IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
November 2023 Vol.:28, Issue:4

Preparation and Evaluation of Sustained Release Lansoprazole Microspheres by Double Emulsification-Solvent Diffusion Method

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Submitted: 22 October 2023
Accepted: 27 October 2023
Published: 30 November 2023

HUMAN JOURNALS
ijppr.humanjournals.com

Keywords: Lansoprazole, hydroxyl propyl methyl cellulose (HPMC K4M), ethyl cellulose (EC), span-80, sustained release, microspheres, double emulsification-solvent diffusion method, zero-order release and higuchi model kinetics.

ABSTRACT

Objective: The aim and objective of the present study are to prepare stable lansoprazole microspheres for sustained release of the drug by using hydrophobic ethyl cellulose (EC) and increased dissolution rate by hydrophilic hydroxy propyl methyl cellulose (HPMC- K4M) using span-80 as a stabilizer and emulsifying agent by double emulsification-solvent diffusion technique. **Materials and methods:** Different batches of lansoprazole-loaded ethyl cellulose and HPMC-K4M microspheres were prepared using W/O/O double emulsification-solvent diffusion method. The prepared microspheres were evaluated and characterized for percentage yield, drug entrapment efficiency and particle size. **Results: L**ansoprazole microspheres showed sustained release property. As a result of these experiments, it was concluded that sustained release microspheres of lansoprazole were successfully prepared using ethyl cellulose and hydroxyl propyl methyl cellulose as the polymers using the double emulsion solvent-diffusion technique.

INTRODUCTION

For decades an acute or chronic illness has been 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[1]. Multiple daily dosing is inconvenient to the patient and can result in missed doses, made-up doses and patient incompliance with the therapeutic regimen. 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 intervals by conventional dosage form[2]. 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 the 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 i.e the drug delivery system should deliver the drug at a rate detected by the needs of the body over an entire period of treatment[3]. The Plasma drug concentration profiles for conventional tablet formulation, a sustained release formulation and a zero order controlled release formulation is shown in figure 1.

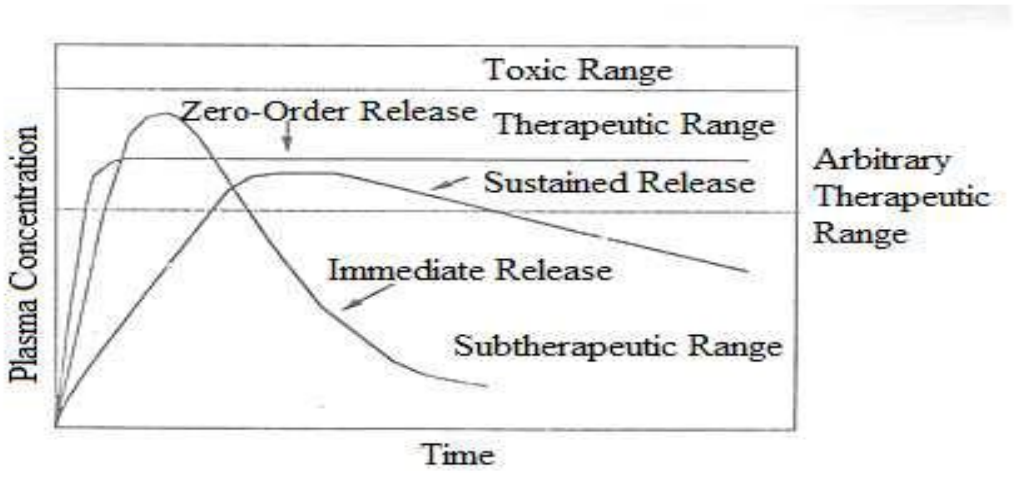

Figure 1: Plasma drug concentration profiles for conventional tablet formulation, a sustained release formulation and a zero-order controlled release formulation.

This is possible through the administration of conventional dosage forms in a particular dose and particular frequency to provide a prompt release of drug. Therefore to achieve and maintain the concentration within the therapeutically effective range by the treatment by repeated administration a day, sustained release drug delivery systems were developed[4]. Conventional oral drug administration does not usually provide rate-controlled release or target specificity, it results in a significant fluctuation in a plasma drug level which leads to several undesirable toxic effects, and poor patient compliance. In many cases, conventional drug delivery provides a sharp increase in drug concentration often achieving toxic levels and following a relatively short period at the therapeutic level of the drug concentration eventually drops off until re-administration[5]. In order to obtain maximum therapeutic efficacy, it becomes necessary to deliver an agent to the target tissue in the optimal amount for the required period of time, thereby causing no toxicity and minimal side effects by sustained release systems. Desired drug release can be provided by rate-controlling membranes or by implanted biodegradable polymers containing dispersed medication. The newer techniques are capable of controlling the rate of drug release, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue[6]. The drug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Novel systems to a greater extent supersede the above loopholes of the conventional pharmaceutical dosage forms and the fascination provided by these new systems is the re-patenting of successful drugs by applying the technology of sustained release drug delivery. The optimization of pharmacological action of drugs coupled with the reduction of side effects remains the challenge of these novel drug delivery systems. With concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled-release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist[7]. The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing a sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. There is a continuously growing interest in the pharmaceutical industry for sustained-release drug delivery systems. Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms. Various terms like 'smart', intelligent', 'novel',

therapeutic have been assigned to controlled release systems[8]. In the last twenty years or so, sustained-release dosage forms, continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release technology has emerged as an important new field in the development of pharmaceutical dosage form. The introduction of sustained release (SR) has given a new breakthrough for novel drug delivery systems (NDDS) in the field of pharmaceutical technology. Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. More precisely, sustained drug delivery can be defined as "Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable effects". In sustained release dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response[9]. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose. The onset of its pharmacologic action is the often delayed and the duration of its therapeutic effects is sustained. A sustained release is facilitated through the consistent rejuvenation of drug molecules. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. The sustained plasma drug levels provided by sustained-release products often eliminate the need for night dosing, which benefits not only the patients but the care given as well. The basic rationale of a sustained drug delivery system is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its unity is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most possible route[10]. Potential advantages of sustained release drug delivery systems are avoiding patient compliance problems, reduction in dosing frequency, avoidances of night time dosing, employ less total drug, minimize or eliminate local and systemic side effects, obtain less potentiating or reduction in drug activity in chronic use, minimize drug accumulation with chronic dosing, improve efficiency in treatment, cure or control condition more promptly, improve bioavailability of some drugs, effective utilization of drug and also associated with disadvantage such as successful fabrication of sustained release products is usually difficult and involves consideration of physicochemical properties of drug, the pharmacokinetic behavior of drug, route of administration, disease state to be treated and most importantly placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug[11].

