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Preparation and Evaluation of Lansoprazole Microspheres

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ABSTRACT

The objective of the current investigation is to formulate ethyl cellulose and hydroxyl propyl methyl cellulose based sustained release microspheres, containing lansoprazole as model drug. Lansoprazole is type-II anti-ulcer agent when administered shows synergetic effect in their action. Microspheres were prepared by W/O/O double emulsion-solvent evaporation method with different stabilizer concentration and at different speeds of emulsification while maintaining constant amount of lansoprazole. Drug-excipient compatibility study was performed prior to formulation development by fourier-transformation infrared spectroscopy (FTIR) and only compatible excipients were used in the fabrication of microspheres. Prepared microsphere formulations were characterized by percentage yield, particle size analysis, drug entrapment efficiency, surface morphology by scanning electron microscopy (SEM), differential scanning colorimetry (DSC) and in-vitro drug release behavior. The preformulation studies like melting point, solubility and UV analysis of lansoprazole were complied with IP standard. Compatibility studies carried out by IR spectroscopy studies revealed that there is no significant interaction between the drugs and polymer. Microspheres were prepared by varying the concentrations of surfactant and speed. Increment in particle size was observed with increased concentrations of emulsifying agent (span-80). Smaller size was obtained with increasing stirring speed. Interestingly, it was observed that the particle size had no significantly influence on the *in-vitro* drug release. Highest entrapment efficacy was observed with F4 formulation, with a surfactant concentration of 0.5% at a speed of 1000 rpm and thus it was selected as best formulation. Increase in the encapsulation efficiency was observed with increase in the speed of rotation at constant surfactant concentration. Increase in the concentration of surfactant at constant speed of rotation resulted in decreased encapsulation efficiency of the drugs. The DSC data indicates that there is no interaction between the drug and two polymers, and it also indicates that both the drugs are dispersed in the polymer in an amorphous state. SEM studies showed that the microspheres were spherical shape with rough surface morphology and particles were abundantly found. Thus, emulsifier produced better surface characteristics. The in-vitro release profile showed a slow and steady release pattern for lansoprazole with 95-98% release within a period of 12 hrs and the drug release was found to be diffusion controlled mechanism with n-value of Korsmeyer Peppas equation indicated non-fickian type of diffusion. As a result of these experiments, it was conclude that sustained release microspheres comprising a combination of lansoprazole were successfully prepared using ethyl cellulose and hydroxyl propyl methyl cellulose as the polymer by using double emulsion-solvent evaporation technique.

Keywords: microspheres, lansoprazole, hydroxyl propyl methylcellulose, ethyl cellulose, and double emulsion-solvent evaporation method.

INTRODUCTION

For decades an acute or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms like tablets, capsules, liquids, creams, pills, aerosols, injectable, and suppositories with their main discrepancy to maintain drug levels within the therapeutic range. However, these conventional dosage forms have some drawbacks. Multiple daily dosing is inconvenient to the patient and can result in missed doses, made up doses and patient incompliance with the therapeutic regimen[1]. When conventional immediate release dosage forms are taken on schedule and more than once daily, there are sequential therapeutically blood peaks and valley associated with taking each dose. It should be emphasized that the plasma

level of a drug should be maintained within the safe margin and effective range. For this, proper and calculated doses of the drug need to be given at different time interval by conventional dosage form.

The novel system of drug delivery offers a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and or targeting the drug to desired site. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration that is the drug delivery system should deliver drug at a rate detected by the needs of the body over an entire period of treatment. The Plasma drug concentration profiles for conventional tablet formulation, a sustained release formulation and a zero order controlled release formulation. This is possible through administration of conventional dosage form in a particular dose and particular frequency to provide a prompt release of drug. Therefore to achieve as well as to maintain the concentration within the therapeutically effective range needed by the treatment by repeated administration a day, results in a significant fluctuation in a plasma drug level, leads to several undesirable toxic effects, and poor patient compliance[2].

Oral Controlled/ Sustained release formulations: Over the few years consumers witnessed the wide spread and availability of plethora of oral controlled release products in the market. For example, by 1998, the U.S. Food and Drug Administration (FDA) approved 90 oral CR products for marketing. The development of technology in leap and bounds and the availability of various polymers and the machinery available to prepare novel designs are currently resulted in the development of these oral CR products in a reproducible manner[3]. Multiparticulate systems are gaining favor over single-unit dosage forms because of their desirable distribution characteristics, reproducible transit time, and reduced chances of gastric irritation owing to the localization of the drug delivery. Although several technologies for the production of multiparticulate systems have been designed, thus far the mainstream technologies are still based on spay drying, spheronization and film coating technology. Reservoir types of devices are often mentioned. However, there is a problem of manufacturing reproducibility and lack of safety[4].

Microspheres: ***"Microspheres are defined as solid spherical particles containing dispersed drug in either solution or micro-crystalline form".*** Microspheres are spherical microparticles ranging in size from 1-1000 micrometers. They may be free flowing, high porosity, high density, and high precision, coated, embedded agents. They vary widely in quality, sphericity, uniformity, and particle size and particle size distribution. Microsphere is a structure made of a continuous phase of one or more miscible polymers in which particulate drug is dispersed, at either the macroscopic (particulates) or molecular (dissolution) level. They are made up of polymeric, waxy or other protective materials that are biodegradable synthetic polymers and modified natural products such as starches, proteins, gums, fats and waxes. The natural polymer include albumin, gelatin etc., and the synthetic polymer include polylactic acid, polyglycolic acid, PLGA, polycaprolactone etc. These polymer particles with porous inner surface and variable surface (from smooth and porous to irregular and nonporous) are produced on a micron scale, capable of releasing a preloaded drug that has been incorporated into a central reservoir and the release of the drug via the surface or bulk degradation of the polymer, with the release kinetics controlled by the type of the polymer and its properties[5]**.**

The solvents used to dissolve the polymeric materials are chosen according to the polymer and drug solubility and stability, process safety and economic considerations. Microspheres are small and have large surface-to-volume ratio. At the lower end of their size range, they have colloidal properties. The interfacial properties of microspheres are extremely important often indicating their activity. Microspheres are well accepted technique for developing a new dosage form, to control and sustain the drug release from the dosage form to improve bioavailability, reduce 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. Microsphere formulations usually improve the prolonging release and localized effect. They also reduce toxicity and improves therapeutic efficacy[6].

