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LANSOPRAZOLE MICROSPHERES FOR IMPROVEMENT IN DISSOLUTION RATE AND SUSTAINED RELEASE PROPERTY

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ABSTRACT

Different batches of lansoprazole loaded ethyl cellulose and HPMC K4M microspheres were prepared using W/O/O double emulsification-solvent diffusion method, to overcome the problem of low encapsulation efficiency of lansoprazole using span-80 as a stabilizer with constant stirring by a magnetic stirrer (Model-1 MLA, Remi motors, vasai, Mumbai, India) at 750- 1000 rpm for 5 hours and centrifuged by cooling centrifuge (Hittich, Zentrifugen, model-1195 a, Mikro 220R, Germany). The prepared microspheres were evaluated and characterized for particle size, percentage yield, drug entrapment efficiency, surface morphology by scanning electron microscopy (SEM), drug-excipient compatibility studies by Fourier transform infrared (FTIR), solid state properties (crystalline or amorphous) by differential scanning colorimetry (DSC), *In-vitro* drug release studies and release kinetics were determined. The optimized formulation F5 was characterized for particle size and surface morphology using optical microscopy method and scanning electron microscopy. Lansoprazole drug release rate was observed highest and improved dissolution rate, with the increase in concentration of HPMC K4M and decreased particle size of microspheres and showed sustained release property of the drug by ethyl cellulose in pH 1.2 up to 92-98.3% were releases within a period of 12 hrs. From the formulation F1 to F5, F5 showed a high dissolution rate of 98.3% and compared with the percentage drug release of pure drug. The data obtained from the dissolution profiles were compared to the different release kinetics models and the regression coefficients. The drug release profile follows zero order release and Higuchi model kinetics, it was found that the optimized formulation of lansoprazole microspheres showed sustained release property and drug release was found to be diffusion controlled mechanism, the n value of Korsmeyer-peppas equation indicated non-fickian type of diffusion.

KEYWORDS

Lansoprazole, Hydroxyl propyl methyl cellulose, Ethyl cellulose, Span-80, Sustained release, Microspheres, Double emulsification-solvent diffusion method, Zero order release and Higuchi model kinetics.

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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, inject able, and suppositories with their main discrepancy to maintain drug levels within the

