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RESEARCH ARTICLE

DESIGN AND IN-VITRO EVALUATION OF STOMACH SPECIFIC FLOATING MICROSPHERES OF OMEPRAZOL

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ABSTRACT

In this present study attempt was made to prepare the floating microspheres of Omeprazol which will help in releasing the proton pump inhibitor drugs in stomach. So that they can be absorbed in stomach for a longer period of time and show better bioavailability. The IR spectrum of pure drug and drug mixture indicated that there was no interaction between polymers and drug. The DSC also revealed that there was no interaction between polymers and drug. The shape of microspheres was almost spherical and smooth as indicated by SEM. Encapsulation efficiency was in the range of 66.23±0.115 to 88.53±0.578%. As the polymer concentration increases, the encapsulation efficiency also increases. *In vitro* buoyancy studies of the prepared microspheres was in the range of 70.9 to 79.1%.Omeprazole release from microspheres was slow and extended period of time due to increase in polymer concentration. The release mechanisms for all the formulation followed by non-fickian diffusion mechanism. The drug release from formulation OMP6 showed 87.26% for a long period of 12hrs and also observed that increase in Eudragit S100 concentration the drug release was decreased. The release mechanisms for all the formulation followed by non-fickian diffusion mechanism.

Key words: Microspheres, Omeprazol, Eudragit, HPMC.

INTRODUCTION

The floating drug delivery system or hydro dynamically balanced systems are among the several approaches that have been made developed in order to increase the gastric transit time of drug. The microspheres are characteristically free flowing powders consisting of natural or synthetic polymers and ideally having a particle size less than 200µm. Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug[1]

Microspheres are one of the multiparticulate delivery system and are prepared to obtain controlled the drug release from the dosage form to improve bioavailability, reduces the adverse action 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.[2]

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 to1.2hr.

The Proton pump inhibitor drugs are used in the treatment when there is more acid secretion in the stomach. These drugs will bind to the H+/K+ ATPase present in the parietal cells in stomach. So to show their maximum action these drugs should remain in the stomach, which is possible by preparing the Floating Microspheres of Proton pump inhibitor drugs.

The proton pump inhibitors are well absorbed in the stomach at pH 5 than in intestine. The floating microspheres are helpful in increasing the absorption of these drugs.

MATERIALS AND METHODS

Omeprazole was obtained as gift sample from Nishka labs, Hyderabad. Ethyl cellulose, HPMC, Dichloromethane, Poly vinyl alcohol, Polyethylene glycol was obtained fromS.D Fine Chemicals Pvt Ltd Mumbai. Eudragit RS100 was obtained from Edict pharmaceuticals, Chennai.

Preparation of Omeprazole Microspheres

The microspheres were prepared by solvent evaporation method.0.46g of polyvinyl alcohol is dissolved in 100ml of distilled water. Different quantities of Ethyl cellulose, HPMC and Eudragit RS100 in individual and combination of these polymers was dissolved in dichloromethane by using magnetic stirrer. A known quantity of Omeprazole (40mg) was dissolved in the above polymeric solution along with 0.1% of polyethylene glycol (surfactant). The resulting solution was then poured into 500ml beaker, containing 150ml of polyvinyl alcohol (0.46%w/v). The mechanical stirrer was used to evaporate dichloromethane completely by stirring at 700rpm for 2hrs.The details of formulation was mentioned in table no.1.

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Table 1: Formulation Table for Omeprazole Microspheres

S.No	Formulation code	Drug (mg)	Ethyl cellulose (gm)	HPMC (gm)	Eudragit RS100 (gm)	DCM (ml)	PVA (ml)	Speed (rpm)
1	OMP1	40	0.8	0.2	0.1	20	150	900
2	OMP 2	40	0.8	0.1	0.2	20	150	900
3	OMP 3	40	0.8	0.1	-	20	150	900
4	OMP 4	40	0.8	-	0.1	20	150	900
5	OMP 5	40	0.8	0.2	-	20	150	900
6	OMP 6	40	0.8	-	0.2	20	150	900
7	OMP 7	40	0.8	0.1	0.1	20	150	900
8	OMP 8	40	0.6	0.2	0.2	20	150	900

HPMC: Hydroxy Propyl Methyl Cellulose, DCM: Dichloromethane, PVA: Polyvinyl

As the solvent was being evaporated, the emulsifier continued to maintain the oil droplets in their spherical configuration and prevented from aggregating until the solvent was completely evaporated, and the microspheres were hardened as discrete particles. Then the microspheres were filtered and washed three times with distilled water, filtered and dried in hot air oven. Then obtained Omeprazole microspheres were performed for further studies.

EVALUATION OF OMEPRAZOLE MICROSPHERES

Bulk density and tapped density

Bulk density and tapped density were measured by using 10ml graduated cylinder. The sample poured in the cylinder was tapped mechanically for 100 times, then tapped volume was noted and bulk density and tapped density were calculated[3].

Each experiment for micromeritic properties was performed in triplicate manner.

Bulk density = Mass / Volume

Tapped density = Mass / Tapped volume

Carr's index:

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. According to the theory, the less compressible material is more flow able. A material having values less than 20 to 30% is defined as the free flowing material, based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula. It is expressed in percentage and is expressed by

$$I = Dt - Db / Dt \times 100$$

Where, **Dt** is the tapped density of the powder and **Db** is the bulk density of the powder.

Hausner's ratio

It indicates the flow properties of the powder and the ratio of Tapped density to bulk density of the powder or granules is called Hausner"s ratio.It is expressed in percentage and is expressed by **H= Dt / Db**

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Angle of repose:

Angle of repose of different formulations was measured by fixed funnel standing method. Microspheres were weighed and passed through the funnel, which was kept at a certain height from horizontal surface. The passed microspheres formed a pile of height 'h' above the horizontal surface and the pile was measured[3]. The angle of repose was determined by

$$\text{Angle of repose } (\theta) = \text{Tan}^{-1} (h / r)$$

Where h is the height of pile and r is radius

Percentage yield:

` Dried microspheres were accurately weighed and the percentage yield[4] was calculated by

% yield = (Practical yield/Theoretical yield) × 100

Study of shape and surface morphology:

Scanning electron microscopy was used to determine shape, surface topography, texture and examine the morphology of fractured or sectioned surface. SEM is commonly used method for characterizing drug delivery systems, owing in large part to simplicity of sample preparation and ease of operation.