Microspheres are in strict sense, spherical solid particles. Microcapsules are small particles that contain an active agent as a core material and coating agent as shell, at present there is no universally accepted size range that particle must have in order to be classified as microcapsules. However, many workers classify capsules smaller than 1 micrometer as nanocapsules and capsules layer more than 1000 micrometer as macroparticles. Commercial microcapsules typically have a diameter between 3-80 micrometers and contain 10-90 weight % cores. Microcapsules usually release their drug at a constant rate (zero-order release), whereas microspheres typically give a first order release of drugs[7].

Microencapsulation is a rapidly expanding technology. It is the process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics or availability of coated materials. Microencapsulation is receiving considerable attention fundamentally, developmentally and commercially[8].

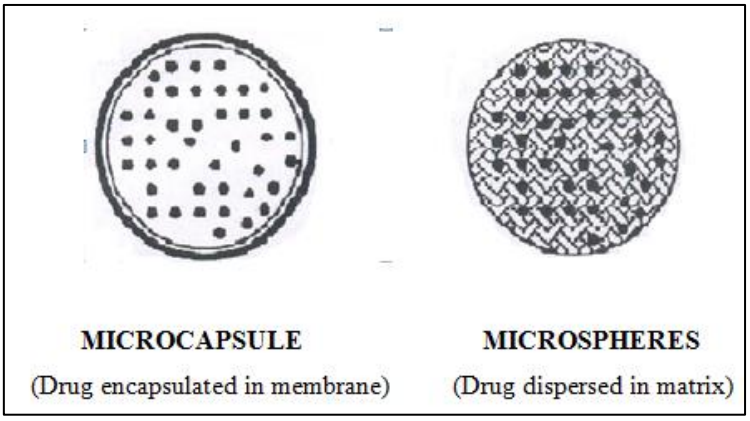

Figure 1: Microcapsule and microsphere drug carrier system

Types of microspheres

1. Bio adhesive microspheres 2. Magnetic microspheres 3. Floating microspheres

4. Radioactive microspheres 5. Polymeric microspheres: The different types of polymeric microspheres can be classified as: a) Biodegradable polymeric microspheres: Natural polymers such as starch are used with b) Synthetic polymeric microspheres[9].

Methods of preparation: Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by microencapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release, method of cross linking, evaporation time and co-precipitation etc. different preparation methods are:

1. Solvent Evaporation Method : Emulsion solvent evaporation technique includes

a) Single emulsion technique b) Double emulsion technique.

2. Solvent extraction method 3. Hot Melt Microencapsulation 4. Phase separation coacervation technique 5. Spray drying and spray congealing 6. Polymerization techniques.

Prerequisites for ideal microparticulate carrier: The materials utilized for the preparation of micro particles should be ideally fulfill the following prerequisites: Longer duration of action, sustains the release of drug, increase of therapeutic efficiency, protection of drugs, reduction of toxicity, biocompatibility, sterilizability, relative stability, dispersibility, targetability and polyvalent[10].

Applications: New applications for microspheres are discovered every day, below are just a few:

- Assay-Coated microspheres provide measuring tool in biology and drug research.
- Buoyancy-Hollow microspheres are used to decrease material density in plastics.
- Ceramics-Used to create porous ceramics used for filters.
- Cosmetics-Opaque microspheres used to hide wrinkles and give color, Clear microspheres provide "smooth ball bearing" texture during application.
- Drug delivery-As miniature time release drug capsule made of, for example, polymers.
- Electronic paper-Dual Functional microspheres used in gyricon electronic paper.
- Personal Care-Added to Scrubs as an exfoliating age.
- Spacers-Used in LCD screens to provide a precision spacing between glass panels.
- Standards-Monodispesre microspheres are used to calibrate particle sieves, and particle counting apparatus.

- Retroreflective-Added on top of paint used on roads and signs to increase night visibility of road stripes and signs.
- Thickening Agent-Added to paints and epoxies to modify viscosity and buoyancy[11].

Medical application

- Release of proteins, hormones and peptides over extended period of time.
- Gene therapy with DNA plasmids and also delivery of insulin.
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria and birth control.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens by intraarterial/intravenous application.
- Tumour targeting with doxorubicin and also treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used in isolation of antibodies, cell separation, and toxin extraction by affinity chromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral and fungal[12].

Radioactive microsphere's application

- Can be used for radioembolisation of liver and spleen tumors.
- Used for radiosynvectomy of arthritis joint, local radiotherapy and interactivity treatment.
- Imaging of liver, spleen, bone marrow, lung etc. and even imaging of thrombus in deep vein thrombosis can be done.

Fluorescent microsphere's application

- Fluorescent microspheres can be used for membrane based technologies for flow cytometry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay.

- Yttrium 90 can be used for primary treatment of hepatocellular carcinoma and also used for pretransplant management of HCC with promising results[13].