There are various approaches in delivering a therapeutic substance to the target site in a sustained-release fashion. The various approaches or the novel drug delivery system includes liposomes, microspheres, nanoparticles etc. One such approach to get a sustained release drug delivery is by using microspheres as carriers for drugs also known as microparticles. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity[12]. It is the reliable means to deliver the drug to the target site with specificity if modified, and to maintain the desired concentration at the site of interest. Microspheres received much attention not only for prolonged release but also for targeting of anticancer drugs. Multi-particulate 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 multi-particulate systems have been designed, thus far the mainstream technologies are still based on spay drying, spheronization, and film coating technology[13]. However, there is a problem of manufacturing reproducibility and lack of safety. 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 distribution. A microsphere is a structure made of a continuous phase of one or more miscible a polymer in which particulate drug is dispersed at 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 a 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[14]**.** 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 a 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, controlling and sustain the drug

release from the dosage form to improve bioavailability, reduce the adverse action and prolong the action of drug, reducing 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 and usually improve the prolonging release and localized effect[15]. Microspheres are in strict sense, spherical solid particles and are fundamentally developed and commercially as bio-adhesive, magnetic, polymeric and synthetic, floating for gastroretentive, diagnostic and smaller amount of drug magnetically targeted, drugs like proteins and peptides can also be targeted through this system, radioactive microspheres are larger than capillaries and get tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest, so these radioactive microspheres deliver high radiation doses to the targeted areas without damaging the normal surrounding tissues. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner and synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible. 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. The different preparation methods are solvent evaporation method, emulsion solvent evaporation technique which includes single emulsion technique and double emulsion technique, solvent extraction method, hot melt microencapsulation, phase separation coacervation technique, spray drying and spray congealing and polymerization techniques. Double emulsion method of microspheres preparation involves the formation of multiple emulsions or the double emulsion of type w/o/w and w/o/o are best suited to water-soluble drugs, peptides, proteins, vaccines and water insoluble drugs. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solutions which contain the active constituents were dispersed in a lipophilic organic continuous phase. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase to prepare the primary emulsion. The primary emulsion is then subjected to the homogenization or the sonication before addition to the aqueous solution of the polyvinyl alcohol (PVA) which results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like luteinizing hormone-releasing hormone (LH-RH) agonists, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the

microspheres using the method of double emulsion solvent evaporation/ extraction. The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of the microsphere or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of physical entrapment, chemical linkage, surface adsorption, heat of polymerization, agitation intensity and addition of additives (surfactant and stabilizers). The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer, if used). The loading is carried out in pre-formed microspheres by incubating them with high concentration of the drug in a suitable solvent. The drug in these microspheres is loaded via penetration or diffusion of the drug through the pores in the microspheres as well as adsorption on their surface. The solvent is then removed, leaving a drug-loaded microsphere. New applications for microspheres are discovered day by day, below are just a few medical applications such as release of proteins, hormones and peptides over extended period of time[16]. Gene therapy with DNA plasmids and also delivery of insulin, vaccine delivery for treatment of diseases like hepatitis, influenza, pertussis, rich in toxoid, diphtheria and birth control. Passive targeting of leaky tumour vessels, active targeting of tumor cells, antigens, by intra-arterial/intravenous application. Tumour targeting with doxorubicin and also in treatment of leishmaniasis. Magnetic microspheres can be used for stem cell extraction and bone marrow purging. Radioactive microspheres application can be used for radioembolisation of liver and spleen tumors. Imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done. 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 pre-transplant management of HCC with promising results. Some microsphere products in the market are tretinoin gel microspheres for the topical treatment of acne vulgaris. Dexamethasone microspheres are used for its anti-inflammatory action. Azithromycin extended-release (Z max, Pfizer Inc) micrspheres 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 (Z max package insert). Acetazolamide microspheres are widely used in the treatment of glaucoma and also used as diuretics which are prepared by solvent evaporation technique[17]. Degradable starch microspheres (DSM) are also known as spherex are most frequently used microsphere systems for nasal drug delivery and the other applications and drugs available in the market are metformin hydrochloride, amoxicillin

trihydrate, ibuprofen, trimetazidine hydrochloride, furosemide, acyclovir, atenolol, propranolol, ranitidine hydrochloride, and glipizide, etc as given in table.1.

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

Sr. No	Drug	Polymer	Result	Method	Use
I. Anticancer and Antitumor					
01	Oxantrazol	Chitosan	Enhance the delivery of drug in the brain 100 times	Combined emulsion	Anticancer
02	Mitoxantrone	Glutaraldehyde-Saturated toluene	Minimize drug toxicity and maximize therapeutic efficacy	Cross linking technique	Antitumor
03	Fluorouracil	Glutaraldehyde, Chitosan, Chitin	Slow-down of release rate of drug Reduce release rate	O/W/O emulsion system	For targeted delivery to treat cerebral tumors Antitumor activity
04	Cisplatin	Glutaraldehyde, Chitosan, Chitin	Slow-down of release rate of drug Reduce release rate	O/W/O emulsion system	For targeted delivery to treat cerebral tumors Antitumor activity
II. NASID					
05	Ketoprofen	Chitosan	Modulate drug release	Multiple emulsion (o/w/o)	Anti-inflammatory
06	Diclofenac sodium	Chitosan, Chondroitin sulfate	Suppress the release rate	Co-acervation phase sepration	Anti-inflammatory
07	Aceclofenac	Eudragit	Controlled release and minimize local side effect	By dissolving drug in polymer	Anti-inflammatory drug
08	Indomethacin	Chitosan	Decrease in the release rate	Co-matrix method	Anti-inflammatory drug
III. Antibiotic					
09	Amoxicillin		Slow release rate	Crosslinking	For helicobacter pylori infection eliminating