Particle Size analysis

Size distribution of the microspheres was determined using the particle size analyzer (Microtrac) equipped with dry accessory system[4].

Drug content and entrapment efficiency

Accurately weighed 100mg of microspheres were powdered in a motar and suspended in 100ml of phosphate buffer pH-6.8 and kept in sonication for 2hrs. Then the samples were centrifuged at 1000rpm for 20mins to remove any the supernatant layer was removed and filtered[43]. From this filtered solution 1ml of sample was withdrawn and diluted to 25ml of phosphate buffer pH-6.8 then it was analyzed spectrophotometrically at 300nm[5].

i) Drug content:

Theoretical drug content
= (Weight of drug loaded / Total weight of Microspheres) X 100

Practical drug content
= Concentration X dilution factor X Conversion factor

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ii) Encapsulation efficiency =

(Actual drug content / Theoretical drug content) X 100

***In vitro* buoyancy studies [6, 7]:**

The microspheres weighing about 0.3 g were spread over the surface of USP XXIII dissolution apparatus (type II) which was filled with 900 ml of SGF (pH 1.2) containing 0.02% tween 20. The medium was agitated with a paddle rotating at 100 rpm for 12 hours. The floating and settled portions of microspheres were recovered separately and were dried and weighed. Buoyancy percentage was calculated by using formula:

$$\% \text{ Buoyancy} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of microspheres}} X\ 100$$

***In-vitro* dissolution studies**

In-vitro dissolution studies of Omeprazole loaded microspheres were performed using USP Paddle Type dissolution test apparatus.100mg of drug loaded microspheres were placed in a muslin cloth and tied to the paddle. 900ml of buffer is used as a dissolution medium. The medium was maintained at 37±0.5ºC at a speed of 100rpm[8].

The *in vitro* dissolution studies were performed at two different pH values i.e. pH

1.2 (simulated gastric fluid pH) for 2 hrs and pH 6.8 (simulated intestinal fluid pH) for 12 hrs. An accurately weighed sample was responded in dissolution medium consisting 900ml of buffer and dissolution was done up to 12hrs.At prefixed time intervals (every 1hour); 1ml of sample was withdrawn and filtered through 0.4 µm membrane filter. The volume of the dissolution medium was adjusted to 900ml at every sampling time by replace same 1ml of dissolution medium[4]. Then the samples were analyzed spectrophotometrically at 300nm.

The release data obtained were fitted into various mathematical models like zero order, Higuchi and Korsmeyer-Peppas to know which mathematical model was best fitting the obtained release profile.

RESULT AND DISCUSSION

PREFORMULATION STUDIES:

Solubility analysis

The available literature on solubility profile of Omeprazole indicated that the drug is Very slightly soluble in water, soluble in methylene chloride, sparingly soluble in ethanol (96 per cent) and in methanol. It dissolves in dilute solutions of alkali hydroxides.

Omeprazole was found to be freely soluble in dichloromethane and Methylene hydrochloride, slightly soluble in ethanol, acetone and methanol, practically insoluble in water. The study was carried out to select suitable dissolution medium for *in-vitro* release studies. The solubility of Omeprazole in acid buffer of pH 1.2 was highest. Hence media containing acid buffer of pH 1.2 were selected for dissolution studies.

FT-IR spectral analysis

The development of a successful formulation depends only on suitable selection of excipients. Hence the physical state of the drug Omeprazole and the polymers, Ethyl Cellulose, HPMC Eudragit S100 individually and the combination of drug and polymers used for microspheres preparation were studied by FTIR (Fourier transform infra-red spectroscopy) to know the drug – polymer compatibility. The physicochemical compatibility of the drugs and the polymer was obtained by FTIR studies (Fig No. 1 to 5). The interpretation values of the FTIR were mentioned in the table No: 2.

In FTIR spectra, C = C–N and S–C = N stretching link vibrations (1624.6 cm–1) and Ar–C–O–CH3 vibration (1202.5 cm–1) accompanied by the resonance band at 1075.4 cm–1 were used to assess the interaction between the polymers and omeprazole in the solid state. The band positioned at 1202.5 cm–1 is related to bending vibrations of the methoxyl groups of Omeprazole

Therefore, there was no alteration and no interaction was observed between polymer and drug in combination. All the characteristic peaks of Capecitabine were present in combination, thus indicating compatibility between drug and polymers and finally confirm that there was no chemical modification of drug has been taken place.