therapeutic range[1]. However, these conventional dosage forms have some drawbacks. Multiple daily dosing is inconvenient to the patient and may lead to lost doses, created up doses and patient incompliance with the therapeutic program[2]. 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[3]. It should be emphasized that the plasma level of a drug should be maintained within the safe margin and effective range[4]. 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 method of up the therapeutic effectiveness of incorporated medicine by providing sustained, controlled delivery and or targeting the drug to desired web site[5]. The goal of any drug delivery system is to supply a therapeutic quantity of drug to the correct web site within the body to realize promptly so maintain the required drug concentration that's the drug delivery system ought to deliver drug at a rate detected by the wants of the body over a complete amount of treatment[6]. This can be attainable through administration of typical indefinite quantity kind in an exceedingly explicit dose and explicit frequency to supply a prompt release of drug, thus to realize in addition on maintain the concentration inside the therapeutically effective vary required by the treatment by recurrent administration on a daily basis controlled release drug delivery systems were developed[7]. Conventional oral drug administration does not usually provide rate-controlled release or target specificity, results in a significant fluctuation in a plasma drug level, leads to several undesirable toxic effects, and poor patient compliance[8]. In many cases, conventional drug delivery provides sharp increase in drug concentration often achieving toxic level and following a relatively short period at the therapeutic level of the drug concentration eventually drops off until re-administration[9]. In order to get most therapeutic effectualness, it becomes necessary to deliver associate agent to the target tissue within the optimum quantity for the specified amount of time, thereby inflicting no toxicity and marginal aspect effects controlled release by systems[10]. Desired drug release are often provided by rate-controlling membranes or by planted perishable polymers containing distributed medication. The newer techniques are capable of dominant the speed of drug release, sustaining the period of therapeutic activity and/or targeting the delivery of drug to a tissue. In distinction to drug delivery system, the word novel is looking one thing out essentially[11]. 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[12]. Novel systems to a greater extent supersede the above loop-holes of the conventional pharmaceutical dosage forms and the fascination provided by these new systems is the reattempting successful drugs by applying the technology of sustained release drug delivery[13]. 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 many measurable reasons for the attractiveness of those dose forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist[15]. 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 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[16]. There is a continuously growing interest in the pharmaceutical industry for sustained release drug delivery systems. Greater attention has been focused on development of sustained or controlled release drug delivery systems with concomitant recognition of the therapeutic advantages of controlled drug delivery[17]. 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, 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[18]. Sustained release technology has emerged as an important new field in the development of pharmaceutical dosage form. Introduction of controlled release has given a brand new breakthrough for novel drug delivery system (NDDS) within 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 exactly, sustained drug delivery may be outlined as "Sustained drug action at a planned rate by maintaining a comparatively constant, effective drug level within the body with concomitant reduction of undesirable effects"[19]. In controlled release indefinite quantity forms, a adequate quantity of drug is at first created accessible to the body to cause a desired medicine response. The remaining fraction is discharged sporadically and is needed to take care of the most initial medicine activity for a few fascinating amount of your time in way over time expected from usual single dose[20]. The onset of its pharmacologic action is the often delayed and the duration of its therapeutic effects is sustained and 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[21]. The sustained plasma drug levels provided by controlled release merchandise usually eliminate the necessity for night dosing, that advantages not solely the patients however the care given yet and therefore the basic explanation of a sustained drug delivery system is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such some way that its unity is maximized through reduction in facet effects and cure or management of condition within the shortest doable time by victimization smallest amount of drug, administered by the foremost doable route[22]. Potential blessings of controlled release drug delivery systems area unit avoid patient compliance issues, reduction in dosing frequency, avoidances of evening time dosing, use less total drug, minimize or eliminate native facet effects, minimize or eliminate general facet effects, acquire less potentiating or reduction in drug activity in chronic use, minimize drug accumulation with chronic dosing, improve potency in treatment, cure or criterion additional promptly, Improve management of condition, i.e., scale back fluctuation in drug level, improve bioavailability of some medication, effective utilization of drug and additionally related to disadvantage corresponding to self-made fabrication of controlled release merchandise is sometimes tough and involves thought of chemical science properties of drug, pharmacokinetic behaviour of drug, route of administration, unwellness state to be treated and most significantly placement of the drug in dose type total can give the specified temporal and abstraction delivery pattern for the drug[23]. 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 systems 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 micro particles and microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity, 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[24]. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs.

MATERIAL

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

METHODS

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 the Table No.1. A mixed solvent system (MSS) of dichloromethane and distilled water were 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 methodology for preparation of microspheres was rumored to beat the matter of low encapsulation potency of water soluble medicine ready by typical W/O/W double emulsion solvent diffusion methodology. The polymer was dissolved in a mixed solvent system (MSS) of dichloromethane and distilled water. 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 400-500 rpm to form w/o primary emulsion. Span 80 as stabilizer and surfactant was dissolved separately in 15 ml of liquid paraffin distilled water and to this prepared w/o primary emulsion was injected with syringe pump and stirred at 1000-1500 rpm on magnetic stirrer to get w/o/o double emulsion i.e multiple emulsion for 4-6 hours for the complete evaporation of solvent to get lansoprazole microspheres. 10 ml of n-hexane was added as the non-solvent to the processing medium to solidify the microspheres after 4 hr of the stirring[25].

Characterization and Evaluation of Lansoprazole microspheres

Particle size analysis

The mean particle size was determined using optical microscopy method. In this method, the sizes of 250 particles were determined and the average particle size was calculated. 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 determination of average particle size of lansoprazole microspheres with optical microscopy, average size of microspheres is reported[26].

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 this microspheres was determined to obtain the theoretical yield. Percentage yield was then determined using the formula[27].

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

Drug entrapment efficiency

The amount of drug entrapped was estimated by dissolving the 100 mg of microspheres in dichloromethane and water in 3:1 ratio under vigorous shaking for 1 hour, the resultant solution is centrifuged both layers were separated and the soluble lansoprazole in water was determined. The drug content in aqueous solution was analyzed spectrophotometrically by using UV-VIS spectrophotometer at 294 nm with further dilutions against appropriate blank. The amount of the drug entrapped in the microcapsules was calculated using the formula[28].

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

Scanning electron microscopy

In order to examine the surface morphology shape and size of the particle scanning electron microscopy was used. A concentrated aqueous suspension was spread over a slab and dried under vacuum. The sample was shadowed in a cathodic evaporator with gold layer 20 nm thick. Photographs were taken using a scanning electron

microscope (Hitachi, S-3700N, and Tokyo, Japan) operated at 20 kV. The smallest size microcapsules were used for determining surface morphology[29].