					infection
10	Gentamicin	PLGA and PCL	Controlled release	Double emulsion technique	Antibiotic
IV. Cardiac agent					
11	Diltiazem	Casein, chitosan	Retard drug release	Colloidal coacervation technique	Calcium channel blockers
12	Propranolol	Chitosan	Enhance Drug encapsulation efficiency	Emulsification co-acervation technique	Calcium channel blockers
13	Nifedipine	Chitosan	More drug entrapment efficiency	Encapsulation	Calcium channel blockers
V. Steroidal					
14	Progesterone	Glutaraldehyde, chitosan	Maintain plasma drug concentration	Crosslinking	Steroid
VI. Anti-diabiatic agent					
15	Insulin	Chitosan	Improve systemic absorption	Crosslinking	Anti-hyperglycemic effect
VII. Diuretics					
16	Furosemide	Chitosan	Reduce effect of external variables	Crosslinking	Diuretics

MATERIALS AND METHODS

Lansoprazole is a gift sample from notch laboratories pvt limited, ethyl cellulose, HPMC K4M, span-80, light liquid paraffin, dichloromethane, methanol, n-hexane are from SD fine chemicals are AR grade. The formulation studies with the lansoprazole obtained were performed using conventional and reported techniques. The UV-Visible spectrum, solubility, flow properties, drug crystallinity were determined.

Preparation of Lansoprazole loaded Ethyl cellulose-HPMC-K4M microspheres: Lansoprazole microspheres were prepared by W/O/O double emulsion solvent diffusion method using HPMC K4M and ethyl cellulose as polymers given in table 2.

Table 02: Composition and formulation design of Lansoprazole microspheres:

S. No	Formulation Code	F1	F2	F3	F4	F5
1	Lansoprazole (mg)	50	50	50	50	50
2	HPMC-K4M (mg)	500	500	500	500	500
3	Ethyl cellulose (mg)	300	300	300	200	200
4	Span-80 (ml)	0.5	1	1.5	2	2.5
5	Dichloromethane (ml)	10	10	10	10	10
6	Distilled water (ml)	5	5	5	5	5
7	Liquid Paraffin (ml)	15	15	15	15	15
8	Stirring Speed (rpm)	750	750	750	1000	1000

A mixed solvent system (MSS) of dichloromethane and distilled water was used for the preparation of microspheres as internal organic phase and aqueous phase. Liquid paraffin and span-80 were used as external oily phase and surfactant/stabilizer. 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/O double emulsion solvent diffusion method as suggested by Rama Rao et al. (2005) with slight modifications. The polymer was dissolved in a mixed solvent system (MSS) of dichloromethane and distilled water as shown in Figure 2.

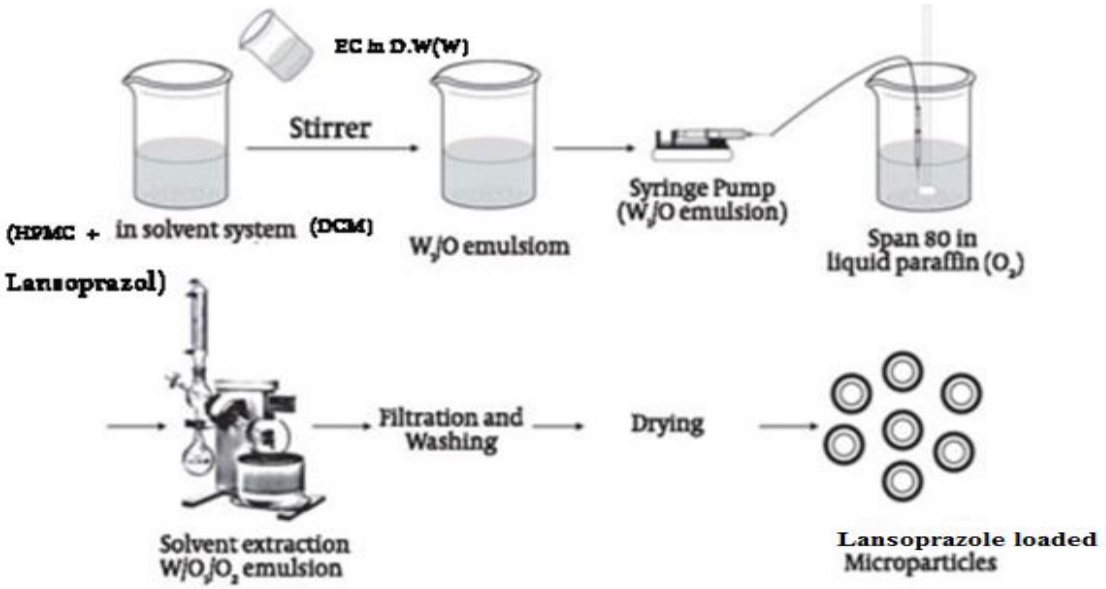

Figure 2: Steps involved in w/o/o double emulsion solvent-diffusion method.

To this polymer solution lansoprazole was added and mixed, in another beaker ethyl cellulose was dissolved in dichloromethane and then added to mixed solvent system and stirred at 500 rpm to form w/o primary emulsion. Span-80 as stabilizer and surfactant was dissolved separately in 15 ml of liquid paraffin and to this prepared w/o primary emulsion was injected with a syringe pump and stirred at 750-1000 rpm on a magnetic stirrer for 10-12 hours, until the complete evaporation of solvent occurs to get w/o/o double emulsion i.e multiple emulsion as lansoprazole microspheres. 10 ml of n-hexane was added as the non-solvent to the processing medium to solidify the microspheres and dried for 4 hours to get microspheres[17, 18].