Some microsphere products in market:

Tretinoin Gel Microsphere: Tretinoin gel microsphere as tretinoin for the topical treatment of acne vulgaris. **Dexamethasone microspheres**: These microspheres are used for its anti-inflammatory action. With previous investigations on dexamethasone loaded microspheres and composites, the suppression of acute inflammation by dexamethasone containing composites is consistent. **Azithromycin microspheres**: Azithromycin extended release (Zmax®, Pfizer Inc) is a novel single-dose administration formulation of azithromycin approved by FDA in June 2005. It is currently being used for the treatment of community acquired pneumonia and acute bacterial sinusitis (Zmax package insert). Azithromycin revolutionized antibiotic care as it shortened treatment time for infections from 7-14 days to 1-5 days with comparable efficacy. **Acetazolamide microspheres**: Acetazolamide is a carbonic anhydrase inhibitor and it is widely used in the treatment of glaucoma and also used as diuretic. The half-life of this drug is relatively short i.e. 3-4 hrs and usually administered 3-4 times daily in the form of an immediate release formulation. **Degradable starch microspheres**: These are the most frequently used microsphere system for nasal drug delivery. Degradable starch microspheres (DSM) are also known as Spherex. These micro- spheres are prepared by an emulsion polymerization technique where starch is cross-linked with epichlorohydrine[14, 15].

Table 1: List of some drugs which were investigated as microspheres:

S. No	Drug	Polymer	Category
1.	**Metformin Hcl**	Sodium alginate	Antidiabetic
2.	**Amoxicillin Trihydrate**	Ethyl Cellulose	Antibiotic
3.	**Ibuprofen**	Sodium alginate	Analgesic
4.	**Trimetazidine Hcl**	Chitosan	Antianginal
5.	**Furosemide**	Sodium alginate, Carbopol	Diuretic
6.	**Insulin**	Sodium alginate, Chitosan	Antidiabetic
7.	**Acyclovir**	Sodium alginate	Antiviral
8.	**Atenolol, Propranolol**	Polyacrylic acid, Polyvinyl pyrrolidine	Blockers
9.	**Rantidine Hcl**	Sodium alginate	Antacid
10.	**Glipizide**	Chitosan	Oral Hypoglycemic

METHODOLOGY

The main aim and objective of present study was to investigate the possibility of obtaining sustained release ethylcellulose and hydroxypropyl methyl cellulose (HPMC) microspheres designed by using double emulsion-solvent evaporation method. Lansoprazole used as model drug for the present investigation. To characterize and evaluate drug loaded microspheres for:

- Percentage yield
- Particle size analysis
- Drug entrapment efficiency
- Surface morphology-Scanning electron microscopy (SEM)
- Fourier- Transformation infra-red (FTIR)
- Differential scanning colorimetry (DSC)
- *In-vitro* release profile
- *In-vitro* release kinetics
- Effect of process parameters on particle size and encapsulation efficiency[16].

a) Pre-formulation Studies: Pre-formulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of Physical and chemical properties of drug substance, alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be produced at large scale. A thorough understanding of physico-chemical properties may ultimately provide a rationale for formulation design or support the need for molecular modification or merely confirm that there are no significant barriers to the compounds development. The goals of the program therefore are:

1. To establish the necessary physico-chemical characteristics of a new drug substance.

2. To determine its kinetic release rate profile.

3. To establish its compatibility with different excipients.

Hence, pre-formulation studies on the obtained sample of drug include physical tests and compatibility studies.

b) Solubility analysis: Pre-formulation solubility analysis was done to select a suitable solvent system to dissolve the drug as well as various excipients used for formulation of microspheres. The solubility of material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged time until equilibrium achieved[17].

c) Melting point determination: Melting point determination of the obtained drug sample was done; as it is a first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by lowering as well as widening in the melting point range.

d) Analytical method development:

i) Preparation of buffer pH 6.8: 50ml of the potassium dihydrogen phosphate (0.2M) was placed in 200ml volumetric flask and to it 22.4ml of sodium hydroxide solution (0.2M) was added and the volume was made upto 200ml with distilled water.

ii) Preparation of standard solution of lansoprazole: Accurately weighed 100 mg of lansoprazole drug was dissolved in 100 mL of (Conc. 1000 µg/mL). From this solution, 10 mL was pipetted out into 100 mL volumetric flask and volume was made up to with methanol (Conc. 100 µg/mL). Further 10ml aliquot was taken from this solution (100µg/ml) and diluted to 100ml with methanol to give 10µg/ml standard solution of drug. Similarly, standard stock solution was prepared in phosphate buffer pH 6.8 and methonol.

iii) Determination of absorption maxima (λ_{max}) for lansoprazole: The solution containing 10 µg/mL of metformin hydrochloride was scanned over the range of 287 to 294 nm against with suitable blank using double beam UV spectrophotometer. The maximum obtained in the graph was considered as λ_{max} for the pure drug.

iv) Standard Calibration Curve of Lansoprazole: Aliquots of 0.5, 1.0, 1.5, 2.0, 2.5 and 2 mL of lansoprazole standard solution (100µg/ml) were transferred to series of 10 mL volumetric flask and volume was made up to mark with methanol to get serial dilution 2-20 µg/mL of drug. The absorbance of solutions was determined at 285 nm against methanol as blank and a calibration curve was obtained. Similarly, standard calibration curve was prepared in phosphate buffer pH 6.8 and methanol[18].

d) PREPARATION OF LANSOPRAZOLE MICROSPHERES: For the preparation of microspheres the double emulsion method was used as suggested by Rama Rao et al. (2005) with slight modifications. The polymer was dissolved in a mixed solvent system (MSS) of acetonitrile and dichloromethane. To this polymer solution lansoprazole was added and mixed. Then metformin was dissolved separately in 3ml of distilled water and added to the polymer solution while stirring to form a primary emulsion. This primary emulsion was stirred at 450 rpm for 15 min using a mechanical stirrer. Then, this w/o emulsion was poured into liquid paraffin containing Span-80 as the surfactant. This was stirred using a mechanical stirrer for 3-5 hrs, for the complete evaporation of the solvent at 750 to 1000rpm. 10 ml of n-hexane was added as the non-solvent after 2 hrs of the stirring process[19, 20].

