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FORMULATION AND EVALUATION OF OMEPRAZOLE MICROSPHERES BY DIFFERENT TECHNIQUES

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ABSTRACT

The intention behind the present work was to develop a microsphere based novel dosage form for sustained delivery of Omeprazole. Omeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, omeprazole blocks the final step in acid production, thus reducing gastric acidity. The microsphere system is based upon the fact that their structure can entrap the drug within them. Comparative study of the Emulsion solvent evaporation method and spray drying technique was done for the preparation of Microspheres using Eudragit RS 100 and Ethyl cellulose with various drug-polymer ratios. For optimization purpose, several factors which affect microsphere's physical properties were investigated. A 32 full factorial design was employed to systematically optimize the drug release profile, encapsulation efficiency & drug content. Characterization techniques followed for the formed microspheres were FTIR, SEM, XRD and Particle size analysis along with the drug content, production yield, encapsulation efficiency and in vitro drug release. The in vitro dissolution studies were done to assess the release pattern of the drug from the Microspheres over a twelve hour period. Microspheres were able to sustain the release of omeprazole upto 12 hrs. All the formulations followed Hixon Crowell & Korsemayer Peppas model kinetics. From the FTIR study it is found that by both the methods Process parameters does not make any structural changes in Omeprazole. XRD study showed that sharp peaks for the pure drug & formulation by both the methods were obtained at the same diffraction angle. Hence, known to possess same internal structure. The mean particle size of Microspheres prepared by both the methods was found in the range of 1-1000 nm. The SEM study was done to evaluate Morphology and surface topography of prepared microspheres. The stability study conducted for optimized formulations of both the methods revealed that formulation is stable having no impact on physical appearance & drug release. In this Study sustained release Microspheres of Omeprazole were prepared successfully by Spray Drying method and Emulsion Solvent Evaporation Method and comparison between the two has been done.

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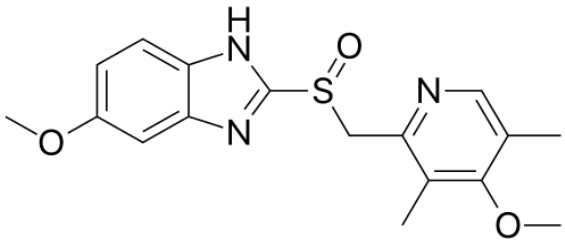
INTRODUCTION

The oral route of drug administration is known to be the most convenient and commonly employed route. Drugs that get easily absorbed in the gastrointestinal tract and having a short half- life get eliminated rapidly through blood circulation. To shun these problems, orally controlled release formulations have been developed, which release drug slowly into the gastrointestinal tract and help in keeping constant drug concentration in the serum for a longer period of time. Oral route of drug administration has broad acceptance. Up to 50–60% of oral solid dosage forms are well-liked because of usual, straightforward and suitable administration with precise dosage, self- medication, pain evasion and most prominently patient compliance. The most admired solid dosage forms are tablets and capsules; these dosage forms may envelop wide range of applications in novel drug delivery systems such as nanoparticles, microparticles, microspheres, nanospheres and microsponges.[1]

Microspheres play a very important role as particulate drug delivery system because of their small size and other efficient properties. Microspheres are characteristically free flowing solid powders, which consist of proteins or synthetic polymer, which are biodegradable in nature.[2]



Chemical Structure of Omeprazole.

Omeprazole belongs to the class of chemical entities known as sulphinylbenzimidazoles. A highly effective inhibitor of gastric acid secretion used in the therapy of stomach ulcers and Zollinger-Ellison syndrome. Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazole, that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell.[3,4]

There are conditions such as Zollinger Ellison syndrome and Mastocytosis for which the recommended daily dose of omeprazole is very high. There arises the problems regarding dosing frequency, maximum dose requirement and fluctuations in the plasma drug concentration. To overcome these problems Microspheres of Omeprazole were prepared. Microspheres releases the drug in controlled rate and overcome the problems of conventional drug delivery system and enhances the therapeutic efficacy of the drug. The main purpose of microspheres is to ensure optimum plasma drug concentration, thus enhancing efficacy, safety and bioavailability of drug with improved patient compliance. An effort has been made to prepare the microspheres of Omeprazole for administration in the intestine for sustained delivery of omeprazole. Comparison between microspheres prepared by spray drying and Emulsion solvent evaporation method has been done to study the change in effects produced by these methods. The formulation of microspheres also increases the gastric residence time. As the gastric residence time of omeprazole is increased it also leads to increase in the bioavailability.

Sustained Release Drug Delivery:[5]

Recently, dosage forms that can precisely control the release rates & target drugs to a specific body site have made an enormous impact in the formulation & development of novel drug delivery system. Sustained release microspheres are one of the multiparticulate delivery systems which are widely accepted to achieve oral controlled drug delivery.

The purpose of a sustained oral release is to deliver a drug at a rate necessary to achieve & maintain constant drug blood level (Fig.1). Sustained release systems are that which achieve slow release of drug over an extended period of time and in this drug is initially made available to the body in amount to cause the desired pharmacological response.[5]

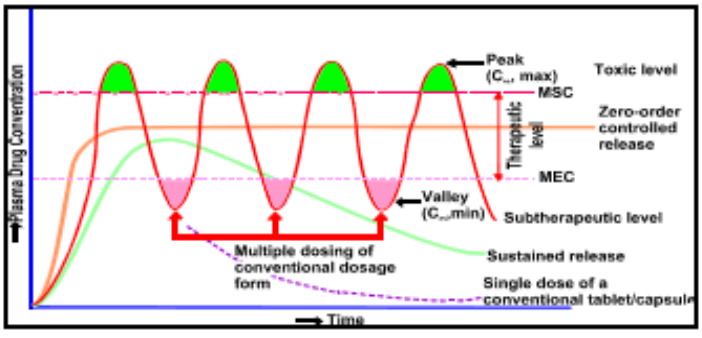


Figure.1 Hypothetical plasma concentration-time profiles from conventional multiple dosing and single doses of sustained and controlled delivery.