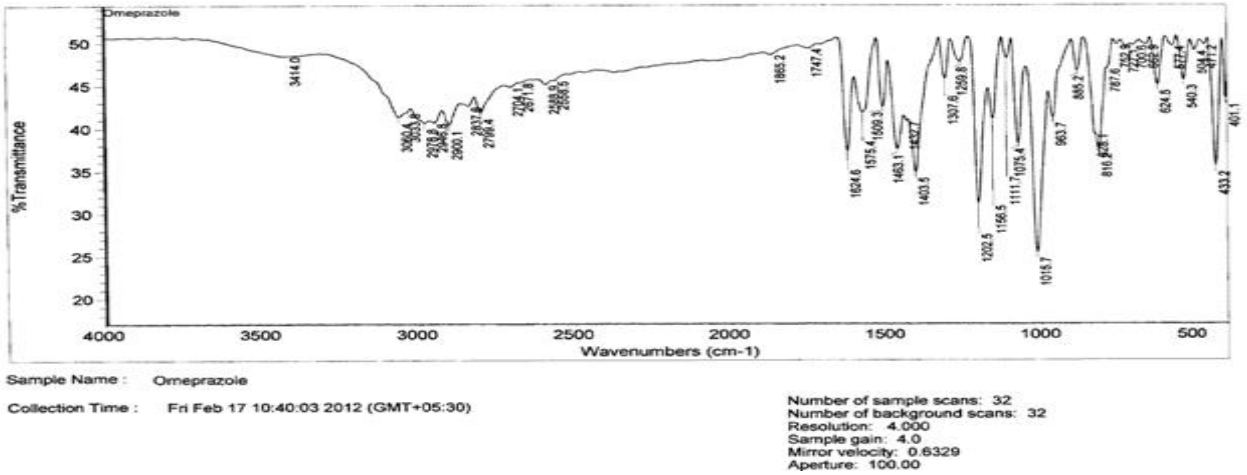

Figure 1: FTIR of pure Omeprazole

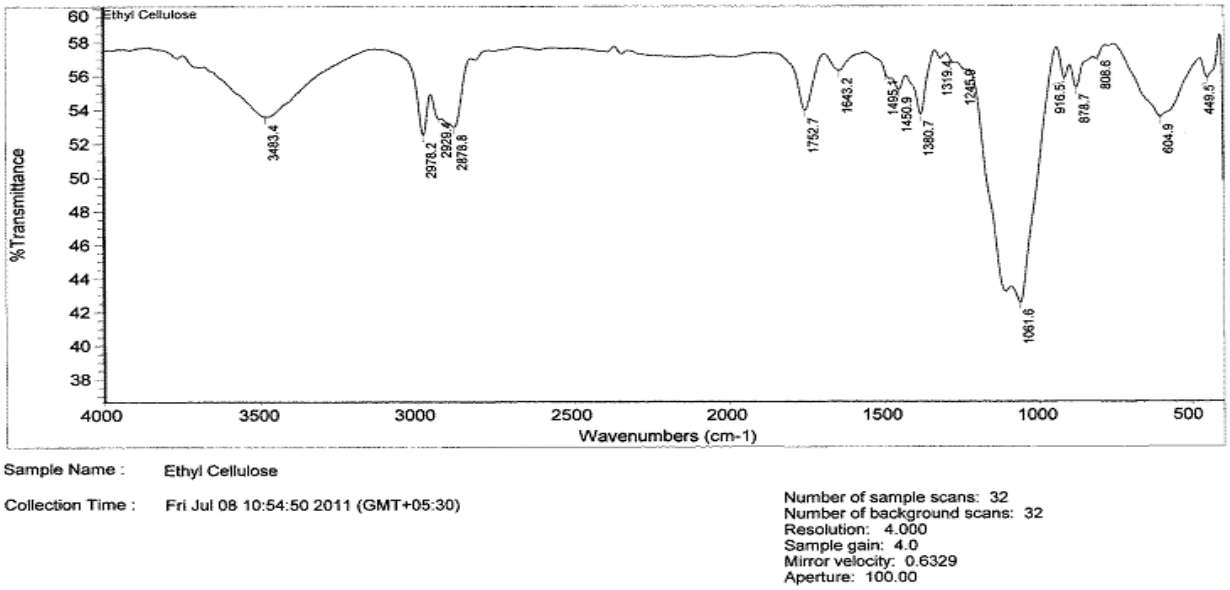

Figure 2: FTIR of Ethyl Cellulose

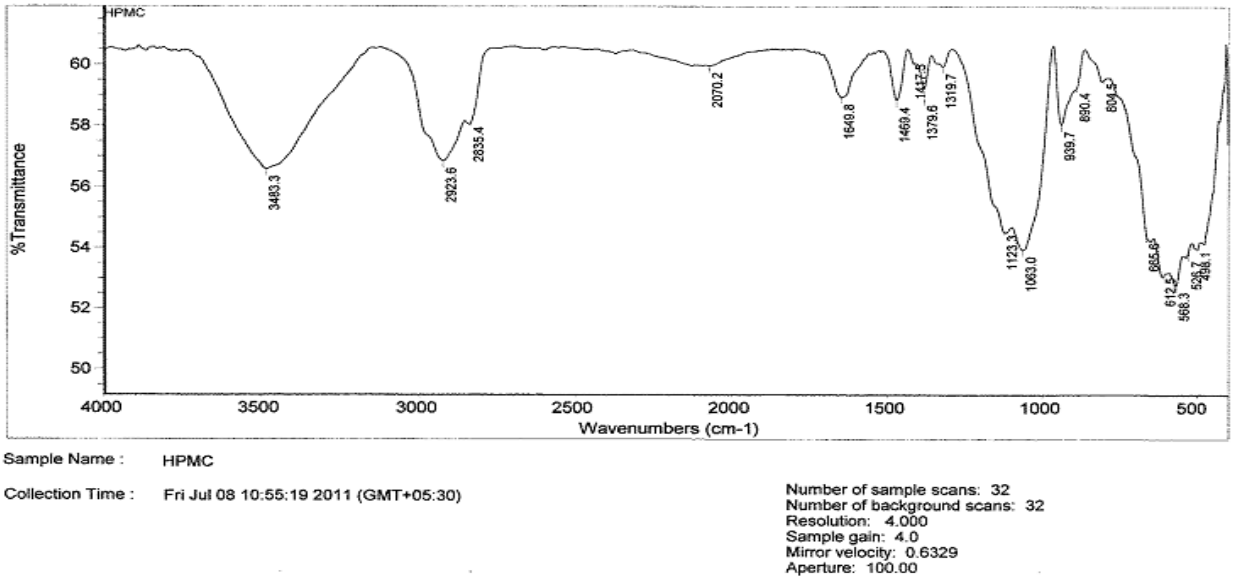

Figure 3: FTIR of HPMC

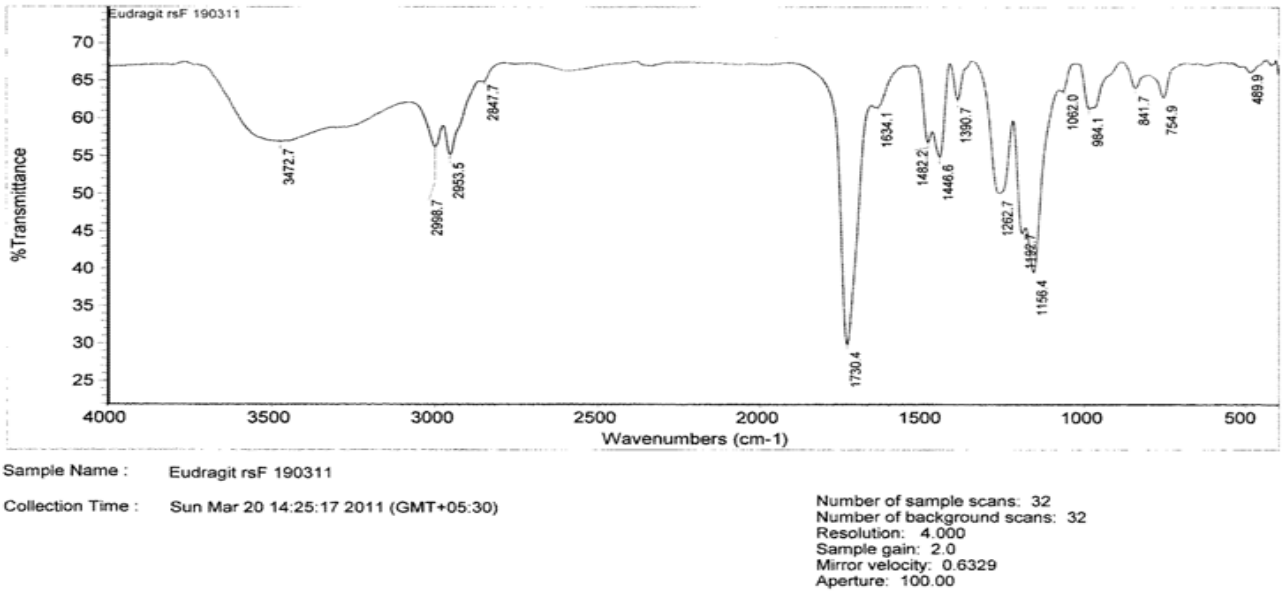

Figure 4: FTIR of Eudragit RS 100

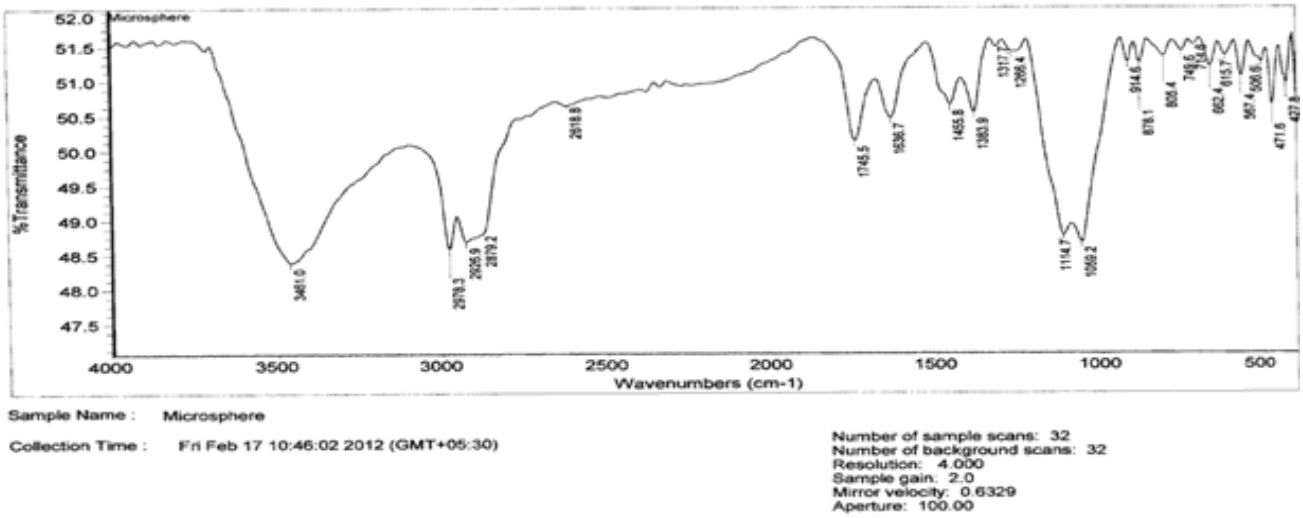

Figure 5: FTIR of Pure Omeprazole, Ethyl Cellulose, HPMC and Eudragit RS 100

Table 2: Comparison of FTIR peaks of drug and polymers

S.No	Formulation	Wave number (cm^{-1})
1	Omeprazole	3060.4, 3033.8, 2976.8, 2956.8, 2900.1, 2837.9, 2799.4, 2704.1, 2671.8, 2588.9, 2558.5, 1865.2, 1747.4, 1624.6, 1575.4, 1509.3, 1463.1, 1432.7, 1403.5, 1307.6, 1259.8,1202.5, 1156.5, 1111.7, 1075.4, 1015.7, 963.7, 855.2, 816.2
2	Ethyl Cellulose	3469.43, 2977.96, 2881.94, 174896, 169.22, 1448.01, 139.70, 1307.151, 1242.98, 1119.18, 1064.87, 918.95, 880.17, 705.16, 657.43, 436.77
3	HPMC	3446.66, 2922.70, 2831.32, 1719.86, 1624.18, 1463.50, 1384.79, 1127.35, 1068.80, 935.823, 661.83, 613.48, 566.45, 447.16
4	Capecitabine + Ethyl Cellulose + HPMC	3468.28, 2974.34, 2921.13, 2858.61, 2786.37, 2611.62, 2153.0, 1974.08, 1826.10, 1768.89, 1731.17, 1616.51, 1486.84, 1446.08, 1380.70, 1105.72, 923.04, 878.02, 811.36, 664.06, 575.70, 481.72, 447.04