Table 2: Formulation design of Lansoprazole microspheres

Formulation Code/ Materials	F1	F2	F3	F4	F5
Lansoprazole (mg)	150	150	150	150	150
HPMC (mg)	300	250	150	200	250
Ethylcellulose (mg)	200	250	250	150	150
Span-80 (%)	0.5	1	2	3	4
Liquid Paraffin (ml)	30	50	50	50	50
Stirring Speed (rpm)	750	750	750	1000	1000

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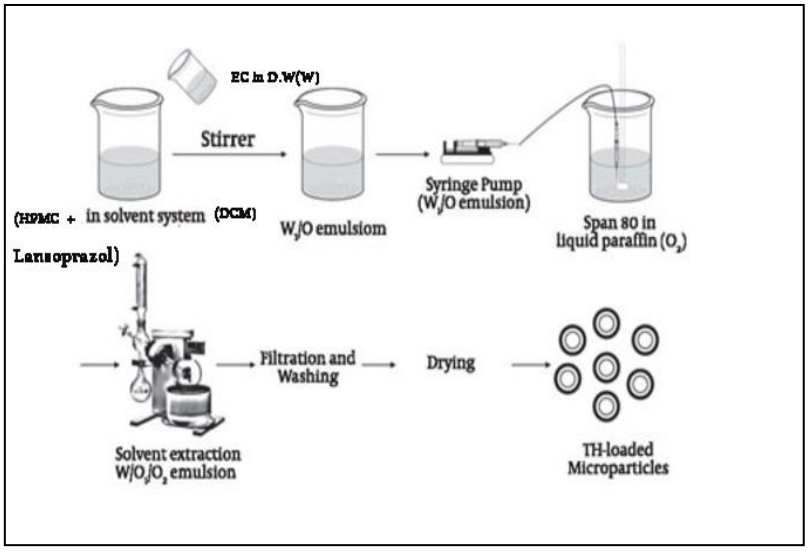

Figure 2: Steps involved in w/o/o double emulsion solvent diffusion method

e) CHARACTERIZATION OF MICROSPHERES

1) Percentage Yield: Percentage practical yield is calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. The prepared microspheres of all batches were accurately weighed. The measured weight of prepared microspheres was divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which give the total percentage yield of floating microspheres. It was calculated by using following equation.

$$\% \text{ Yield} = \text{actual weight of product/total weight of excipients and drug} \times 100$$

2) Particle Size Analysis: The mean particle size was determined by using optical microscope. In this method 25 particles size was determined by using stage micro meter. The average particle size was determined in this method. The eye piece was adjusted and the stage micrometer was adjusted according to the eye piece. Calibration factor was calculated by the following formula: Calibration factor =stage micrometer/eye piece. A minute quantity of prepared microspheres was spread on a clean glass slide. Then particle size of the microspheres were measured, from which average particle size was calculated which was then multiplied with the obtained calibration factor .In this way, the average particle size was calculated for all the six batches[21].

3) Drug Entrapment Efficiency: Microspheres equivalent to 50 mg of the drug were taken for evaluation. Microspheres formulation was dissolved in aliquot amount of methanol by continuous shaking, in a 10 mL volumetric flask and the volume was made up to the mark. The solution was filtered and the absorbance was measured after suitable dilution. The amount of drug entrapped was estimated spectrophotometrically (UV 1700, Shimadzu, Japan) at two different wavelengths i.e., 233nm for metformin and at 276nm for glipizide, against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula:

$$\% \text{ Drug entrapment} = \frac{\text{Amount of drug actually present (DC)}}{\text{Theoretical drug load expected}} \text{ X } 100$$

(DC- Actual Drug Content)

4) Scanning Electron Microscopy (SEM): The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). It images the sample surface of a solid specimen by using a focused beam of high-energy electrons. The signal contains information about surface topography, texture, external morphology of fractured or sectioned surface, chemical composition, crystallographic information, and electrical conductivity.

In order to examine the particle surface morphology and shape, Scanning Electron Microscopy (SEM) was used. Microspheres were scanned and examined under Electron Microscope. Dry microspheres were spread over a slab. The sample was shadowed in a cathodic evaporator with gold layer 20 nm thick. Photographs were taken using an S-3700N Scanning Electron Microscope (Hitachi) operated at 20 kV[22].

5) Compatibility studies of drug and polymer by Fourier- Transformation infra-red (FTIR): FTIR spectrum of drug, polymer and physical mixture of drug with polymers were obtained on FTIR instrument. Sample about 5 mg was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 Psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the spectrum was scanned over the wave number range of 4000-400 cm^{-1}. IR helps to confirm the identity of the drug and to detect the interaction of the drug with the carriers.

6) Differential scanning calorimetry (DSC): Differential Scanning colorimetry is used to determine drug excipient compatibility studies, and also used to observe more phase changes such as glass transition, crystallization, amorphous forms of drugs and polymers. The physical state of drugs and polymer was analyzed by Differential Scanning calorimeter (Schimadzu). Approximately 10 mg of sample was analyzed in an open aluminum pan, and heated at scanning rate of 10°C/min between 0°C and 400°C. Magnesia was used as the standard reference material[23].

***7) In-vitro* release study:** The drug release rate from microspheres was determined by using USP dissolution apparatus Type-II (Electro lab USP Type-II). A weighed amount of microspheres equivalent to 25 mg of drug (Lansoprazole) was weighed and placed in a non-reacting mesh that had a smaller mesh size than the microspheres. Dissolution medium used was 0.1 N HCl (pH 1.2, 750 ml) for first 2 hours and maintained at 37 ± 0.5°C at a rotation speed of 100 rpm. 5 ml of sample was withdrawn at each 15 min interval for the first hour followed by 30 min interval, later this interval was extended to 1 h. Sample was then passed through a 5 µm membrane filter, and analyzed spectrophotometrically at 285 nm present in the dissolution medium respectively. The initial volume of dissolution medium was maintained by adding 5 ml of fresh dissolution media after each withdrawal. The dissolution study was continued with using phosphate buffer (pH 6.8 ± 1, 900ml) for next 10 h. The cumulative % drug release was calculated using standard calibration curve[24,25].