Potential Advantages of Sustained Release Dosage Form [6,7]

- Better patient compliance due to reduced frequency of dosing.
- Uniform level of drug in blood is maintained.
- Quantity of drug required is less.
- Minimize or eliminate local or systemic side effects.
- Minimize drug accumulation with chronic dosing
- Improved efficiency in treatment.
- Cure or control condition more promptly.
- Improved control of condition i.e. reduced fluctuation in drug level.
- Improves bioavailability of some drugs.
- Make use of special effects, e.g. sustained release aspect for relief of arthritis by dosing before bedtime.
- Economic
- Overall, administration of sustained release form enables increase reliability of therapy.

MICROSPHERES:[2]

Microspheres:

Microspheres are solid spherical particles ranging in size from 1-1000µm. They are spherical free flowing particles consisting of proteins or synthetic polymers, which are biodegradable in nature.

The site-specific microparticulate delivery systems allow an effective API concentration to be maintained for a longer interval in the target tissue and result in decreased side effects associated with lower plasma concentrations in the peripheral blood circulation.

There are two types of microspheres:

- Microcapsules
- Micromatrices

Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersing throughout the microspheres matrix.

Microparticles have many advantages:[2]

(i) Delayed or sustained release
(ii) Prevention of side effects related to the presence of the drug in the stomach
(iii) Protection of the drug from degradation in the acidic environment of the stomach
(iv) Reduction in frequency of administration and avoidance of peak and valley effects in blood level
(v) Biocompatibility
(vi) Easy preparation
(vii) Relative stability
(viii) To obtain controlled or targeted release.

METHODS OF PREPERATION[2]

- Solvent evaporation technique
- Emulsion cross linking method
- Coacervation method
- Spray drying technique
- Emulsion-solvent diffusion technique
- Multiple emulsion method
- Ionic gelation

Emulsion solvent evaporation technique

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % PVA as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (Eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 12 hrs (Fig.2)[2]

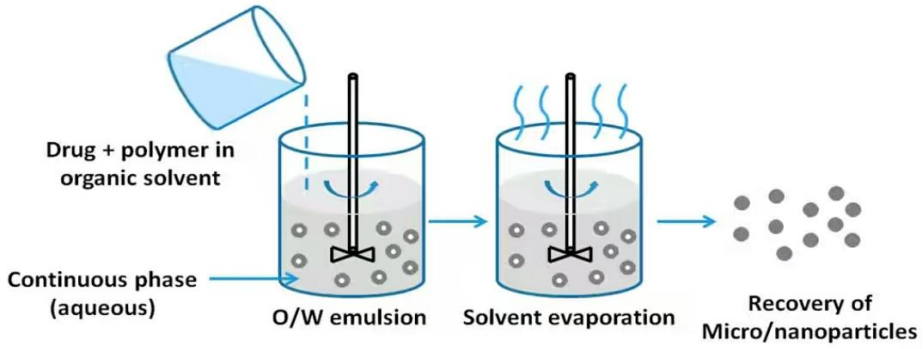


Figure 2. Emulsion Solvent Evaporation Method.

Several variables have been identified which can influence the properties of the microspheres, including drug solubility, internal morphology, solvent type, diffusion rate, temperature, polymer composition, viscosity and drug loading. The effectiveness of the solvent evaporation method to produce microspheres depends on depends on the successful entrapment of the active agent within the particle. And thus this this method is most successful with drug which are either insoluble or poorly soluble in the aqueous medium which comprises the continuous phase. Many types of drugs with different physical and chemical properties have been formulated into polymeric systems.[8]

The microencapsulation of pharmaceutical compounds by the solvent evaporation method has been investigated extensively during the past 25 years. The premise for this method is the emulsification of a polymeric solution in an aqueous continuous phase. The o/w emulsion is produced by the agitation of two immiscible liquids. The drug substance is either dispersed or in solution in the polymer/solvent system or is captured in the dispersed phase of the emulsion. Agitation of the system is continued until the solvent partitions into the aqueous phase and is removed by evaporation. This process results in hardened microspheres which contain the active moiety.[8]

Spray drying technique

This was used to prepare polymeric blended microsphere loaded with drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent.[2]

Spray-drying is a rapid, continuous, cost-effective, reproducible and scalable process for the production of dry powders from a fluid material by atomization through an atomizer into a hot drying gas medium, usually air. Often spray-drying is considered only a dehydration process, though it also can be used for the encapsulation of hydrophilic and hydrophobic active compounds within different carriers without substantial thermal degradation, even of heat-sensitive substances due to fast drying (seconds or milliseconds) and relatively short exposure time to heat. The solid particles obtained present relatively narrow size distribution at the submicron-to-micron scale.[9]

Spray-drying is a technique based on the transformation of a fluid into a dry powder by atomization in a hot drying gas stream that is generally air. The spray-drying process consists of four fundamental steps: (i) atomization of the liquid feed, (ii) drying of spray into drying gas, (iii) formation of dry particles and (iv) separation and collection of the dry product from the drying gas. First, the fluid is fed into the drying chamber by a peristaltic pump through an atomizer or nozzle that can be a rotary atomizer, a pressure nozzle or a two-fluid nozzle and the atomization occurs by centrifugal pressure or kinetic energy respectively. The small droplets generated (micrometer scale) are subjected to fast solvent evaporation leading to the formation of dry particles that are separated from the drying gas by means of a cyclone or bag filter that deposes them in a glass collector situated in the bottom of the device.[9]

MATERIALS AND METHODS

Materials:

Omeprazole was obtained as gift sample from Inventia Healthcare ltd Mumbai, Eudragit was obtained as a gift sample from Evonik pharma Mumbai, PVA, Dichloromethane and Dibutyl Pthalate were purchased from Modern Science lab Nashik. All the other ingredients used were of analytical grade, and were used as procured.

Methods:

Characterization of pure Drug:

Melting Point:

Melting point of the drug was determined by using capillary tube method

Solubility:

Saturation solubility of Omeprazole was determined in Water and Ethanol. All media was prepared and excess amount of drugs was added to 50 ml of each medium placed in the 100 ml conical flask and kept for shaking on mechanical shaker for 24 hr. After 24 hr of shaking, 1 ml of aliquot was taken out from each sample and filtered through Whatman filter paper. Absorbances were measured and calculations for solubility were done.