Drug-excipient compatibility studies

Sample regarding five mg was mixed completely with a hundred mg KBr IR powder and compacted beneath vacuum at a pressure of regarding twelve Psi for three minutes. The resultant disc was mounted in a very appropriate holder in IR photometer (Shimadzu 8400S, Tokyo, Japan) and therefore the spectrum was scanned over the frequency vary of 4000-400 cm-1 in a very scan time of twelve minutes[30-31].

***In-vitro* drug release**

Accurately weighed samples were added to 900 ml of 0.1 N HCL buffer media P^H 1.2 phosphate buffer at 37 ± 0.5°C and stirred at 100 rpm. An aliquot of 10ml was withdrawn at different time intervals at each 15 minutes for the first hour followed by 30 minutes upto 12 hours. The sample was then passed through a 5 µm membrane filter, filtered samples were assayed spectrophotometrically (Merck, Thermo scientific Evoluation 201) at 294 nm respectively for lansoprazole drug. The dissolution study was continued with using buffer (0.1 N HCL pH 1.2, 900ml) for next 12 hr. The dissolution of microspheres was compared with the dissolution of equivalent amount of the pure drug lansoprazole and identified the sustained release property. The cumulative % drug release was calculated using standard calibration curve[32].

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[33].

RESULTS AND DISCUSSION

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 lamda max 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 and it revealed that it is freely soluble in ethanol, chloroform, dichloromethane, 0.1 N HCL and methanol. It is practically insoluble in distilled water. The mean particle size of the developed formulations of microspheres was found to be in the range of 146 to 234 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 No.2. 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 90%. The Particle size and Percentage yield of all the formulations were shown in the Table No.2. 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 No.2. From the encapsulation potency values it absolutely was ascertained that increase within the speed of rotation from 750 rev to a thousand rev at constant wetting agent concentration, resulted in higher encapsulation potency. This could ensue to the formation of larger emulsion droplets at low speed making certain enough drug diffusion out of the microspheres before they harden. From the encapsulation potency values it absolutely was ascertained that by keeping the speed of rotation constant, there was a big decrease in encapsulation potency of the medicine with increase in

concentration of wetting agent 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. Surface morphology of the microspheres was examined by scanning electron microscopy. The microspheres of optimized formulation were examined. The scanning electron microscopy 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. Scanning electron microscopy pictures are shown in figure 1 from figure it was concluded that the average particle size was found to be in a 44.8 to 286 micron range (µm). 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, hydroxypropyle methyle cellulose, Ethyl Cellulose and their physical mixture is shown in Figures 5-8. In experimental results were assessed on the basis of physical data obtained for drugs and polymers as well as formulations. The FTIR spectra of microspheres of lansoprazole using ethyle cellulose and HPMC is as follows. The IR spectrum obtained of lansoprazole, ethyle cellulose and HPMC (F4) were identical and there was no change in the functional group absorption of any molecule present in formulated product. The final conclusion was absorved that, there is compatability between the drug and excipients in their use. 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 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. The cumulative present drug release of F1 to F5 formulations at various time intervals was calculated and tabulated in Table No.3 and the cumulative present drug release in all formulations was plotted against time in Figure 2-3 and among all the batches slow and constant release was observed with F4 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, 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 wide accustomed make sure whether or not the discharge 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 as shown in Table No.4.

Table No.1: 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 (mg)	500	500	500	500	500
3	Ethyl cellulose (mg)	300	300	300	200	200
4	Span-80 (%)	0.5	1	2	3	4
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	1000	1000	750