RESULTS AND DISCUSSION

In the present investigation an attempt has been made to formulate microspheres of lansoprazole by using biocompatible polymer like ethylcellulose and hydroxyl propyl methylcellulose as carrier for sustained release. Microspheres were prepared by double emulsion-solvent evaporation method and prepared microspheres are subjected for characterization and evaluation studies. The UV absorbance of lansoprazole in the range of 0-50µg/ml of the drug in methanol and pH 6.8 (PBS) buffers showed linearity at lambda max of 285 nm. The linearity was plotted for absorbance against concentration. Preformulation study for lansoprazole has been performed to know the drug physical properties so as to design it to a suitable formulation. The solubility of pure drug lansoprazole in 10 mg/10 ml of solvent was carried out and it reveals that it is freely soluble in ethanol, chloroform and dichloromethane. It is soluble in 0.1 N HCl and methanol and poorly soluble in water. The melting point of the pure drug (lansoprazole) was determined at 178-182**.** Ethyl Cellulose microspheres were prepared by W/O/O double emulsion solvent diffusion method. This method for preparation of microspheres was reported to overcome the problem of low encapsulation efficiency of water soluble drugs prepared by conventional W/O/W double emulsion solvent diffusion method. The mean particle size of the developed formulations of microspheres was found to be in the range of 41.1 to 280 µm for F1-F5. Minimum size was obtained from batch F4 having 3% span 80 concentration at a stirring speed of 1000 rpm. It was found that the mean particle size was decreased with an increase in the stirring speed and stabilizer concentration. Percentage yield of all the formulations was calculated and reported in the table. Percentage yield in the range of 48% to 93.3% was observed for the formulations F1-F5. Maximum yield was obtained from formulation F4 with a yield of 93.88%. The drug entrapment efficacy of microspheres for F1 to F5 was in the range of 10.4-58% for lansoprazole. Highest entrapment efficacy was observed with F4 formulation, with a percentage entrapment of 57.9% for lansoprazole. The results of percentage drug entrapment efficiency are shown in the table. From the encapsulation efficiency values it was observed that increase in the speed of rotation from 750 rpm to 1000 rpm at constant surfactant concentration, resulted in higher encapsulation efficiency. This may be due to the formation of larger emulsion droplets at low speed ensuring enough drug diffusion out of the microspheres before they harden. From the encapsulation efficiency values it was observed that by keeping the speed of rotation constant, there was a significant decrease in encapsulation efficiency of the drugs with increase in concentration of surfactant for the secondary emulsion. This may be due to the fact that increase in surfactant concentration proportionally increases miscibility of light liquid paraffin (processing medium) which may increase the extraction of drug into the processing medium.

Table 3: Particle size, percentage yield and entrapment efficiency data of microspheres

Formulation	Particle size (µm)	Percentage (%) Yield	Drug Entrapment efficiency (%)
F1	146	61%	10.4%
F2	234	68.92%	48%
F3	204	48%	57.5%
F4	226	93.88%	57.9%
F5	223	71.88%	53%

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Surface morphology of the microspheres was examined by scanning electron microscopy (SEM). The microspheres of optimized formulation were examined. The SEM results showed that the microspheres were spherical in nature with rough surface morphology. In addition, micropores were observed on the surface of microspheres at higher magnifications. SEM pictures are shown in figure, it was concluded that the average particle size was found to be in a 44.8 to 286 micron range (µm)**.**