FTIR Spectroscopy:

FTIR spectrum was taken and sample was scanned over wavenumber range of 4000–400 cm^{-1} .The instrument used was Brucker spectrophotometer.

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.

DSC study:

Thermal analysis was performed using a differential scanning calorimeter equipped with a computerized data station. The sample of pure drug, and physical mixture were heated at a scanning rate of 10°C/min between 30 and 350°C and 40 ml/min of nitrogen flow. The differential scanning calorimetry analysis gives an idea about the interaction of various materials at different temperature. It also allows us to study the possible degradation of the material.

Drug-Excipient Interaction study:

Drug–excipient interactions were investigated by FTIR and DSC studies.IR spectra were recorded to check compatibility of drug with excipients, using FTIR spectrophotometer. DSC helps in assessing physical properties of the sample nature (crystalline or amorphous) and indicates any probable interaction among drug and excipients. Omeprazole and physical mixture were subjected to thermal analysis.

PREPARATION OF OF OMEPRAZOLE MICROSPHERES:

By Spray Drying:

Microspheres of Omeprazole were prepared by spray drying the drug and polymers solutions. Ethanolic solution of drug and polymer was prepared and cross linker was added to the solution. The spray drying conditions were selected and set: Inlet temperature: 130^{0C}; Outlet temperature: 90^{0}c; Feed Rate: 3ml/min; Cooling Temperature: 90^{0C}; Pressure: 2bar. When the liquid was fed to the nozzle with peristaltic pump, atomization occurred by the force of the compressed air, disrupting the liquid into small droplets. The droplets together with hot air, were blown into a chamber where the solvent in the droplets was evaporated and discharged out through an exhaust tube. The dry product was the collected in a collection bottle.

By Emulsion Solvent Evaporation Method:

The microsponges containing Omeprazole were prepared by quasi- emulsion solvent diffusion method using an internal phase that consisted of Eudragit RS-100, Ethyl Cellulose and dibutyl phthalate (1% w/v) dissolved in 10 ml of dichloromethane: ethanol (1:1). Dibutyl phthalate was added to enhance the plasticity of the polymer. This was followed by the addition of DOM dissolved under ultra-sonication at 35 °C. The mixture was then poured into aqueous solution of PVA which served as the external phase with 60 min stirring at 400rpm.The microsponges were formed due to the removal of dichloromethane and ethanol from the system by evaporation. Prepared microsponges were then filtered, washed with distilled water and subjected to drying at 40 °C for 12 h in hot air oven. Lastly microsponges obtained were weighed to determine production yield.

EVALUATION OF OMEPRAZOLE MICROSPHERES:

Infrared spectroscopy.

It was done using Attenuated Total Reflectnce. ATR spectra of Omeprazole, physical mixtures of Omeprazole, Eudragit RS 100 and Ethyl cellulose and microspheres formulation by both Quasi emulsion solvent evaporation method and spray drying method were recorded.

Production yield:

Microspheres production yield was determined by the formula mentioned below:

Production yield PY= Practical mass of microspheres/ Theorotical Mass(polymer+drug) X 100

Actual drug content and encapsulation efficiency:

The weighed amount of drug loaded microspheres (10 mg) was kept in 100 ml methanol for 12 h with continuous stirring. sonicated. samples were analyzed at 305 nm against blank using UV spectrophotometer.(Shimadzu 2458) Estimation of drug content and encapsulation efficiency for all batches were done using the following expressions:

$$\textbf{Actual drug content (\%)} = M_{act}/M_{ms\ X}\ 100$$
$$\textbf{Encapsulation effieciency} = M_{act}/M_{the\ X}\ 100$$

where Mact = actual Omeprazole content in weighed quantity of microspheres,
Mms = weighed quantity of microspheres and
Mthe = theoretical Omeprazole content in microspheres

Scanning electron microscopy (SEM):

For assessing morphology and surface topography, prepared microspheres were examined under scanning electron microscope operating.. SEM photomicrographs were taken by scanning electron microscope for studying surface morphology of Microspheres. Each sample was mounted on to aluminum stub using double-sided adhesive tape and then coated with gold palladium alloy using fine coat sputter.. The samples were then examined with 1500X and 7000X magnification using scanning electron microscope.

Particle size analysis:

Particle size analysis of prepared microspheres was carried by using Malvern Mastersizer.

X-ray diffraction study:

X-ray powder diffraction (XRPD) patterns were recorded by using X-ray diffractometer. The drug, placebo, Microspheres by Emulsion Solvent Evaporation Method & Spray Drying were subjected to X-ray crystallographic studies. The powder X-ray diffraction patterns were recorded using an X-ray diffractometer, with Cu as anode material and crystal graphite monochromator operated at a voltage of 45 kV and a current of 40 mA. The samples were analyzed in the 2θ angle range of 3 to 30º.

In vitro drug release:

Dissolution studies were carried out with the USP type-I (rotating basket) apparatus in phosphate buffer Ph 6.8 for 12 hrs. The % drug release upto 12 hrs was calculated.The drug release rate from Microspheres was determined using USP apparatus type I (lab India, India). The dissolution test was performed using 900ml of Phosphate buffer ph 6.8 for 12 hrs at 37 0.5°C and 50 rpm. A sample (10 ml) was withdrawn at a specific interval and replaced with fresh dissolution medium of same quantity. Absorbance of the solutions was measured at 305 nm by UV-Visible Spectrophotometer (UV-2450 SHIMADZU).The drug release and drug release kinetics was calculated.

Stability study:

In any rational design and evaluation of dosage forms for drugs, the stability of the active component is a major criterion in determining their acceptance or rejection. The Microspheres were subjected to the accelerated storage condition for duration of 1 Month. **(**40ºC ± 2ºC/ 75%RH ± 5% RH) The Samples were observed periodically for any change in the appearance and drug release.