Characterization and Evaluation of Lansoprazole microspheres:

Percentage yield: To determine the yield, the weight of microspheres obtained at the end of preparation was determined. The total weight of raw materials used to obtain these microspheres was determined to obtain the theoretical yield.

The percentage yield was then determined using the formula:

Percentage yield = (Practical yield/theoretical yield) x 100.

Drug entrapment efficiency (EE): The amount of drug entrapped was estimated by dissolving the 100 mg of microspheres in dichloromethane and water in a 3:1 ratio under

vigorous shaking for 1 hour, the resultant solution was centrifuged both layers were separated and the soluble lansoprazole in water was determined. The drug content in aqueous solution was analyzed spectrophotometrically by using a UV-VIS spectrophotometer (Merck, Thermoscientific Evoluation 201) at 294 nm with further dilutions against appropriate blank. The amount of the drug entrapped in the microcapsules was calculated using the formula:

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

Particle size analysis: The mean particle size was determined using the optical microscopy method. In this method, the sizes of 250 particles were determined and the average particle size was calculated. An optical microscope can detect particles of sizes in micron with accuracy. If particles produced are in this size range, this technique can be conveniently used to measure the particle size and determine of average particle size of lansoprazole microspheres with optical microscopy, the average size of microspheres is reported.

Scanning electron microscopy: In order to examine the surface morphology shape and size of the particle scanning electron microscopy (SEM) was used. A concentrated aqueous suspension was spread over a slab and dried under a vacuum. The sample was shadowed in a cathodic evaporator with a gold layer 20 nm thick. Photographs were taken using a scanning electron microscope (Hitachi, S-3700N, Tokyo, Japan) operated at 20 kV. The smallest size microcapsules were used for determining surface morphology.

Drug-excipient compatibility studies (FTIR studies): FTIR spectrum of drug, polymer and physical mixture of drug with polymers and optimized formulation were obtained on FTIR instrument. Sample of 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 an IR spectrophotometer (Shimadzu 8400S, Tokyo, Japan) and the spectrum was scanned over the wave number range of 4000-400 cm-1 in a scan time of 12 minutes. IR helps to confirm the identity of the drug and to detect the interaction of the drug with the carriers.

Differential scanning calorimetry (DSC): DSC studies were performed to understand the nature of the encapsulated drug in the polymer and the physical state of drug in the polymer matrix would also influence its release characteristics. To probe this effect, DSC analysis was

performed. Thermal analysis and properties of the powder samples (Lansoprazole and optimized microspheres) were investigated with a DSC (Shimadzu DSC 60, Tokyo, Japan). Approximately 10 mg of the sample was analyzed in an open aluminum pan, and heated at scanning rate of 10°C/min between 0°C and 400°C under nitrogen atmosphere. Magnesia was used as the standard reference material to identify physical changes of drug in the formulation. Hence, it indicates the physical nature of the drug is changed in the formulation from crystalline to amorphous.

***In-vitro* drug release:** *In-vitro* dissolution studies of samples were carried out using USP XIV (Electro lab TDT-082, Model-ETC 11L, Mumbai, India) apparatus II paddle method by dispersed powder technique. Accurately weighed samples were added to 900 ml of P^H 1.2 (0.1 N HCl) phosphate buffer as dissolution media at 37 ± 0.5°C and stirred at 100 rpm. An aliquot of 5 ml was withdrawn at different time intervals of 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hr for every one hour up to 12 hours. The solid particles were prevented from pipetting by withdrawing the sample through a pipette fitted with a cotton plug. An equal volume of fresh dissolution medium was immediately replaced. The sample was then passed through a 5µm membrane filter, filtered samples were assayed spectrophotometrically (Merck, Thermoscientific Evoluation 201) at 294 nm respectively for the lansoprazole drug. The dissolution of microspheres was compared with the dissolution of an equivalent amount of the pure drug lansoprazole and identified the sustained release property. The cumulative % drug release was calculated using the standard calibration curve.

Drug release kinetics: The obtained dissolution data was fitted into mathematical equation for zero order, first order, highuchi model and korsemeyer equation/peppa's model in order to describe the kinetics and mechanism of drug release from the microcapsules formulations. To analyze the *in-vitro* release data various kinetic models were use to describe the release kinetics. The zero order describes the systems where the drug release rate is independent of its concentration. The first order describes the release from system where release rate is concentration-dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time-dependent process based on fiction diffusion[19, 20].

RESULTS AND DISCUSSION

The preformulation studies like melting point, solubility and UV analysis of lansoprazole complied with IP standards. The UV absorbance of lansoprazole in the range of 0-50 µg/ml

of the drug in methanol and 0.1 N HCL pH 1.2 buffers showed linearity at wave length maxium of 294nm. 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 different solvents was carried out, it is practically insoluble in distilled water and it is freely soluble in methanol, chloroform, dichloromethane, ethanol and 0.1 N HCL. Percentage yield of all the formulations was calculated and found to be in the range of 72.45 to 89.92% for the formulations F1-F5, maximum yield was obtained from formulation F4 with a yield of 89.92%. The drug entrapment efficacy of microspheres for F1 to F5 was in the range of 72.23 to 88.64% for lansoprazole drug, highest entrapment efficacy was observed as 88.64% for F4. From the entrapment efficiency values it was observed that an increase in the speed of rotation from 750 rpm to 1000 rpm at constant surfactant concentration, resulted in higher entrapment efficiency. This may be due to the formation of larger emulsion droplets at low speed, ensuring that enough drug diffusion out of the microspheres before they harden, there was a significant increase in encapsulation efficiency of the drugs with increase in rpm from 750 to 1000 and an increase in concentration of stabilizer. The mean particle size of the developed lansoprazole microspheres formulations was found to be in the range of 220 to 350 µm for F1-F5 with the optical microscopy method, minimum size particles were obtained for batch F4 having 2% 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. The percentage yield, entrapment efficiency and particle size results were given in Table 3.