5	Eudragit RS100	3472.7, 2998.7, 2953.5, 2847.7, 1730.4, 1634.1, 1482.2, 1446.6, 1390.7, 1262.7, 1192.7, 1156.4, 1062.0, 984.1, 841.7, 754.9, 489.9
6	Omeprazole + Ethyl Cellulose + HPMC + Eudragit S 100	3451.0, 2978.3, 2925.9, 2879.2, 2618.8, 1745.5, 1636.7, 1455.8, 1383.9, 1317.7, 1268.4, 1114.7, 1059.2, 914.6, 878.1, 805.4, 749.6

DSC studies

DSC thermograms of Omeprazole, Ethyl cellulose, HPMC and Eudragit RS100 along with their combination of drug with excipients were presented in Figures. 6-9. In case of Omeprazole, endothermic peak were observed at 157.7^{0}C, which corresponds to melting process and the other at 423.7^{0}C due to thermal decomposition. Thermograms of HPMC showed endothermic peaks at 48.7^{0}C and Eudragit RS100 showed two endothermic peaks one at 65.6^{0}C, which corresponds to melting process and the other at 216.9^{0}C due to thermal decomposition Combination of drug and polymers showed endothermic peak at 93.3^{0}C, 381.2^{0}C it may be concluded that the drug has not shown any interaction with different polymers used in preparing the different formulations.