RESULTS AND DISCUSSION:

RESULT AND DISCUSSION

PREFORMULATION STUDY:

Organoleptic properties:

Omeprazole was studied for organoleptic characters such as color, odour, appearance and melting point. The results are reported in following table(Table.1):

Table: 1 Comparison of results of identification test of Omeprazole with the reported standards.

Sr. No.	Organoleptic properties	Observed	Reported
1.	Colour	White	White
2.	Odor	Characteristic	Characteristic
3.	Appearance	Crystalline	Crystalline
4.	Melting point	155-160^{0}c	156^{0}c

Determination of Solubility:

A solvent under consideration (Water, Methanol) was saturated with the drug powder and the vials were allowed to stand at room temperature (25˚C) for 1 day with frequent shaking. The solution was filtered using Whatmann filter paper. The filtrate was analysed for drug content using UV spectroscopy. The results for solubility of Omeprazole in water and ethanol are reported in following table.(Table.2).

Table: 2 Solubility of Omeprazole.

Solvent	Obsereved solubility	Reported solubility
Water	0.325 mg/ml	0.359 mg/ml
Ethanol	5.27 mg/ml	5 mg/ml

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 (Figure.4) The maximum absorption value of pure drug Omeprazole was found at 306 nm wavelength.(Figure.3) Therefore 306 nm were recorded as λ max of the pure drug Omeprazole. The observed λ max value of drug was found to be similar as given in literature. Hence the drug was considered to be pure.

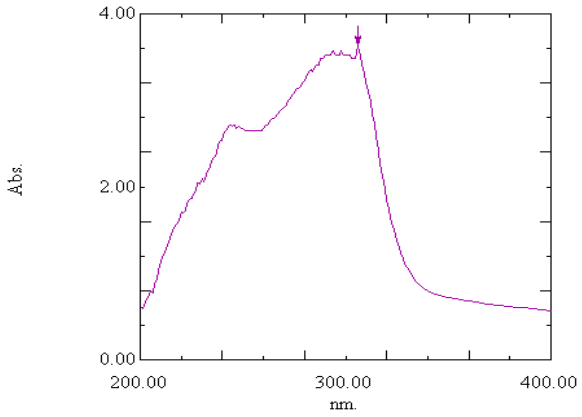


Figure 3. UV Visible Spectrum of Omeprazole in Methanol.

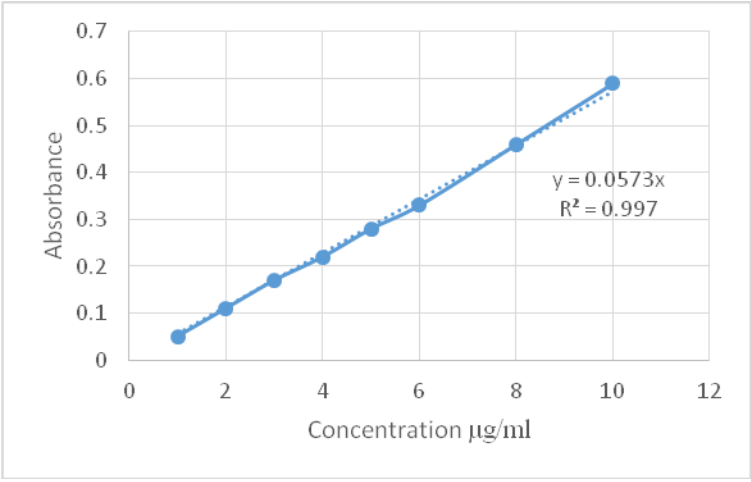


Figure 4. Calibration Curve for Omeprazole in Methanol.

IR SPECTROSCOPY:

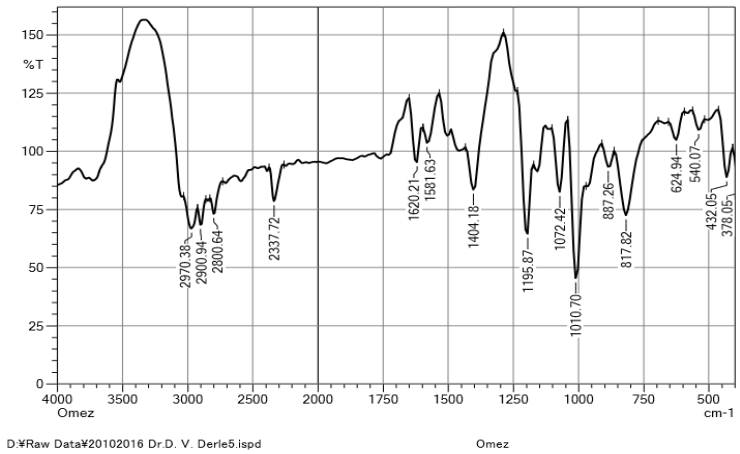


Figure 5. FTIR Spectrum of Omeprazole.

The above fig. (Figure.5) shows FTIR spectrum of pure Omeprazole. This spectra shows presence of all the peaks which are present in standard IR spectra of Omeprazole.

DSC STUDY

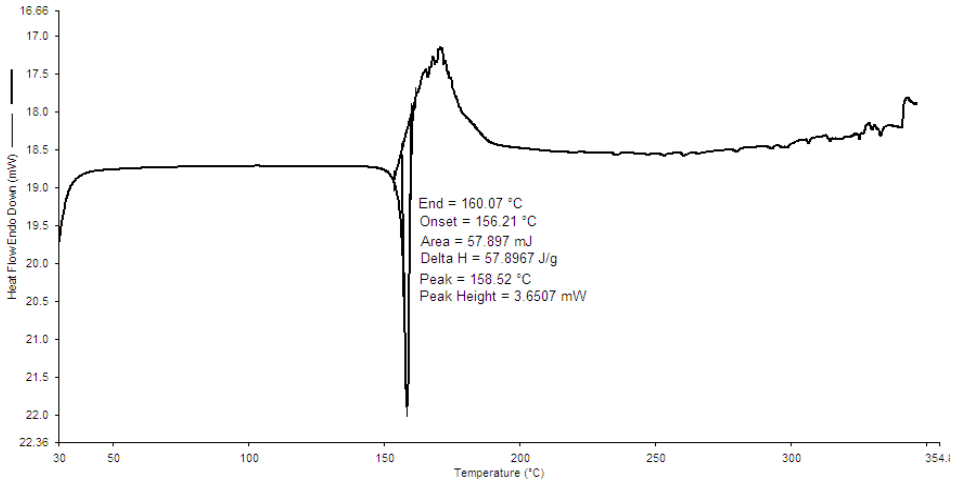


Figure 6. DSC Spectrum of Omeprazole.

