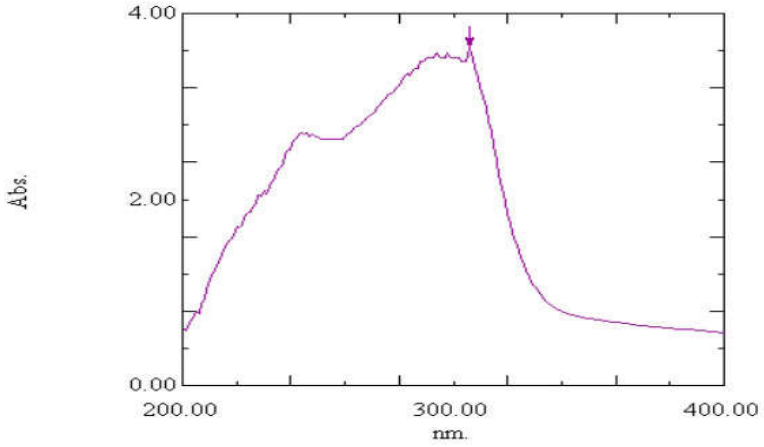

Figure 4: UV Visible Spectrum of Omeprazole

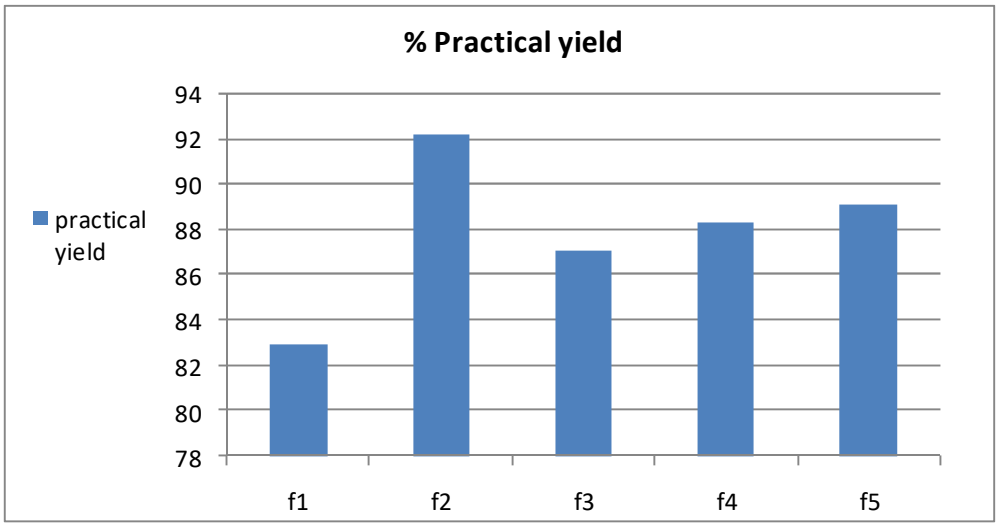

Figure 5: Graph of Percentage yield

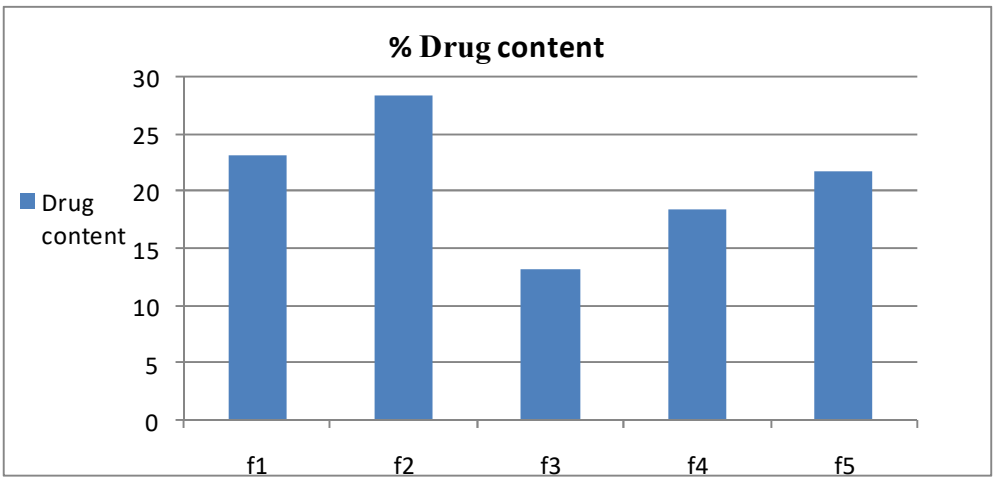

Figure 6: Graph of drug content

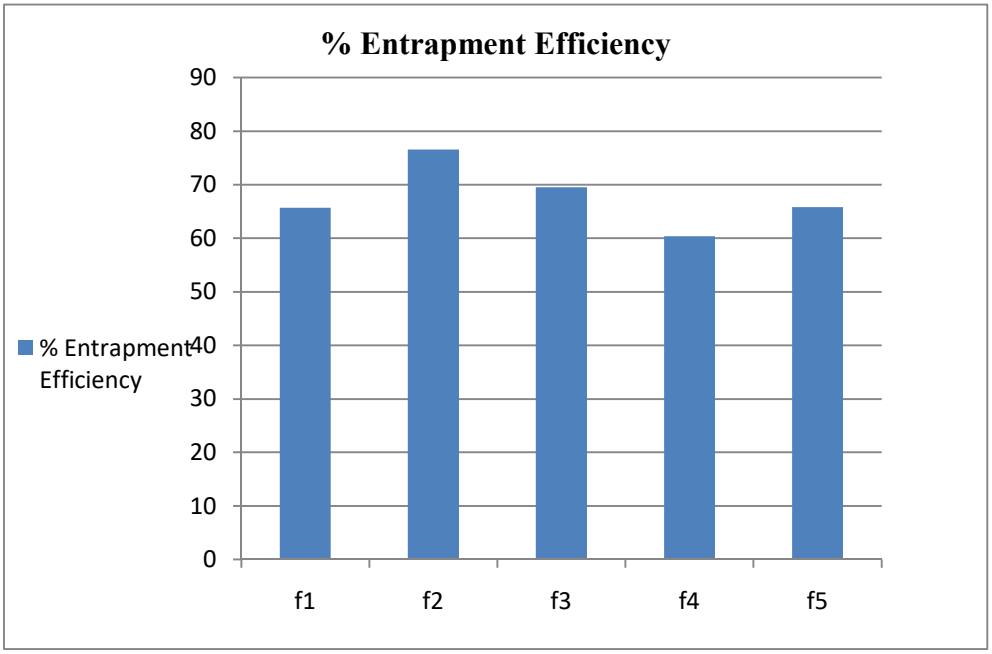

Figure 7: Graph of entrapment efficiency

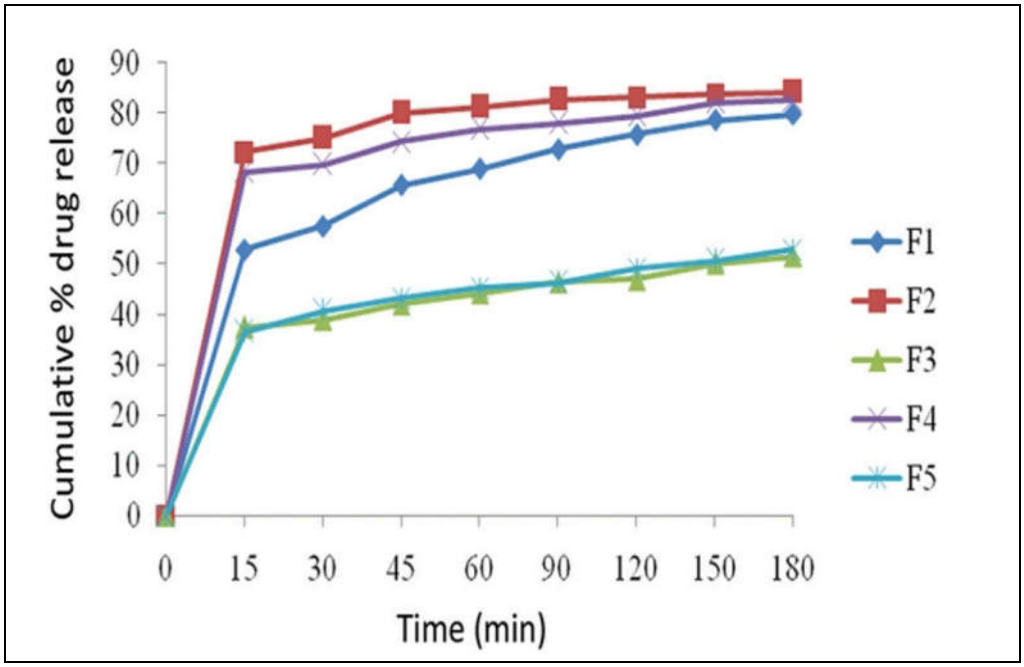

Figure 8: *In-vitro* drug release of microspheres

Table 6: Dissolution profile of microspheres

Time	F1	F2	F3	F4	F5
30 min.	54.2	71.3	35	66.2	35
1 hr	56.5	73.2	36.5	67.3	37.2
2hr	63.5	75.5	37.3	69.2	37.7
3hr	65.5	76.2	38.7	70.3	38.5
4hr	67.8	77.3	39.4	72.5	40.2
5hr	69.2	78.5	40.2	74.4	41.5
6hr	71.3	79.5	41.5	76.2	42.3
7hr	72.4	80.2	42.5	78.2	43.2

Table 7: Evaluation of microspheres of Omeprazole

Formula	Percentage yield	Drug content	Entrapment Efficiency	Particle size	Drug release
F1	86.92±0.029	23.2±0.36	65.7 ±1.02	129.5±0.36	70.67± 1.24