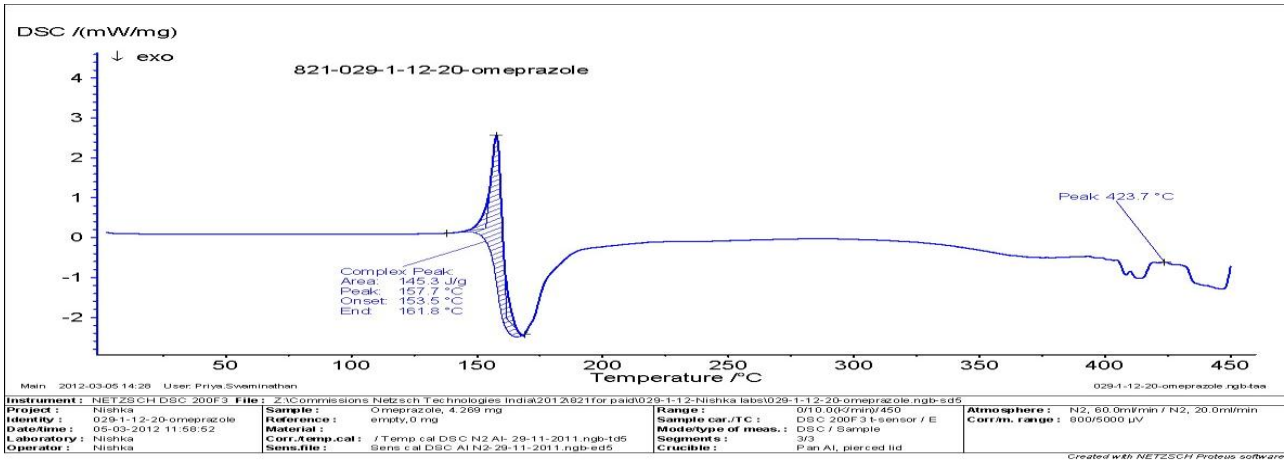

Figure 6: DSC Curve of Omeprazole

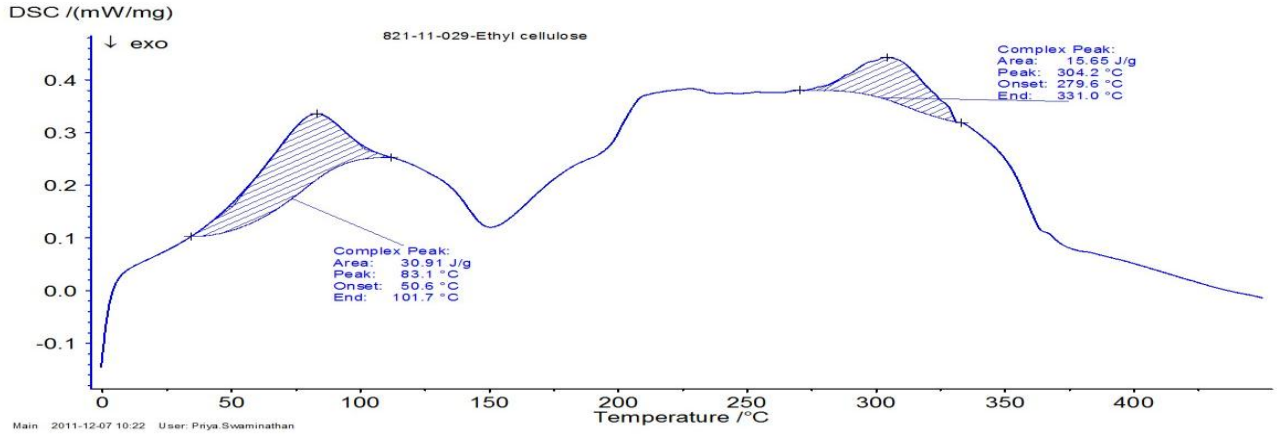

Figure 7: DSC Curve of Ethyl Cellulose

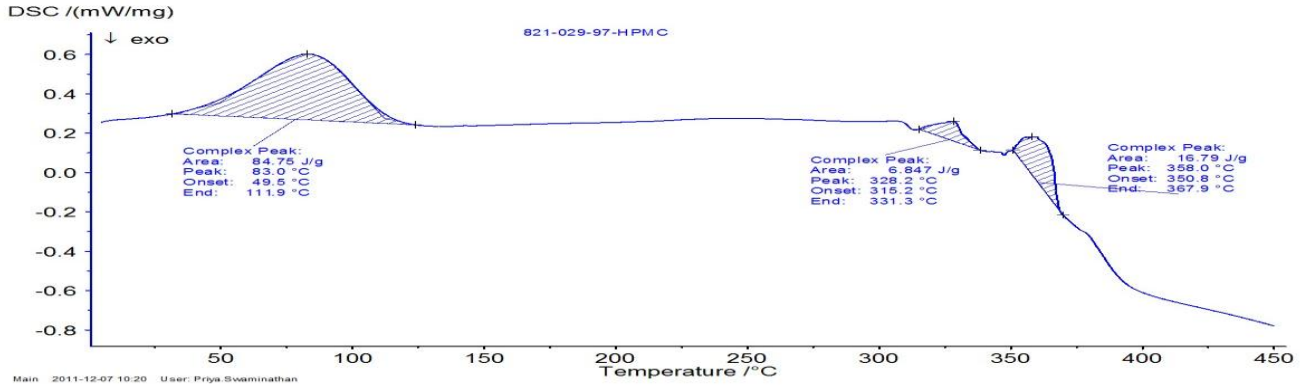

Figure 8: DSC Curve of HPMC

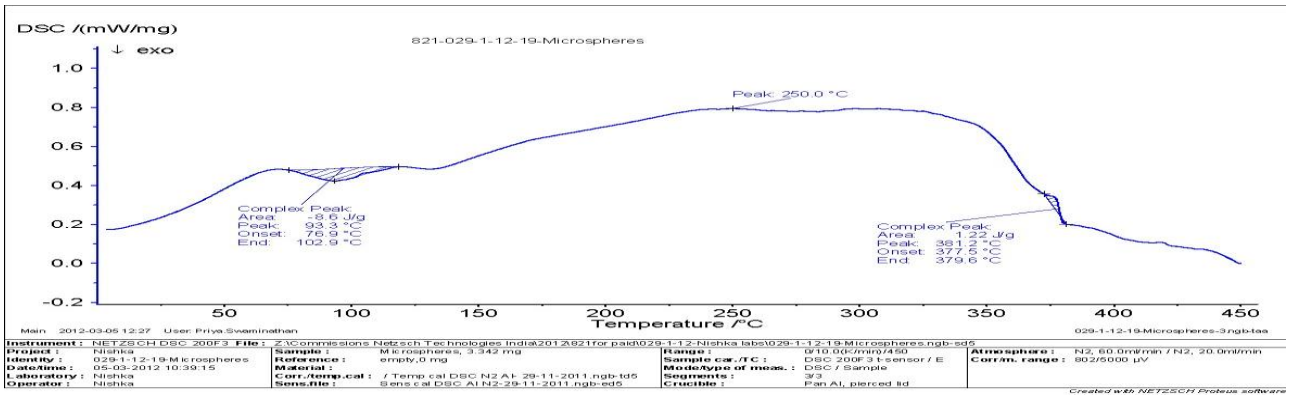

Figure 9: DSC of physical mixture of Omeprazole, Ethyl Cellulose, HPMC and Eudragit RS 100

Thus from IR spectra studies and DSC thermograms we can draw a conclusion that the drug remains in its normal form without undergoing any interaction with the polymers

Micromeritic properties Omeprazole microspheres:

Bulk and Tapped density: Bulk density and Tapped densities showed good packability of the microspheres. The values are given in table no.3

Hausner's ratio: Hausner's ratio range from 1.129±0.0028 to 1.231±0.0040. OMP8 has lowest hausner's ratio indicating good flow. The values are given in table no.4

Carr's index: Carr's index range from 12.231±0.2531 to 18.768±0.262. OMP3 has lowest Carr's index indicating good compressibility. The values are given in table no.4

Angle of repose: All the formulations showed excellent flow ability as expressed in terms of angle of repose value in the range 17.36 ± 0.51 to 29.11 ± 2.39. OMP4 has lowest among all formulations showing excellent flow. The values are given in table no.4

Table 3: Flow properties of Omeprazole loaded microspheres

S.No	Formulation code	Bulk density ± S.D	Tapped density ± S.D
1	OMP1	0.462±0.0065	0.528±0.0084
2	OMP2	0.502±0.0077	0.581±0.0102
3	OMP3	0.463±0.0113	0.527±0.0144
4	OMP4	0.614±0.0124	0.714±0.0167
5	OMP5	0.494±0.0076	0.583±0.0109