DSC of pure Omeprazole (Figure.6) showed a characteristic, sharp endothermic peak at 160^0c which is associated with the melting point of drug & indicated the crystalline nature of omeprazole.

COMPATIBILITY STUDY:

IR Spectroscopy

Following fig (Figure.7) shows that the FTIR spectra of Omeprazole & its physical mixture (1:1) with Ethyl Cellulose & Eudragit RS 100. 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.

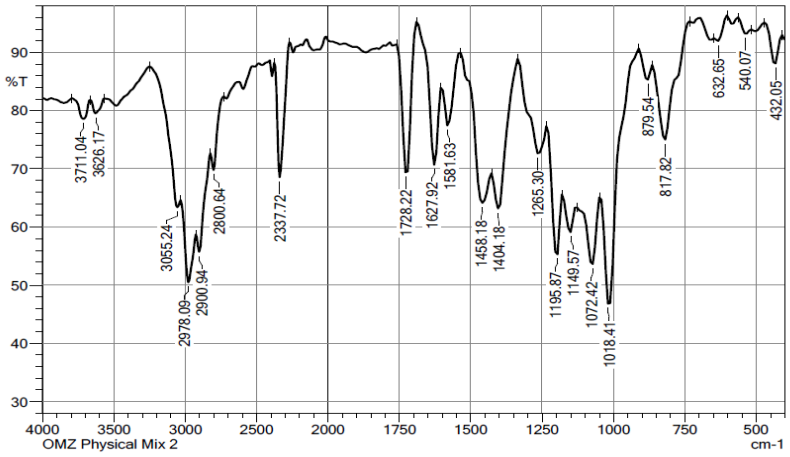


Figure 7. FTIR Spectrum of Physical mixture of Omeprazole.

DSC

DSC of pure Omeprazole showed a characteristic, sharp endothermic peak at 160^0c which is associated with the melting point of drug & indicated the crystalline nature of omeprazole. The thermogram of physical mixture of Omeprazole (figure.8) exhibited endothermic peak at 157^0c, which is peak of the drug, indicated that there is no interaction between the drug & excipients used in the formulation & they are compatible each other.

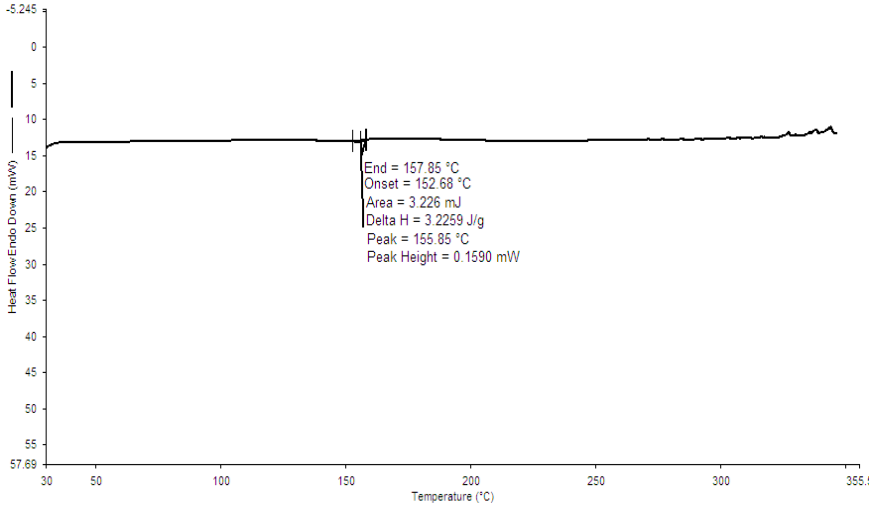


Figure 8. DSC Spectrum of Physical mixture of Omeprazole.

EVALUATION OF THE PREPARED MICROSPHERES:

PRODUCTION YIELD, DRUG CONTENT & ENCAPSULATION EFFICIENCY:

Production Yield was obtained comparatively more in case of the Spray Drying. This might be because the Spray Drying technique allows complete evaporation of the solvent at elevated temperature which does not takes place by the emulsion solvent evaporation Method. By the Emulsion Solvent Evaporation method Drug content was found more this is because in this method solidification occurs by the counter diffusion of the organic solvents. The diffused aqueous phase within the drug: polymer droplets decreases the drug & polymer solubility in the aqueous phase resulting in the coprecipitation of both the components. No significant effect of the process parameters of both the methods was observed on Encapsulation efficiency. Following table (Table.3) shows the results for all the three parameters for both the methods.

Table: 3 Production yield, Drug Content & Encapsulation efficiency.

Formulation code	Production yield (%)		Actual drug content (%)		Encapsulation efficiency (%)	
	D	E	D	E	D	E
1	36.92	30.76	23.34	26.56	73.35	73.99
2	45.00	28.66	21.03	26.98	74.36	80.2
3	48.66	37.83	21.9	26.09	74.5	68.33
4	43.75	45.17	23.5	26.43	73.29	71.41
5	35.96	24.80	21.09	26.71	73.2	73.21
6	49.46	20.89	22.27	26.34	7284	78.02
7	49.00	16.00	22.49	26.78	72.66	69.32
8	44.80	16.15	23.5	26.18	72.53	72.02
9	41.42	18.21	22.7	26.63	73.42	80.41

D: Spray Drying; E: Emulsion Solvent Evaporation

IN VITRO DRUG RELEASE:
By Spray Drying:

Table: 4 In vitro Drug release from different formulations (Spray Drying).