Table No.2: Mean particle size and Percentage yield of Lansoprazole microspheres

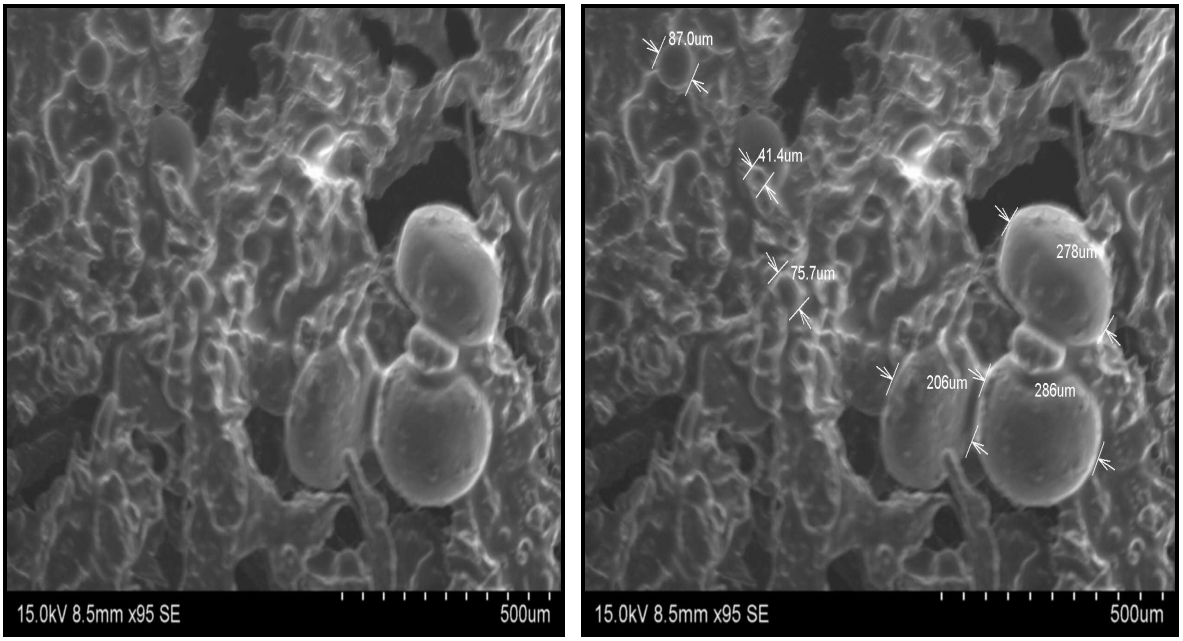
S.No	Formulation code	Particle size (µm)	Percentage yield	Entrapment Efficiency
1	F1	350	72.45	72.23
2	F2	320	74.56	74.93
3	F3	280	78.07	79.62
4	F4	220	89.92	88.64
5	F5	250	82.27	81.37

Table No.3: *In-vitro* cumulative percentage drug release data of Lansoprazole

S.No	Time (hr)	F1	F2	F3	F4	F5
1	0.25	5.41	6.52	7.77	10.61	9.44
2	0.5	10.02	14.93	16.54	21.83	17.97
3	0.75	16.52	17.83	22.18	26.35	23.73
4	1	20.43	22.86	26.27	32.04	28.82
5	2	30.24	34.65	37.74	49.22	39.91
6	3	33.55	38.09	40.43	56.86	47.09
7	4	36.83	40.55	46.15	64.31	53.16
8	5	39.98	45.58	52.36	71.79	61.18
9	6	45.41	53.52	59.28	78.96	72.15
10	7	52.25	61.15	66.04	84.42	77.84
11	8	57.08	69.53	73.38	86.21	82.18
12	9	64.22	74.69	79.19	90.81	88.86
13	10	69.78	80.48	86.75	94.27	92.23
14	11	73.93	82.62	89.68	96.34	93.68
15	12	77.24	85.71	92.72	98.65	94.82

Table No.4: Release kinetics data of Lansoprazole from optimized formulation F4

S.No	Time (h)	Cumulative (%) Release Q	Root (T)	Log (t)	Log (%) Release	Log (%) Remain
1	0	0	0	-	-	2.000
2	0.25	5.45	0.500	-0.602	0.736	1.976
3	0.5	10.09	0.707	-0.301	1.004	1.954
4	0.75	16.53	0.866	-0.125	1.218	1.922
5	1	20.46	1.000	0.000	1.311	1.901
6	2	30.28	1.414	0.301	1.481	1.843
7	3	33.57	1.732	0.477	1.526	1.822
8	4	36.87	2.000	0.602	1.567	1.800
9	5	39.95	2.236	0.699	1.602	1.779
10	6	45.42	2.449	0.778	1.657	1.737
11	7	52.2	2.646	0.845	1.718	1.679
12	8	57.04	2.828	0.903	1.756	1.633
13	9	64.21	3.000	0.954	1.808	1.554
14	10	69.75	3.162	1.000	1.844	1.481
15	11	73.97	3.317	1.041	1.869	1.415
16	12	77.02	3.464	1.079	1.887	1.361