Table 03: Characterization of Lansoprazole microspheres

S.No	Formulation	Particle size (µm)	Percentage yield	Entrapment Efficiency
1	F1	350	72.45	72.23
2	F2	320	74.56	74.93
3	F3	280	78.07	79.62
4	F4	220	89.92	88.64
5	F5	250	82.27	81.37

Surface morphology of optimized lansoprazole microspheres was examined by scanning electron microscopy (SEM) which showed that the microspheres were spherical in nature with smooth surface, wavy and free-flowing nature as shown in figure 3.

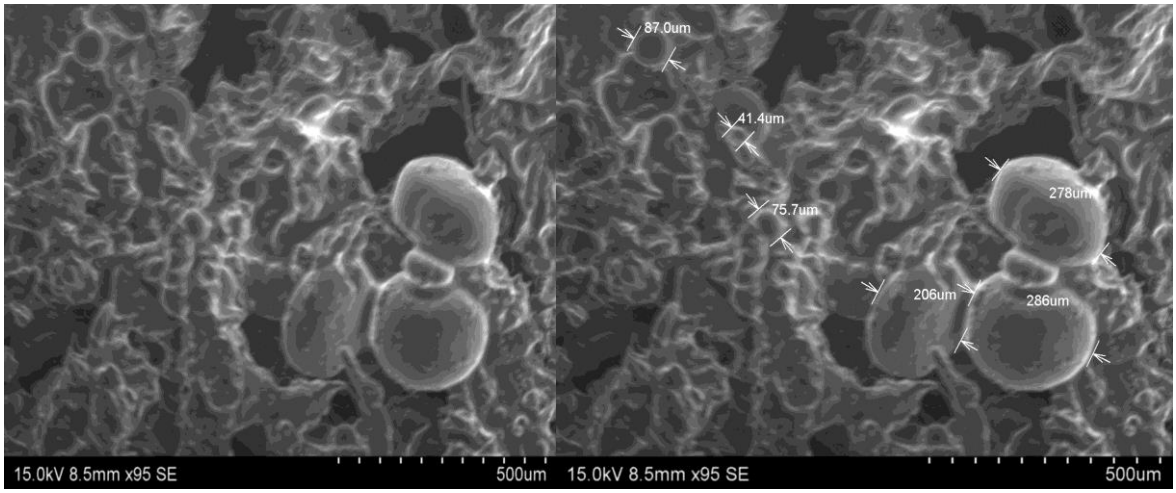

Figure 3: SEM pictogram of microspheres of optimized formulation (F4), particles are in spherical shape and micron range (µm).

From the figure the particle size was concluded and found to be 44.1 to 286µm for optimized F4 formulation which are within micron-size particle**.** Drug-polymer compatibility studies were carried out by using FTIR spectral studies to establish the possible interaction in the formulations. The FTIR spectrum of lansoprazole, hydroxypropyl methyle cellulose, Ethyl Cellulose & their physical mixture is shown in Figure 4, 5, 6, 7 and 8. Our experimental results were assessed on the basis of physical data obtained for drugs and polymers as well as optimized microsphere formulations. The IR spectrum obtained of lansoprazole, ethyl cellulose, HPMC, physical mixture and optimized formulation F4 were identical and there was no change in the functional group absorption of any molecule present in the formulated product. The final conclusion was observed that, there is compatibility between the drug and excipients as shown in FTIR spectra.

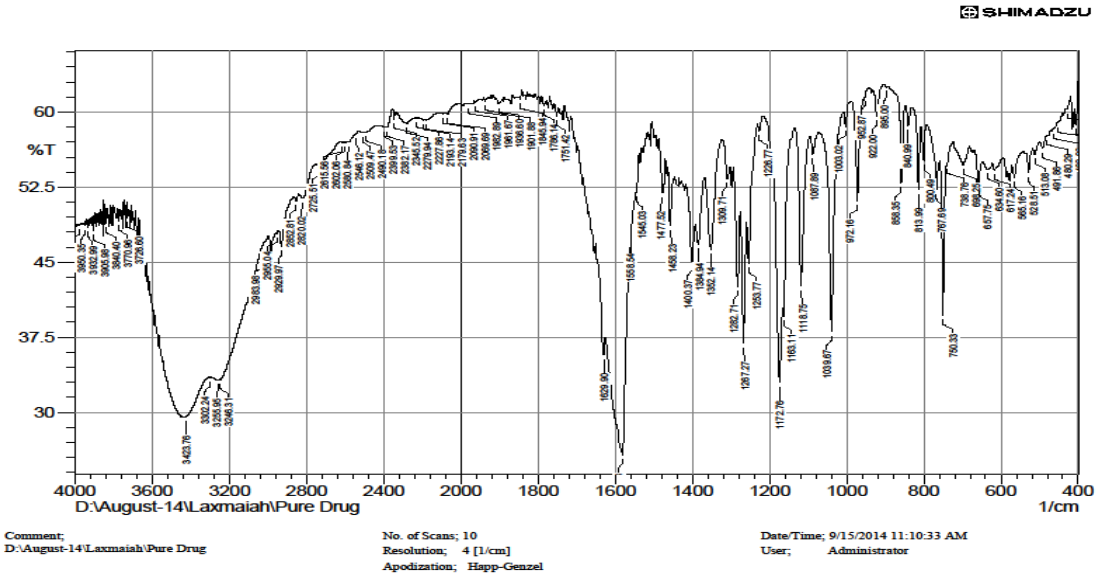

Figure 4: FTIR Spectra of pure drug (Lansoprazole)