Time (hr.)	D1	D2	D3	D4	D5	D6	D7	D8	D9
1	19.62	23.34	19.00	27.27	26.45	23.76	21.17	10.93	9.41
4	44.04	46.96	28.43	46.93	38.52	46.05	38.92	22.69	29.77
8	76.77	71.93	71.30	69.81	61.72	74.53	73.28	55.72	66.57
12	84.31	81.59	80.21	87.78	83.87	79.47	83.43	82.57	80.61

From the above table (Table.4) it is observed that at middle concentration of Polymer & Crosslinker, an increase in drug release is observed. As the concentration of Polymer & Crosslinker is increased, a gradual decrease in drug release was observed. F4 shows maximum drug release. All the formulations show drug release upto 12 hrs.(Figure.9).

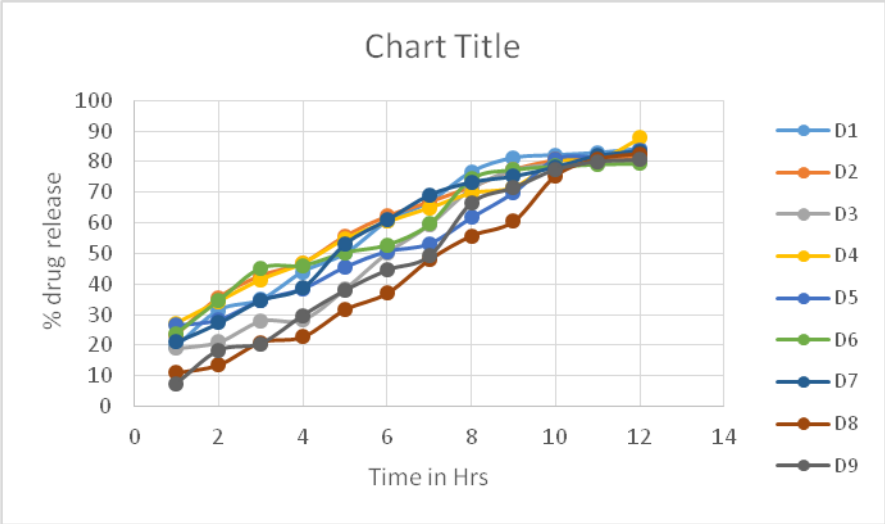


Figure 9. Drug release profile of D1 to D9 by Spray Drying.

By Emulsion solvent Evaporation method:

Table: 5 In Vitro Drug release from different formulations (Emulsion Solvent Evaporation Method).

Time (hr)	E1	E2	E3	E4	E5	E6	E7	E8	E9
1	22.10	29.03	21.07	22.09	19.00	17.96	7.41	17.96	28.31
4	39.95	45.84	41.25	39.95	31.89	45.65	29.99	41.13	39.40
8	66.32	59.55	66.94	66.32	63.08	76.32	61.43	70.23	65.99
12	86.61	85.49	86.53	84.43	84.47	86.37	85.59	86.30	85.86

From the above table (Table.5) it is observed that at middle concentration of Polymer & lower concentration of PVA, an increase in drug release was observed. As the concentration of Polymer was increased, a gradual decrease in drug release was observed. F1 shows maximum drug release. All the formulations show drug release upto 12 hrs. (Fig.10).

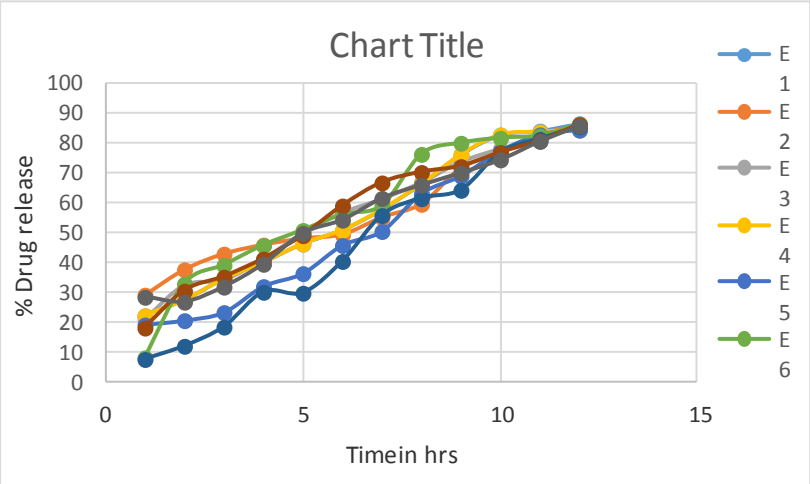


Figure 10. Drug release profile of E1 to E9 by Emulsion Solvent Evaporation Method.

SEM:

By Spray Drying:

Morphology and surface topography of prepared microspheres by Spray Drying method were discovered by SEM analysis. The representative SEM images of the prepared Microspheres are shown (fig.11). SEM results indicated that Microspheres formed by Spray Drying Method are not porous as those formed by Emulsion solvent Evaporation Method. Because, by Spray Drying method counter diffusion of organic solvents does not takes place which leads to the formation of pores. In this method solidification occurs just by evaporation of the solvent at elevated temperature. Formation of the pores is advantageous because as these pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increases the rate of solubilization.

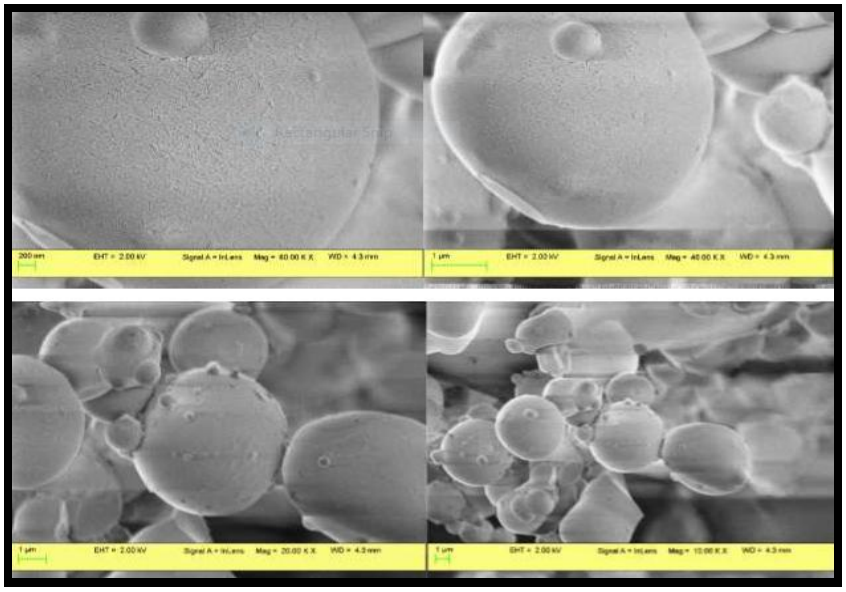


Figure 11. SEM images of the Microspheres by Spray Drying (D4).