Particles in spherical shape Particles in micron range (µm)

Figure No.1: SEM pictogram of microspheres of optimized formulation (F5)

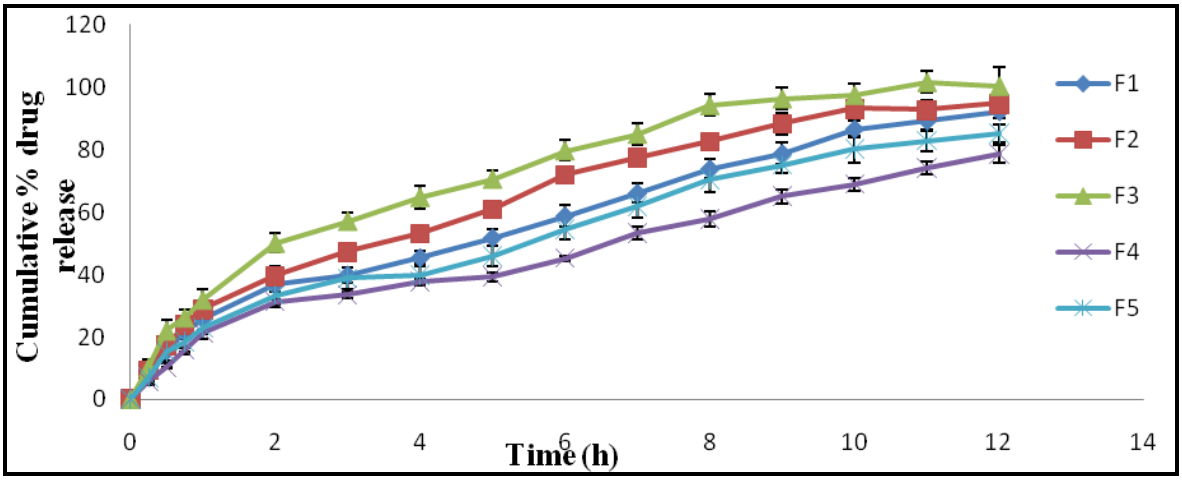


Figure No.2: Comparison of cumulative percentage drug release (lansoprazole) of all the formulations