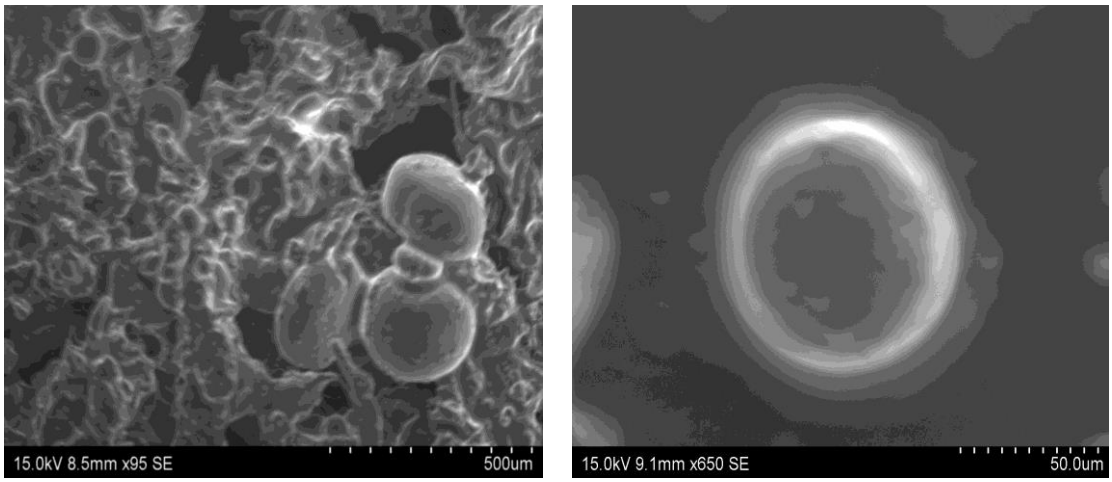

Figure 3: Particles in spherical shape

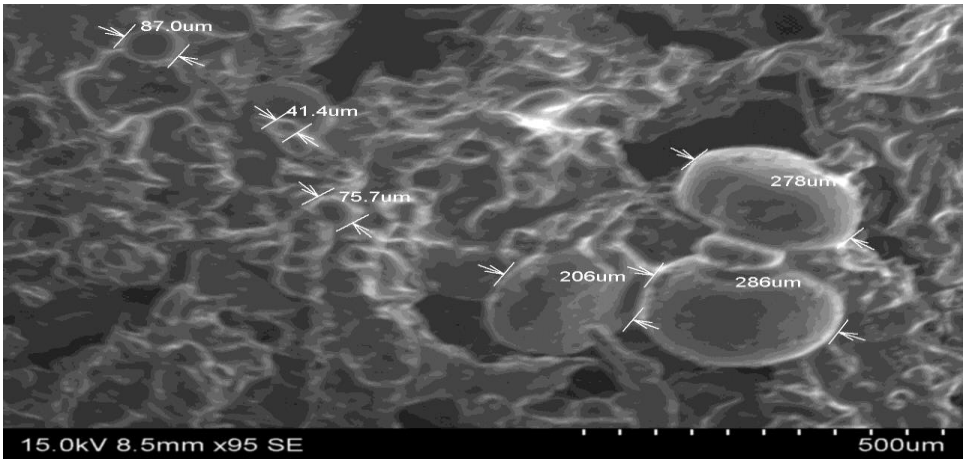

Figure 4: Particles in micron range (µm) SEM pictogram of microspheres of optimized formulation (F4).

The cumulative present drug release of F1 to F5 formulations at various time intervals was calculated and tabulated, the cumulative present drug release in all formulations was plotted against time, among all the batches slow and constant release was observed with F-4 formulation. Among the different formulations prepared using different surfactant concentration and at different speed of rotation, it has been observed that the formulation prepared using 0.5% span-80 concentration at a speed of 1000 rpm resulted in maximum entrapment efficiency and least cumulative percentage drug release. Therefore, these formulations F-3 and F-4 were considered as the optimized formulations.

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Table 4: In-vitro cumulative percentage drug release data of lansoprazole:

TIME (hr)	F1	F2	F3	F4	F5
0.25	7.77	9.44	10.61	5.41	6.52
0.5	16.54	17.97	21.83	10.02	14.93
0.75	22.18	23.73	26.35	16.52	17.83
1	26.27	28.82	32.04	20.43	22.86
2	37.74	39.91	49.22	30.24	34.65
3	40.43	47.09	56.86	33.55	38.09
4	46.15	53.16	64.31	36.83	40.55
5	52.36	61.18	71.79	39.98	45.58
6	59.28	72.15	78.96	45.41	53.52
7	66.04	77.84	84.42	52.25	61.15
8	73.38	82.18	86.21	57.08	69.53
9	79.19	88.86	90.81	64.22	74.69
10	86.75	92.23	94.27	69.78	80.48
11	89.68	93.68	96.34	73.93	82.62
12	92.72	96.82	98.65	77.24	85.71

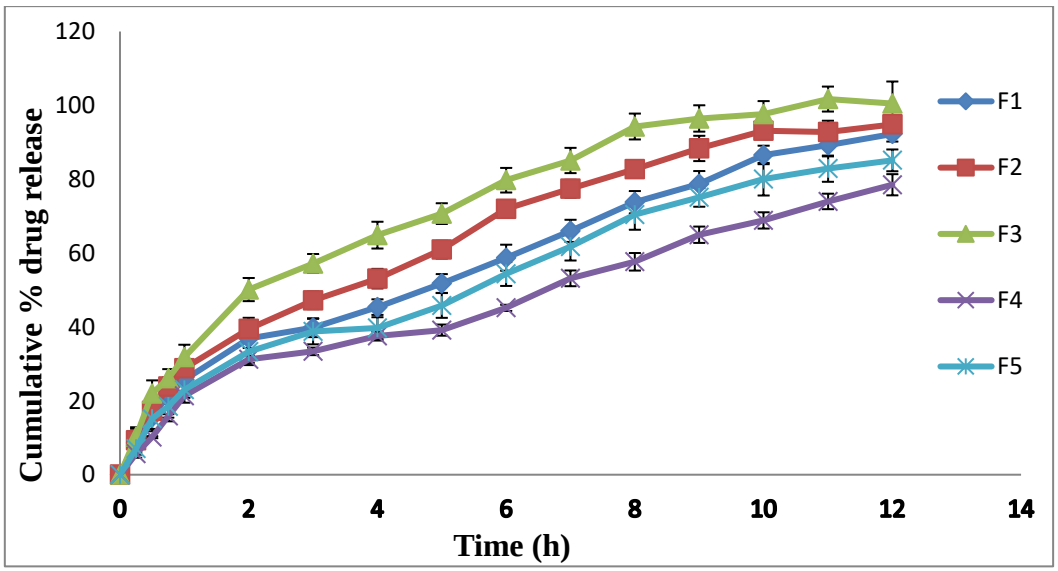

Figure 5: Comparison of cumulative percentage drug release (lansoprazole) of all the formulations

The in-vitro release data obtained from optimized Formulation F4 was fitted in various kinetic dissolution models such as zero order, first order, Higuchi model and Korsmeyer-Peppas model. The Peppas model is widely used to confirm whether the release mechanism is Fickian diffusion, non-Fickian diffusion or zero order. 'n' value could be used to characterize different release mechanisms. Optimized formulation F4 is following Higuchi model release mechanism for the drug (lansoprazole), with first order release kinetics and it follows non Fickian diffusion when it applied to the Korsmeyer-Peppas model for mechanism of drug release. The results are shown in table.