By Emulsion Solvent evaporation:

Morphology and surface topography of prepared microspheres by Emulsion Solvent Evaporation method were discovered by SEM analysis. The representative SEM images of microsponges are shown (Figure.12) SEM results indicated that microsponges formed were porous and predominantly spherical. By diffusion of solvent from surface of microsponges, pores were induced. Moreover, it was exposed that the distinctive internal structure comprised spherical cavity. The internal structure consisted of numerous pores and appearance of particles was such that they were perfect to be called microsponges.

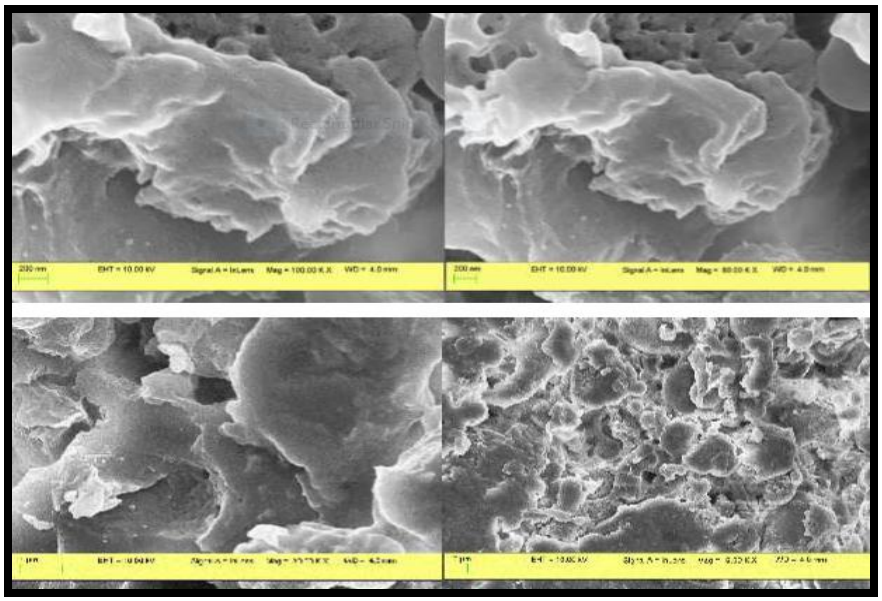


Figure 12. SEM images of the Microspheres by Emulsion Solvent Evaporation Method (E1).

PARTICLE SIZE ANALYSIS:

The mean particle size of Microspheres prepared by both the methods was found in the range of 1-1000 nm. Visual inspection of all the batches for particle size using optical microscope revealed that, in case of Spray Drying the particle size was increased by increase in the concentration of crosslinker as due to increase in the drug & polymer crosslinking, polymer wall thickness is increased. In case of the Emulsion Solvent Evaporation Method the particle size was increased with increase in PVA concentration as it increases apparent viscosity which further results in larger emulsion droplet formation and finally greater microsphere size.

X-RAY DIFFRACTION STUDY:

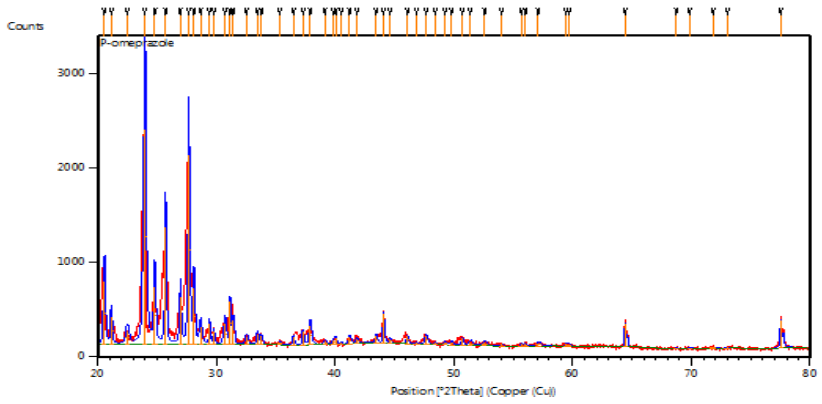


Figure 13. XRD pattern of Omeprazole.

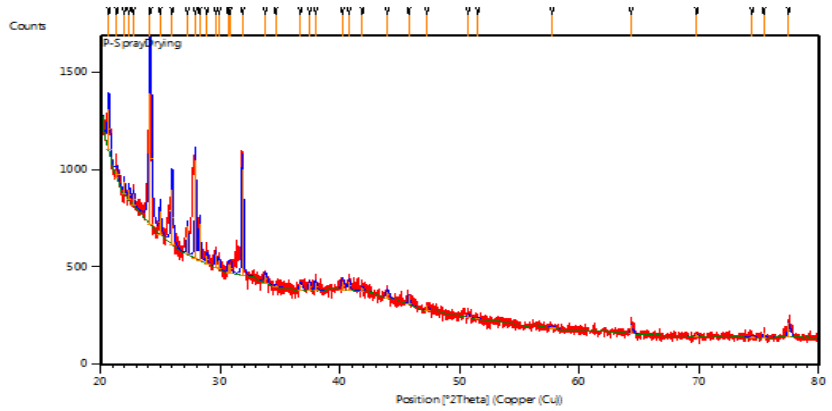


Figure 14. XRD pattern of Microsphere formulation by Spray Drying (D4).