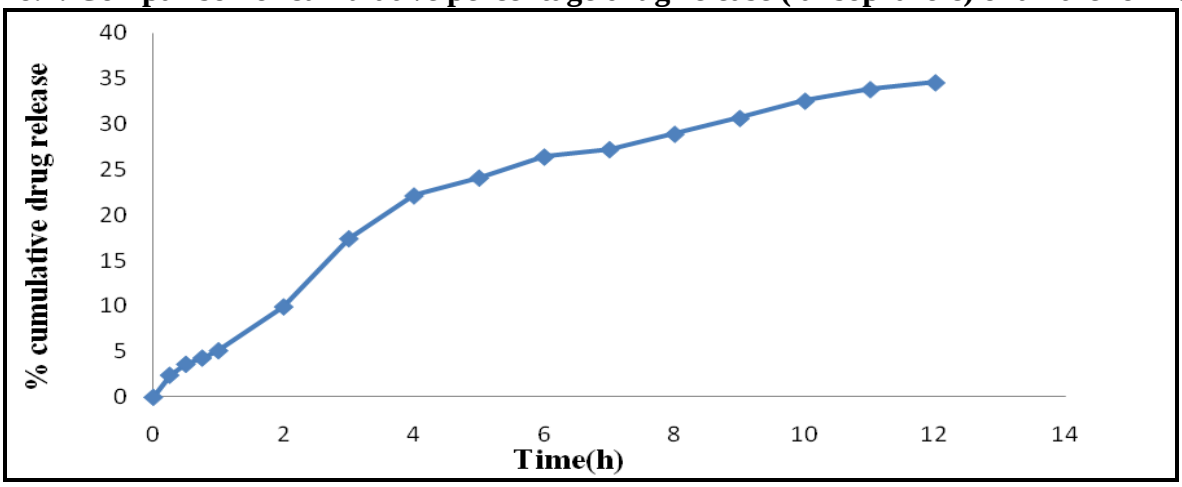


Figure No.3: *In-vitro* release profile of optimized formulation F4

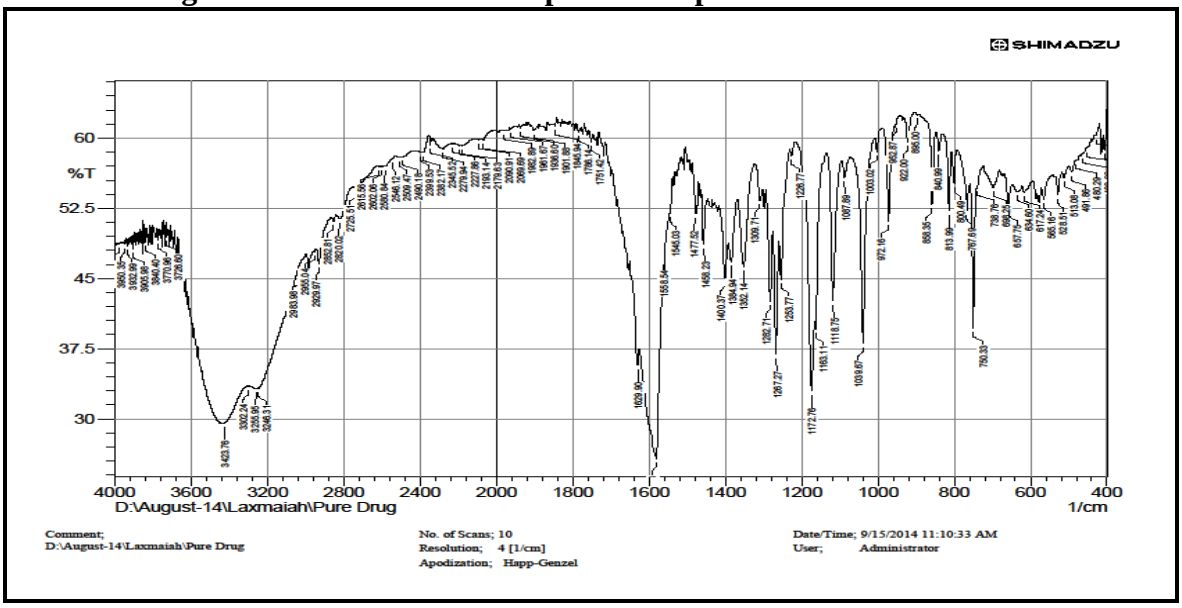


Figure No.4: FTIR Spectra of pure drug (Lansoprazole)

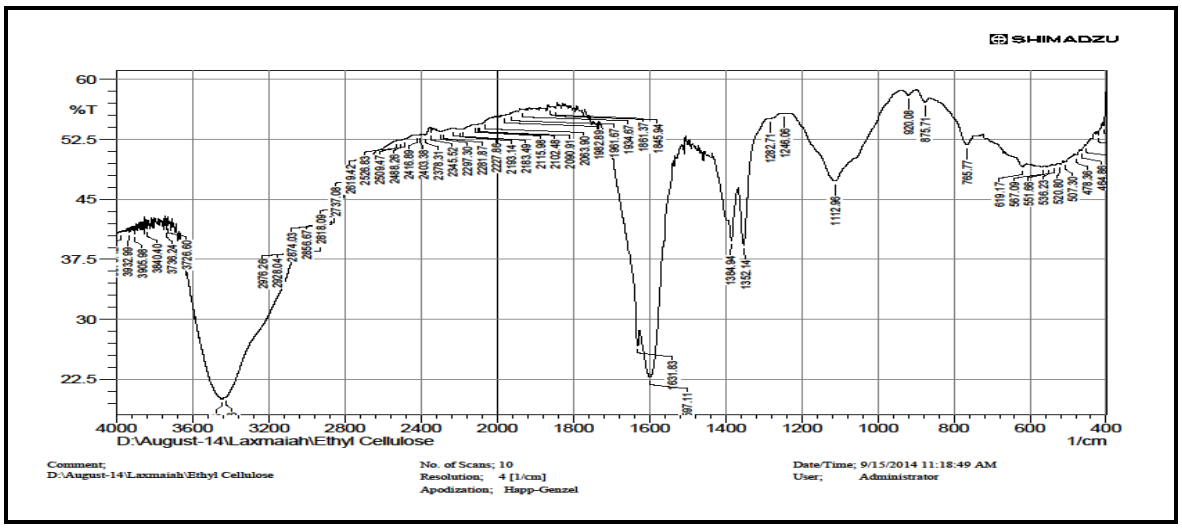


Figure No.5: FTIR spectrum of polymer (Ethyl cellulose)