6	OMP6	0.450±0.0061	0.538±0.0086
7	OMP7	0.462±0.0065	0.528±0.0084
8	OMP8	0.502±0.0077	0.581±0.0102

Table 4: Derived properties of Omeprazole loaded microspheres

S.No	Formulation code	Hausner's ratio ±S.D	Carr's index± S.D	Angle of repose ± S.D
1	OMP1	1.141±0.002	12.382±0.164	23.12 ±1.042
2	OMP2	1.159±0.002	13.732±0.195	19.17 ± 0.973
3	OMP3	1.139±0.003	12.231±0.253	18.20 ± 0.234
4	OMP4	1.162±0.003	13.974±0.271	17.36 ± 0.517
5	OMP5	1.231±0.004	18.768±0.262	25.29 ± 1.544
6	OMP6	1.168±0.003	13.684±0.272	18.19 ± 0.932
7	OMP7	1.147±0.002	14.347±0.254	20.17 ± 0.471
8	OMP8	1.129±0.003	13.723±0.132	19.15 ± 0.535

Percentage yield

The percentage yield of all the formulations was found to be satisfactory with range of 86.92±0.029 to 96.88±0.016. It also observed that as increase in the polymer concentration the percentage yield also increased. The values are given in table No. 5

Table 5: Percentage Yield of Omeprazole loaded microspheres

S.No	Formulation code	Yield (%) ± S.D
1	OMP1	86.92±0.029
2	OMP2	92.16±0.043
3	OMP3	88.08±0.029
4	OMP4	96.35±0.016
5	OMP5	88.32±0.016
6	OMP6	96.88±0.016
7	OMP7	90.93±0.016
8	OMP8	91.95±0.016

SEM Analysis:

SEM analysis was performed on the prepared Omeprazole loaded microspheres to accesses their surface morphological characteristics as shown in figure No.10. SEM was performed for best formulations to assess their surface. The polymer surface of the microspheres appeared spherical with smooth texture surface.

The micrographs do not show any pores on microspheres. Smooth surface reveals complete removal of Dichloromethane from microspheres.