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Table 5: Release kinetics data of Lansoprazole from optimized formulation F4:

Time (h)	Cumulative (%) Release Q	Root (T)	Log (t)	Log (%) Release	Log (%) Remain
0	0	0			2.000
0.25	5.45	0.500	-0.602	0.736	1.976
0.5	10.09	0.707	-0.301	1.004	1.954
0.75	16.53	0.866	-0.125	1.218	1.922
1	20.46	1.000	0.000	1.311	1.901
2	30.28	1.414	0.301	1.481	1.843
3	33.57	1.732	0.477	1.526	1.822
4	36.87	2.000	0.602	1.567	1.800
5	39.95	2.236	0.699	1.602	1.779
6	45.42	2.449	0.778	1.657	1.737
7	52.2	2.646	0.845	1.718	1.679
8	57.04	2.828	0.903	1.756	1.633
9	64.21	3.000	0.954	1.808	1.554
10	69.75	3.162	1.000	1.844	1.481
11	73.97	3.317	1.041	1.869	1.415
12	77.02	3.464	1.079	1.887	1.361

Drug polymer compatibility studies were carried out by using FTIR spectral studies to establish the possible interaction in the formulations. Our experimental results were assessed on the basis of physical data obtained for drugs and polymers as well as formulations. The IR spectrum obtained of lansoprazole, ethyl cellulose and HPMC and optimized formulation- F4 were identical and there was no change in the functional group absorption of any molecule present in formulated product as shown in figures. The final conclusion was observed that, there is compatibility between the drug and excipients in their use.

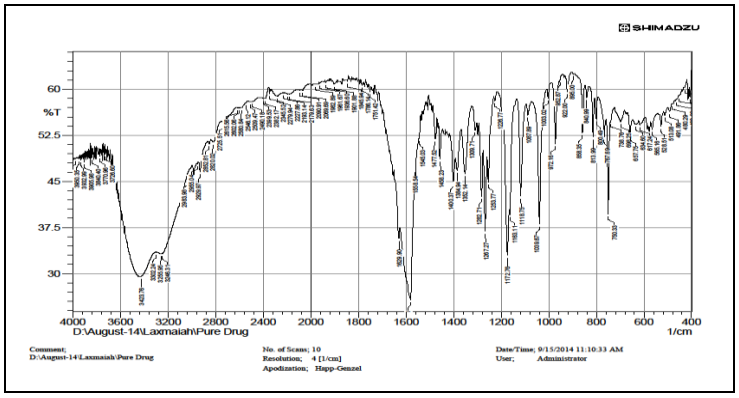

Figure 6: FTIR Spectra of pure drug (Lansoprazole)

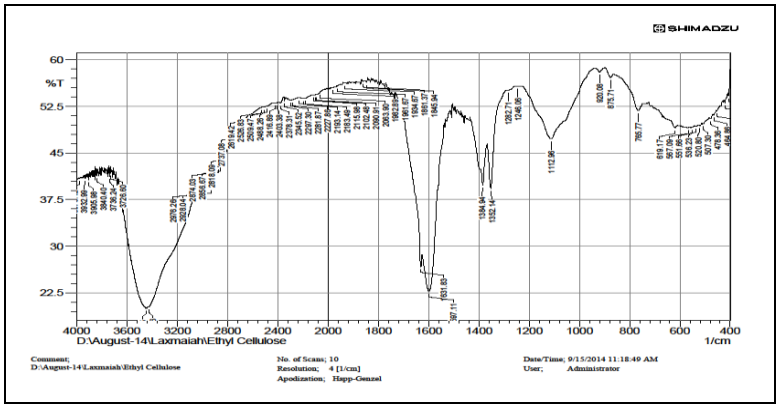

Figure 7: FTIR spectrum of polymer (Ethyl cellulose)

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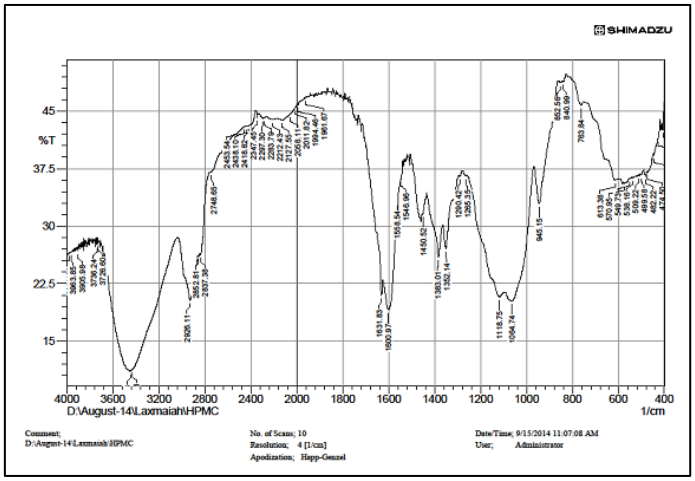

Figure 8: FTIR spectrum of polymer (HPMC).