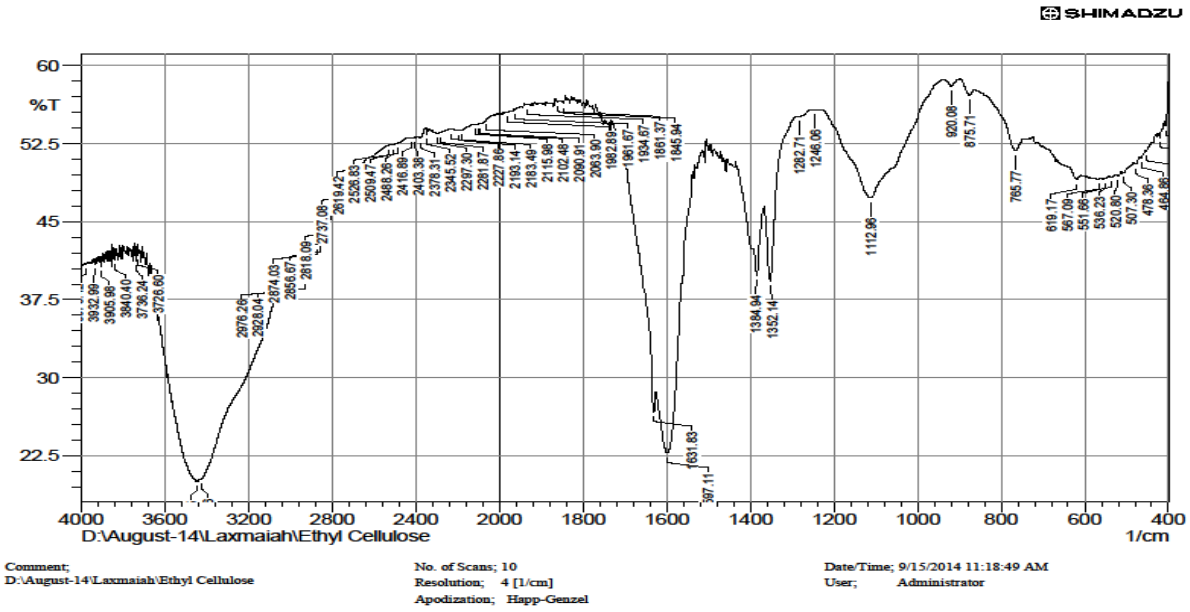

Figure 5: FTIR spectrum of polymer (Ethyl cellulose)

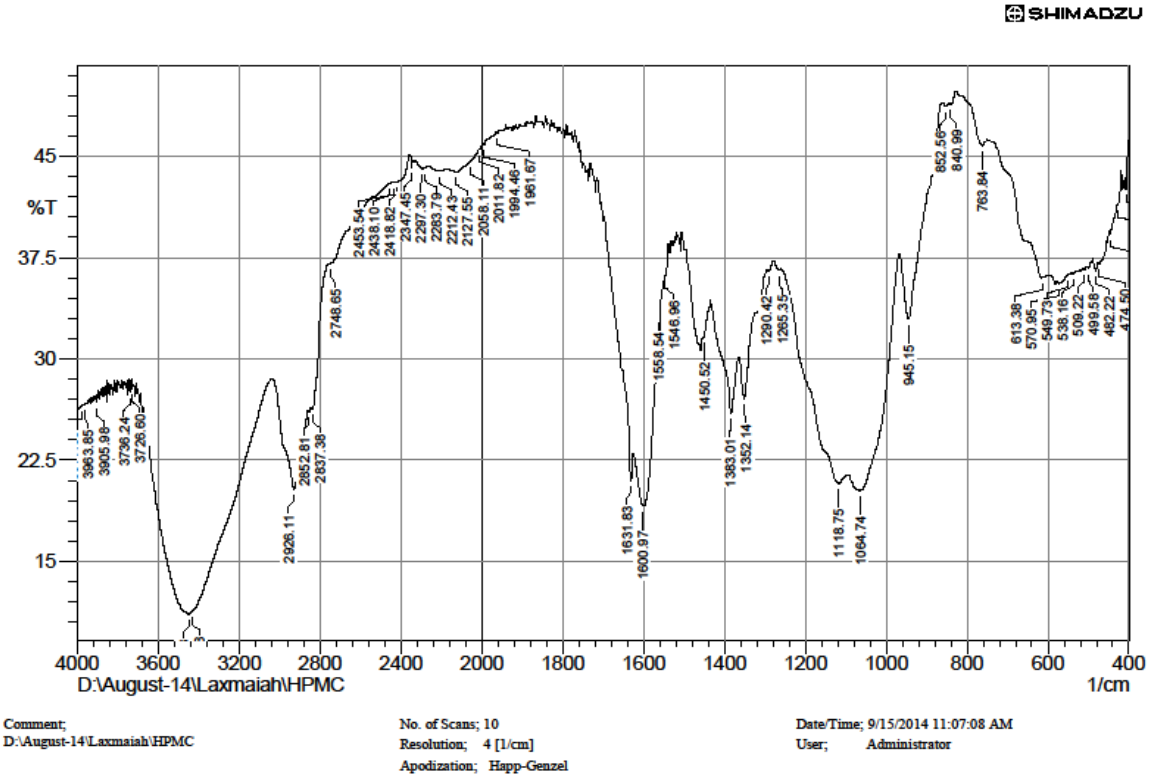

Figure 6: FTIR spectrum of polymer (HPMC).