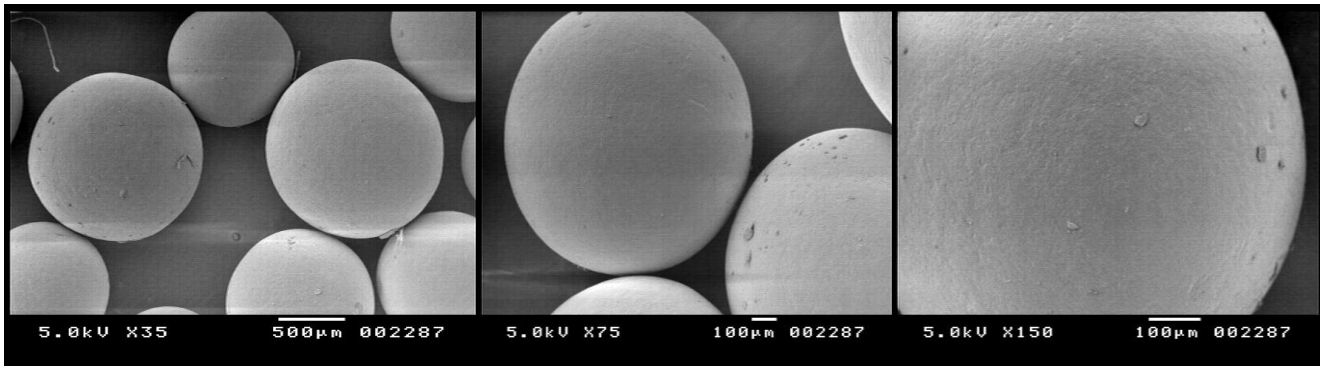

Figure 10: SEM images of Omeprazole loaded microsphere

Drug content and encapsulation efficiency

The drug content of microspheres determines the amount of drug entrapped in the microspheres Actual drug content and encapsulation efficiency of all the formulations are shown in table No.6. Many factors affect the entrapment efficiency of the drug in microspheres. E.g. Nature of the drug, polymer concentration, drug-polymer ratio and stirring speed etc. Generally low concentration of polymer shows low encapsulation efficiency.

It was observed that the encapsulation efficiency increases with increase in polymer concentration. The encapsulation efficiency was good for preparation, but highest for formulation OMP6

Table 6: Drug entrapment efficiency of Omeprazole loaded microspheres

S.No	Formulation code	Theoretical drug loading (%)	Actual drug loading ±S.D	Drug Entrapment Efficiency ± SD
1	OMP1	3.508772	16.56±0.03	66.23±0.115
2	OMP2	3.508772	16.95±0.02	67.8±0.1
3	OMP3	4.255319	17.41±0.014	69.63±0.058
4	OMP4	4.255319	21.51±0.014	86.03±0.057
5	OMP5	3.846154	22.13±0.014	88.53±0.578
6	OMP6	3.846154	19.34±0.015	77.36±0.587
7	OMP7	3.846154	18.67±0.028	74.667±0.115
8	OMP8	3.846154	18.02±0.025	72.1±0.1

***In vitro* buoyancy studies:**

In vitro buoyancy studies of the prepared microspheres were evaluated in SGF pH 1.2. The formulations containing ethyl cellulose and Eudragit RS100 (OMP6 and OMP4) gave the floating ability in the range of 79.1% and 76.3%. The formulations containing Ethyl cellulose, Eudragit RS100 and HPMC combination (OMP1-OMP3, OMP5 and OMP7-OMP8) gave the floating ability in the range of 71.5-76.1% as shown in Table No.7.

In case of formulation OMP8, the buoyancy percentage decreased as Compared to other formulations as decrease in polymer concentration of ethyl cellulose but was less as compared to Eudragit S100 containing formulations. Formulation OMP6 containing more concentration of Eudragit RS100 gave best floating ability of 79.1% in SGF pH 1.2 for 12 hours. This may be due to its low bulk density. Also, high population of small size microspheres and low population of big ones, allow for more complete and effective filling of available liquid surface.

Table 7: In-vitro Buoyancy studies of Omeprazole microspheres

S.No	Formulation code	Percentage of Buoyancy (%)
1	OMP1	74.8
2	OMP2	76.1
3	OMP3	70.9
4	OMP4	76.3
5	OMP5	72.8
6	OMP6	79.1
7	OMP7	73.6
8	OMP8	71.5

***In-vitro* drug release:**

For all the Eight formulations there was no occurrence of initial burst release, but the release was constant in a controlled manner for a prolong period of time up to 12hrs.

The above results indicated that the formulations OMP1-OMP8 are containing different ratios of individual and combination of polymers. The drug release showed in OMP1, OMP2 and OMP6 was 94.75%, 96.92%, and 87.26% for 12hrs. OMP3 and OMP8 showed 96.94% and 98.83% for 8hrs. OMP4 to OMP5 showed 98.96% and 96.83% of drug release for 9hrs.The *in vitro* drug release obtained for different formulations and comparison of drug release profiles for all the formulations showed in Fig 11-19.