F2	92.16±0.043	28.5±0.59	76.6 ±0.94	205.1±0.42	93.64±3.05
F3	87.08± 0.029	13.1±1.02	69.5±1.26	168.3±0.53	79.13±1.44
F4	88.32± 0.016	18.4±0.48	60.4±0.46	195.7±0.18	67.25±1.67
F5	89.04± 0.025	21.8±1.14	65.8±1.31	179.4±0.24	58.66±1.77

CONCLUSION

In this present study formulations of enteric coated Omeprazole granules are formulated into a tablet. The Omeprazole compressible enteric coated granules were prepared by using different enteric coated polymers such as HPMC Phthalate, Eutragit NE30D and Kollicoat MAE30DP with different ratios and plasticized with PEG. The Omeprazole granules which are coated with 8% Eutragit and plasticized with 2%PEG meet the USP criteria in drug release. Finally I conclude that formulation shows the best release in the layers Omeprazole and that may fulfils the objective of the study. In this study attempt have been made to prepare omeprazole magnesium microspheres by solvent evaporation method using ethyl cellulose hpmc as synthetic polymer. Process parameters such as stirring speed, stirring time were optimized. The effect of polymer Concentration up on particle size, drug

content, entrapment efficiency and drug release was studied.

In this study the Formulations have been prepared at 1:5 and 1:10 organic to aqueous phase ratio. The effect of polymer Concentration up to f2 formulation on product yield 92.16%, particle size 205.1%, drug content 21.8%, entrapment efficiency 76.6% and drug release was 93.64% studied.F2 formulation was found to be better because of high practical yield, good drug content and high entrapment efficiency.Out of the 5 formulations prepared at organic to aqueous phase ratio F2 formulation was showing better results 80.2%, and F2 formulation was able to delayed the drug release up to 7hrs.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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