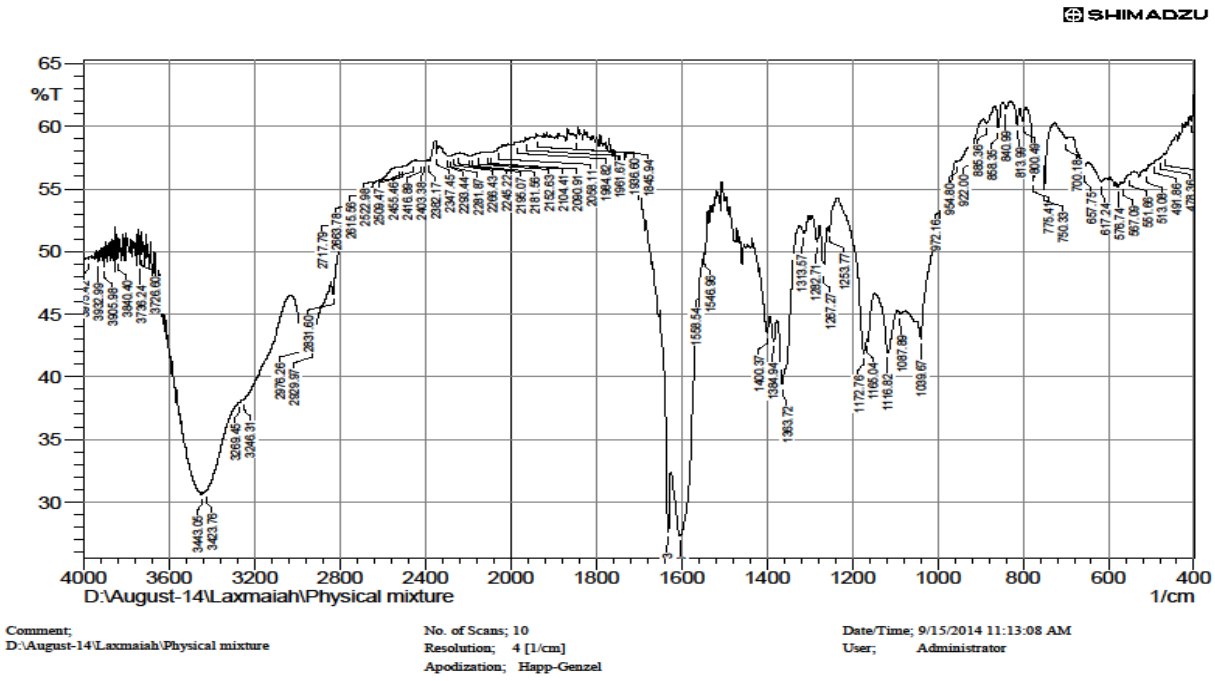

Figure 7: FTIR Spectra of Physical mixture.

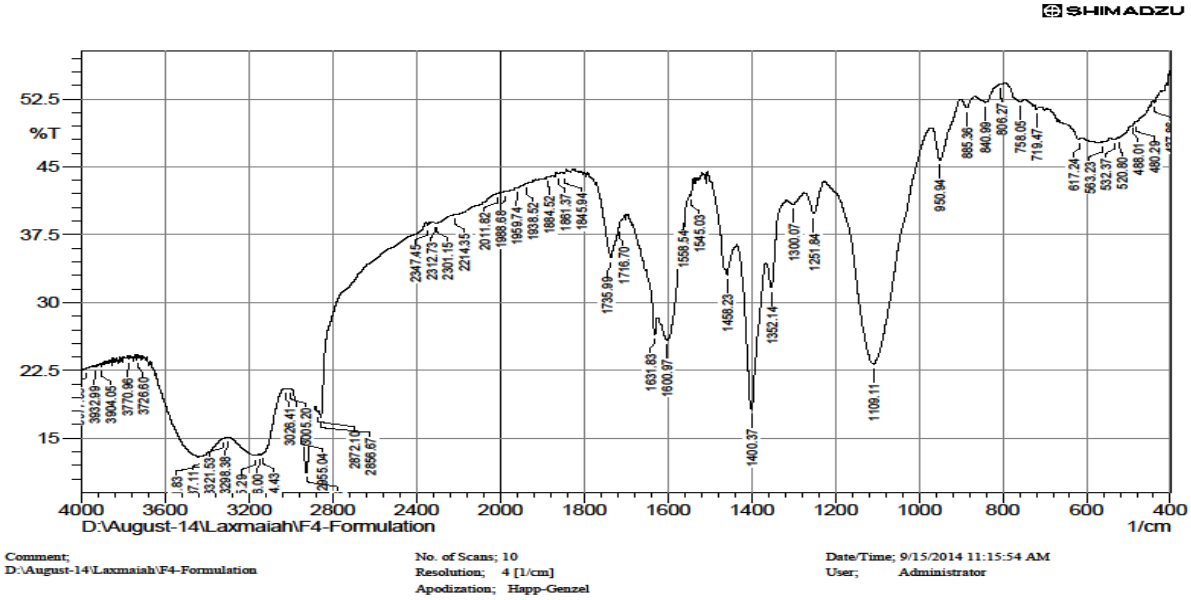

Figure 8: FTIR Spectra of optimized lansoprazole microsphere formulation F4

The DSC thermogram of lansoprazole exhibits an endothermic peak at 171^{o}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 a semi-crystalline 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. DSC studies were performed to understand the nature of the encapsulated drug in the matrix. The physical state of the 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 F5 as shown in figure 9 and 10.

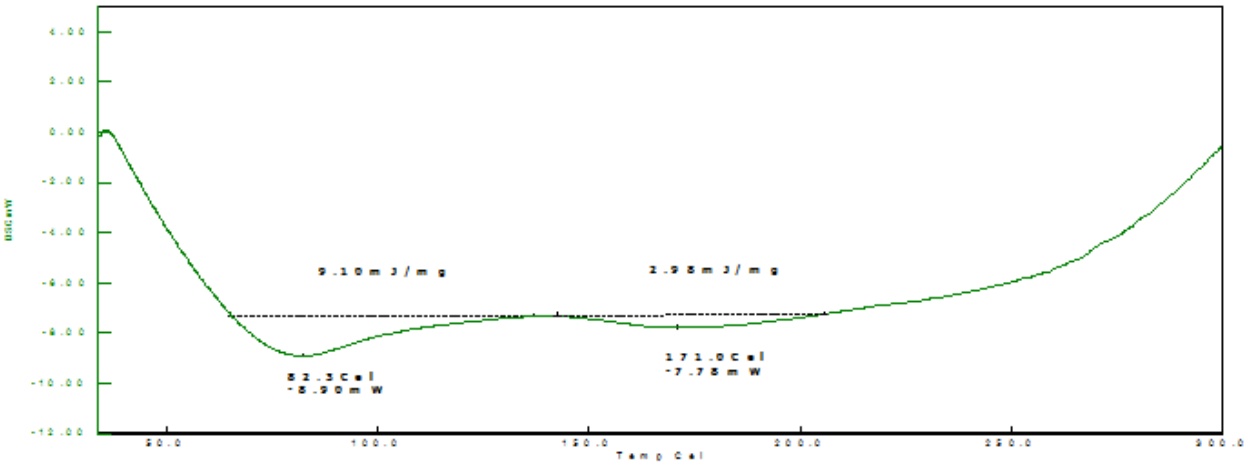

Figure 9: DSC thermogram of pure drug (Lansoprazole)