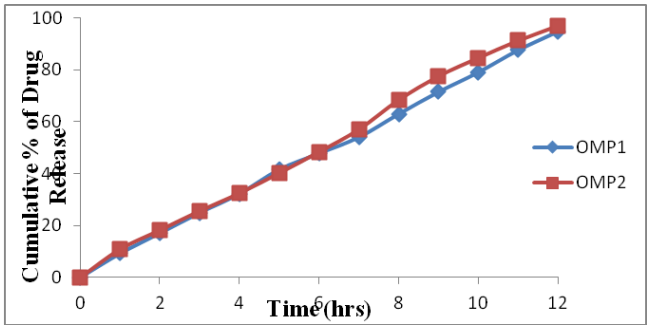

Figure 11: Comparative Zero order plot for formulations OMP1-OMP2

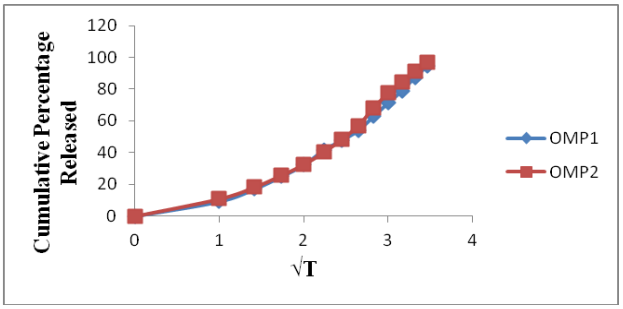

Figure 2: Comparative Higuchi plot for formulations OMP1-OMP2

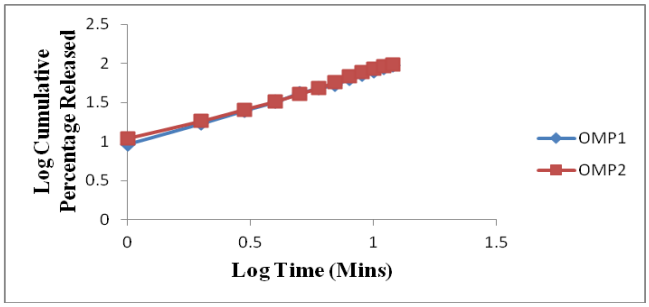

Figure 13: Comparative Peppa's plot for formulations OMP1-OMP2

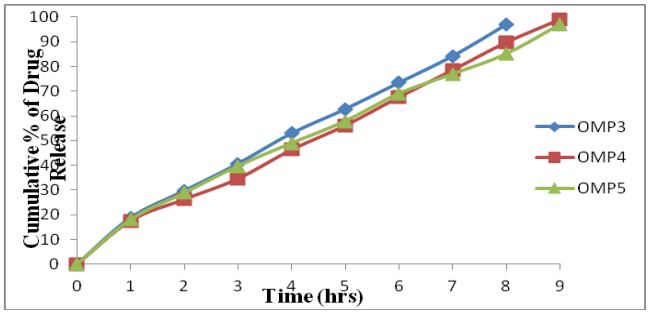

Figure 14: Comparative Zero order plot for formulations OMP3-OMP5

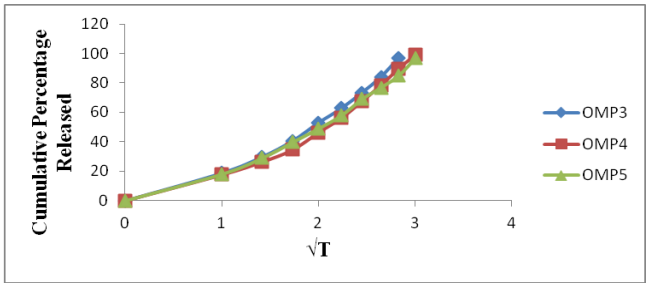

Figure 15: Comparative Higuchi plot for formulations OMP3-OMP5

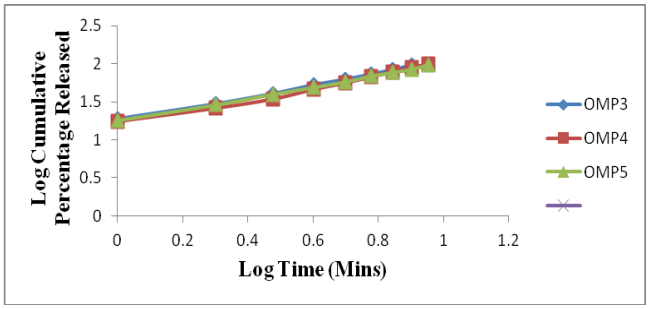

Figure 16: Comparative Peppa's plot for formulations OMP3-OMP5

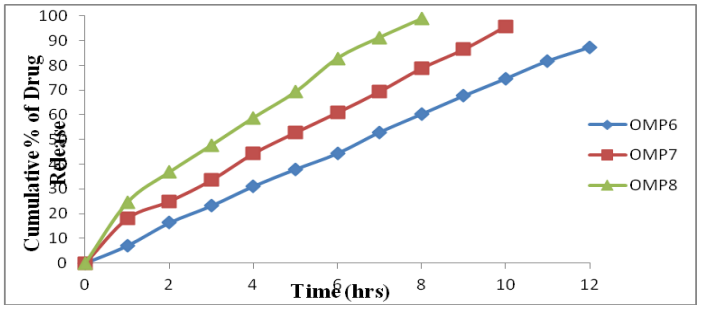

Figure 17: Comparative Zero order plot for formulations OMP6-OMP8

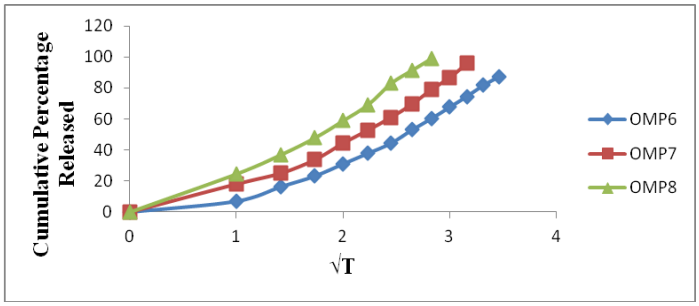

Figure 18: Comparative Higuchi plot for formulations OMP6-OMP8

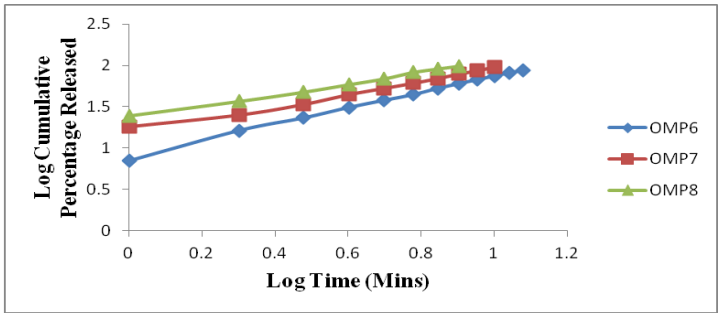

Figure 19: Comparative Peppa's plot for formulations OMP6-OMP8

From the results obtained it was observed that the drug release from the formulations decreased with increase in polymer concentration.

The formulations OMP6 and OMP1 showed longer duration of drug release for 12hrs in simulated intestinal fluid in addition to completely retarding the drug release in gastric medium. This is due to the combination of Ethyl cellulose and Eudragit S100.

It also observed that the release was decreased when there was a increase in the concentration of Eudragit S100. OMP6 formulation showed 87.26% of drug release for a longer period of time up to 12hrs.

So that OMP6 was taken as a best formulation to achieve a prolonged maintenance of effective concentrations of drug

All the prepared formulations are having diffusion exponent value (n) more than 0.45 and less than 1, this indicates that the release mechanism follows non – Fickian diffusion.

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CONCLUSION

Over the years, attempts have been made to control the time course and specificity of the drug in the body through a verity of drug modifications and dosage forms. The need of making any drug microspheres is to produce a drug delivery system which is safe and capable of producing consistent therapeutic blood levels of drug in the body for required period of time. It is also improves keeping and handling properties of the drug. In this study microspheres prepared by solvent evaporation method using Ethyl cellulose, HPMC and Eudragit S 100 showed promising results in delivering the drug, and the prepared Omeprazole microspheres exhibited prolonged intestinal gastric release, avoid gastric erosion side effects and thus improve patient compliance.

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