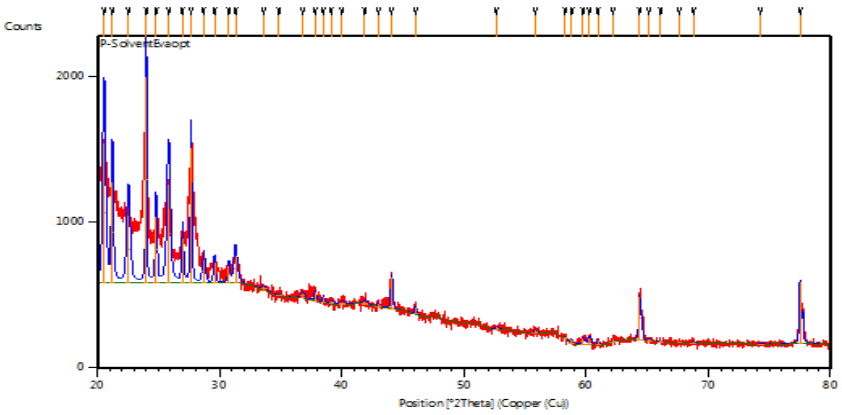


Figure 15. XRD pattern of Microsphere formulation by Emulsion Solvent Evaporation Method (E1).

To evaluate physicochemical characteristics of prepared microspheres, XRPD method was implied. In X-ray diffractogram, (Figure 13,14,15)sharp peaks at diffraction angle (2θ) 24° were obtained in both Omeprazole & its formulation by both the methods (Spray Drying, Emulsion Solvent Evaporation Method).

For determination of occurrence of crystal habit modifications and polymorphs in drug crystals, XRPD is a valuable technique. In general when diffraction patterns are identical for two forms of crystals, they are known to possess the same internal structures and when patterns are nonidentical, crystals have diverse internal structures known as polymorphs. In the present study, samples depicted spectra with similar peak positions (2θ values). Consequently, no existence of polymorphs of Omeprazole in these samples was verified.

For crystalinity determination, a comparison of some representative peak heights with those of a reference in diffraction patterns has been done. Final formulation of microspheres showed peaks at diffraction angle similar to that of XRD pattern of Omeprazole but with some higher intensity, indicating its crystalline nature. XRD analysis revealed that the crystalline nature of drug was not completely lost and was found to remain thermally stable in the final formulation.

STABILITY STUDY:

The stability studies of the optimized formulation revealed that no significant changes occured in the physical parameters when stored at temperature & humidity conditions of 40^0c/ 75 % RH & at room temperature. No significant changes in the physical appearance, % cumulative drug release at 12 hrs. & the drug content was observed over a period of one month.

COMPARISON

In the present thesis Omeprazole Microspheres are prepared by Spray Drying and Emulsion Solvent Evaporation method. From the comparison point of view no method alone proved to be best over another. Both the methods have found to be having some kind of advantages and disadvantages as well.

Spray drying technique is very appealing both under laboratory and industrial scale because it is rapid, continuous, reproducible and single-step. Another remarkable advantage of spray-drying is the possibility to dry a broad spectrum of compounds including heat-sensitive substances without major degradation effects. Spray Drying has the less chances of manual errors as compared to Emulsion Solvent Evaporation Method.

Depending upon the results obtained from present work Spray drying method gave superior results for production yield. This might be because in this method complete evaporation of the solvent takes place at elevated temperature. Though production yield is high, loss occurs during the collection due to the loss of product on the walls of the drying chamber and the low capacity of the cyclone to separate fine particles. From the SEM results of Omeprazole Microspheres it is found that the Microspheres obtained by Spray Drying do not have porous structure. Whereas, by Emulsion Solvent Evaporation porous Microspheres are obtained. As the pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increases the rate of solubilization.

In case of Emulsion Solvent Evaporation Method manual errors are more compared to spray drying. From the results obtained Emulsion Solvent Evaporation Method gave better results for Encapsulation Efficiency and Drug Content, because in this method solidification occurs by the counter diffusion of the organic solvents. The diffused aqueous phase within the drug: polymer droplets decreases the drug & polymer solubility in the aqueous phase resulting in the coprecipitation of both the components. No significant difference in in vitro drug release was observed in microspheres by both the methods.

The Emulsion Solvent Evaporation Method gave better results as compared to Spray Drying technique but it can be performed only for the small scale preparations whereas Spray Drying technique can be used for large scale preparations also.

CONCLUSION

- All the drug and excipients obtained were of appropriate standards.
- From the IR and DSC studies it is concluded that the drug is compatible with excipients and there is no interaction between them.
- Sustained release Microspheres of Omeprazole were prepared by Emulsion Solvent Evaporation method and Spray Drying Method & comparison between the two was done.
- A 3^2 full factorial design was applied using Eudragit RS 100 & Ethyl Cellulose as release retarding polymers.
- The Microspheres were evaluated for Encapsulation efficiency, Drug content, Drug release, FTIR, SEM, XRD & Particle size analysis.
- All the microspheres were found to release the drug upto 12 hrs.
- Most of the formulations followed Hixon Crowell and Korsemayer-peppas model.
- As the concentration of polymer was increased, a decrease in drug release was observed.
- For Spray Drying Method formulation D4 was found to be optimized formulation & for Emulsion Solvent Evaporation Method formulation E1 was found to be optimized formulation using design expert software.
- After comparison between the two methods it was found that, apart from production yield Emulsion Solvent Evaporation method show better results as compared to Spray Drying method.
- Thus the sustained release Microspheres of Omeprazole were prepared & compared successfully between the two methods. Such formulation reduces the dosing frequency of the drug & enhance patient compliance.

ABBREVIATIONS

UV - ultra Violet Spectroscopy
DSC - Differential Scanning Calorimetry
XRD - X-Ray Diffraction
GIT - Gastro Intestinal Tract
SEM - Scanning Electron Microscopy
PVA - Polyvinyl Alcohol
IR - Infra Red Spectroscopy

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CONFLICT OF INTEREST

The authors do not report any conflict of interest.

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