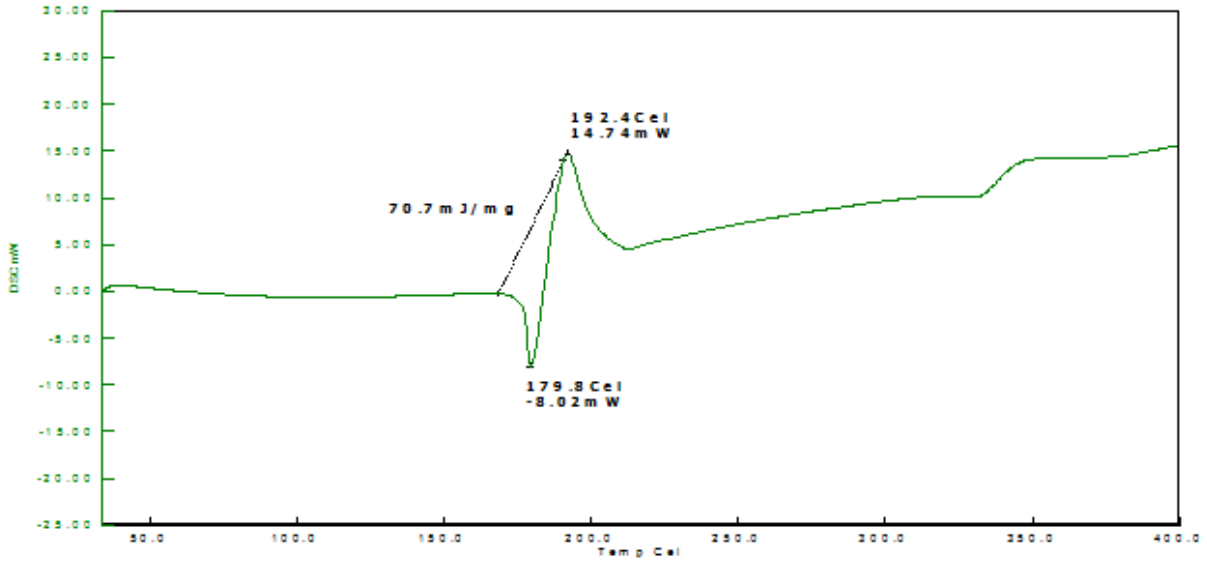

Figure 10: DSC Thermogram of optimized lansoprazole microsphere formulation-F4

The cumulative amount of drug release of F1 to F5 formulations at various time intervals was calculated and tabulated in Table no 4 and plotted a graph figure 11 and among all the batches shown better and sustained release property, it was observed that F4 formulation showed best and 98.65% drug release compared to others.

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

Time (hr)	F1	F2	F3	F4	F5
0.25	5.41	6.52	7.77	10.61	9.44
0.5	10.02	14.93	16.54	21.83	17.97
0.75	16.52	17.83	22.18	26.35	23.73
1	20.43	22.86	26.27	32.04	28.82
2	30.24	34.65	37.74	49.22	39.91
3	33.55	38.09	40.43	56.86	47.09
4	36.83	40.55	46.15	64.31	53.16
5	39.98	45.58	52.36	71.79	61.18
6	45.41	53.52	59.28	78.96	72.15
7	52.25	61.15	66.04	84.42	77.84
8	57.08	69.53	73.38	86.21	82.18
9	64.22	74.69	79.19	90.81	88.86
10	69.78	80.48	86.75	94.27	92.23
11	73.93	82.62	89.68	96.34	93.68
12	77.24	85.71	92.72	98.65	94.82

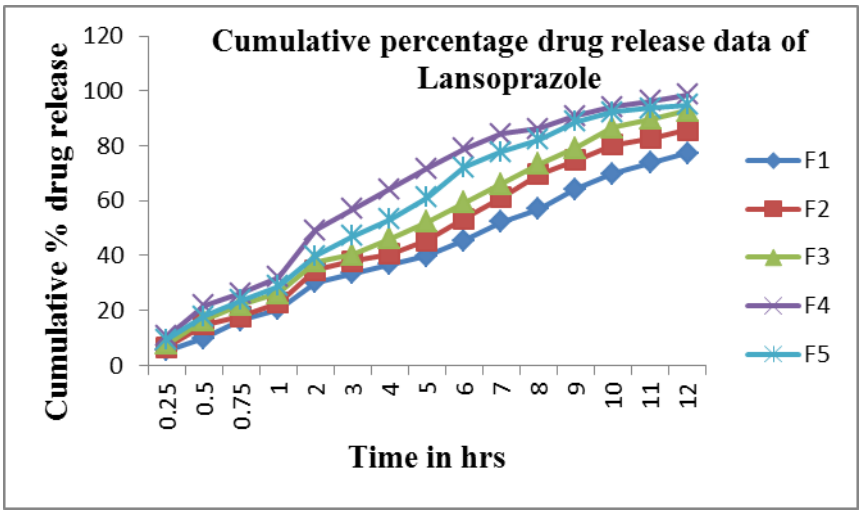

Figure 11: Comparison of cumulative percentage drug release of all the formulations

Among the different formulations prepared using different surfactant concentration and at different speed of rotation, it has been observed that the formulation prepared using 1.5% span-80 concentration at a speed of 1000 rpm resulted in maximum entrapment efficiency and highest cumulative percentage drug release Therefore, this formulation was considered as

the optimized formulation. 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 fiction or non fickian diffusion or zero order and '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 as in table no 5.

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

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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