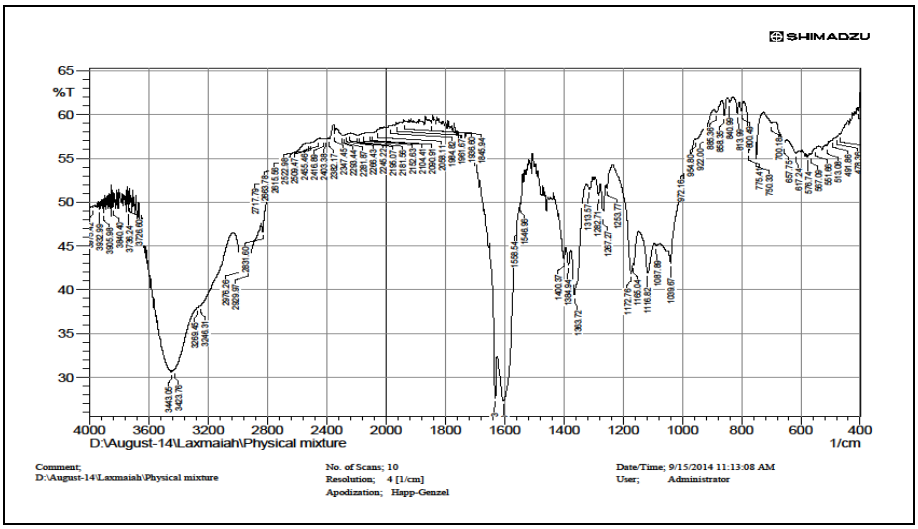

Figure 9: FTIR Spectra of physical mixture

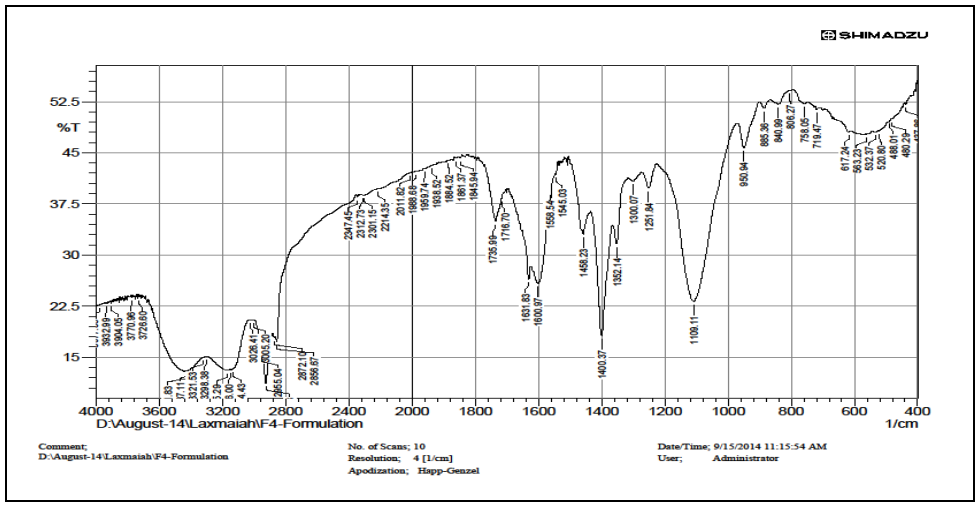

Figure 10: FTIR Spectra of optimized formulation (F4)

DSC studies were performed to understand the nature of the encapsulated drug in the matrix. The physical state of drug in the polymer matrix would also influence its release characteristics. To probe this effect, DSC analysis was performed on a) Lansoprazole

and b) formulation F4 as shown. The DSC thermogram of lansoprazole exhibits an endothermic peak at 171°C. corresponding to its melting transition point. There was no peak detected in the temperature ranges of the drug in the optimized formulation (lansoprazole loaded ethyl cellulose and HPMC microspheres). The absence of drug peak may be due to conversion of drugs from crystalline state to semicrystalline or amorphous state. The absence of detectable crystalline domains in the optimized formulation clearly indicates that the drug lansoprazole existed in amorphous or disordered-crystalline form of a molecular dispersion in the polymer matrix.

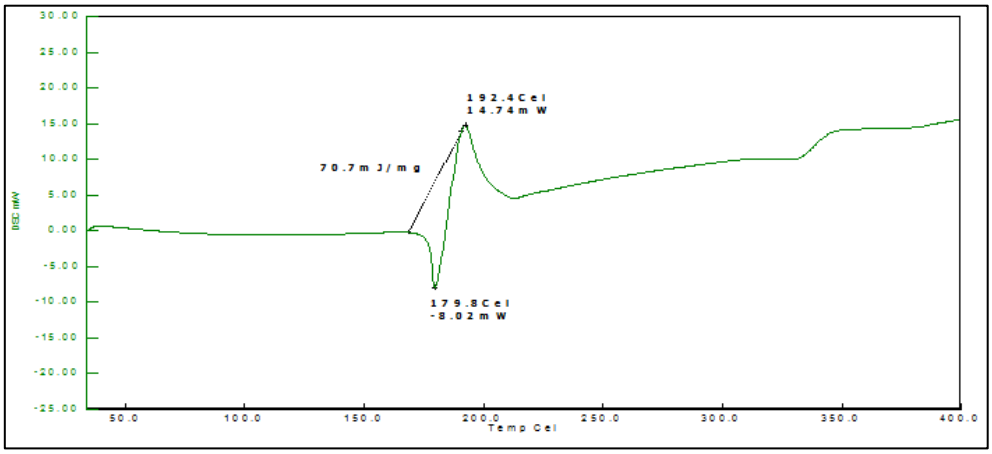

Figure 11: DSC thermogram of pure drug (Lansoprazole)

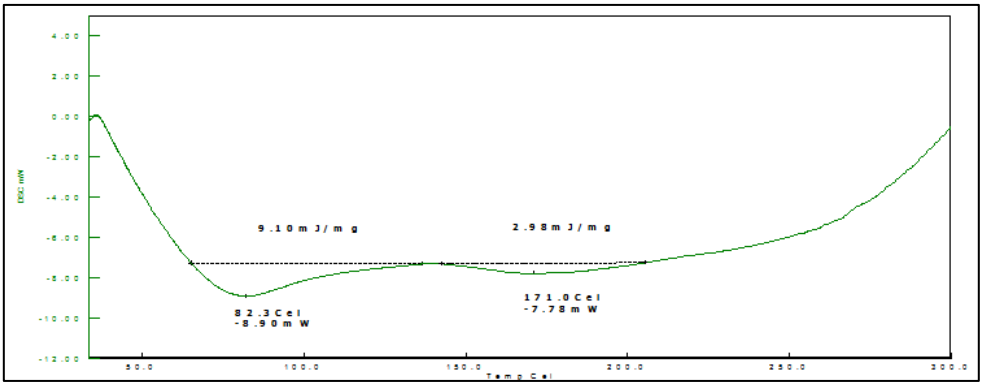

Figure 12: DSC thermogram of optimized formulation F-4

CONCLUSION

From the study, it is evident that promising sustained release microspheres of lansoprazole may be developed by W/O/O double emulsion-solvent diffusion technique by using ethyl cellulose and hydroxyl propyl methyl cellulose polymer.

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