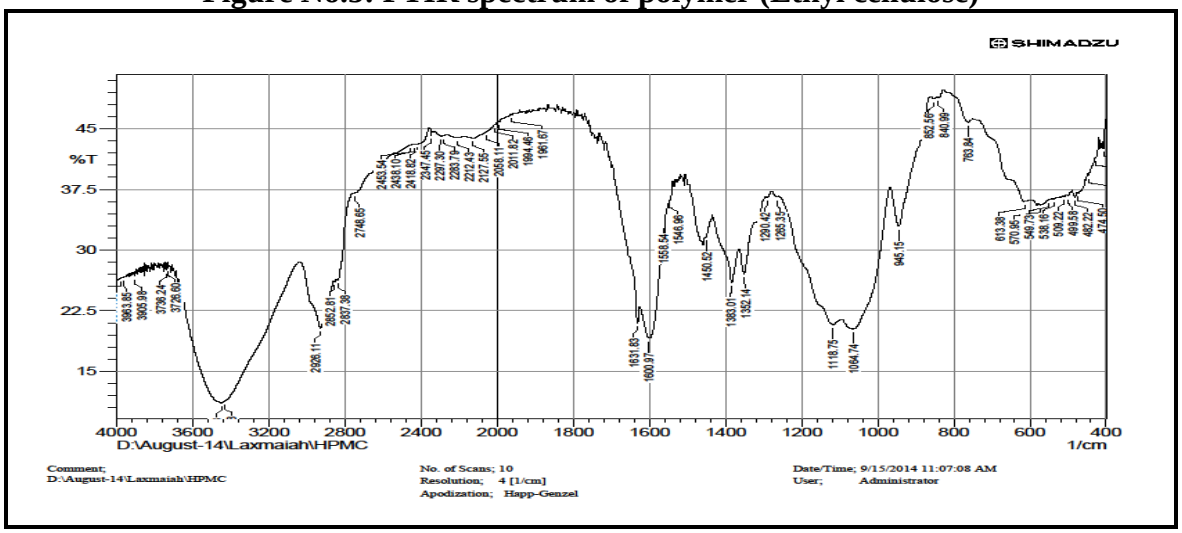


Figure No.6: FTIR Spectrum of polymer (HPMC)

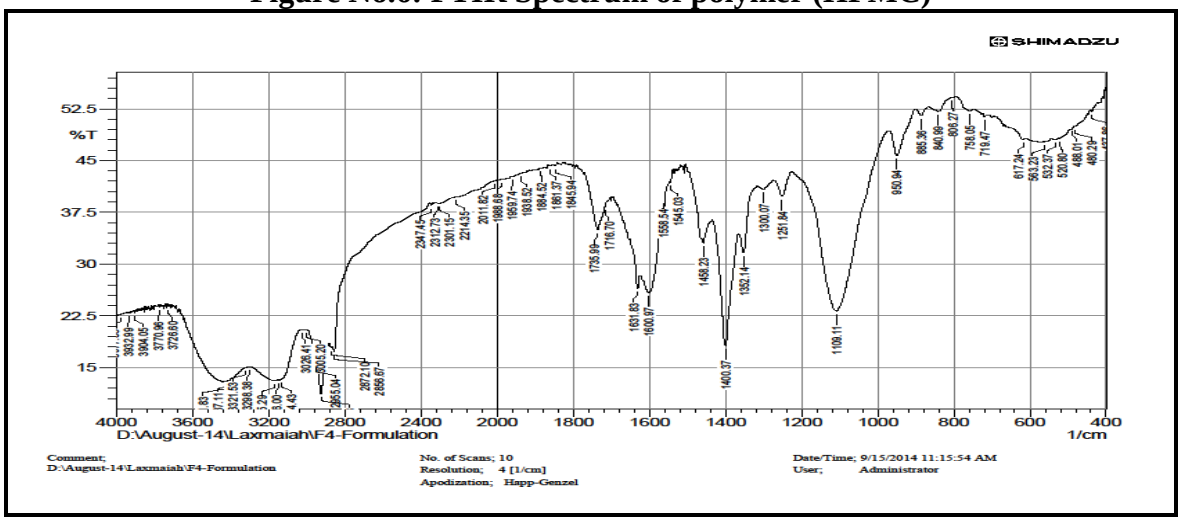


Figure No.7: FTIR Spectra of optimized formulation(F4)

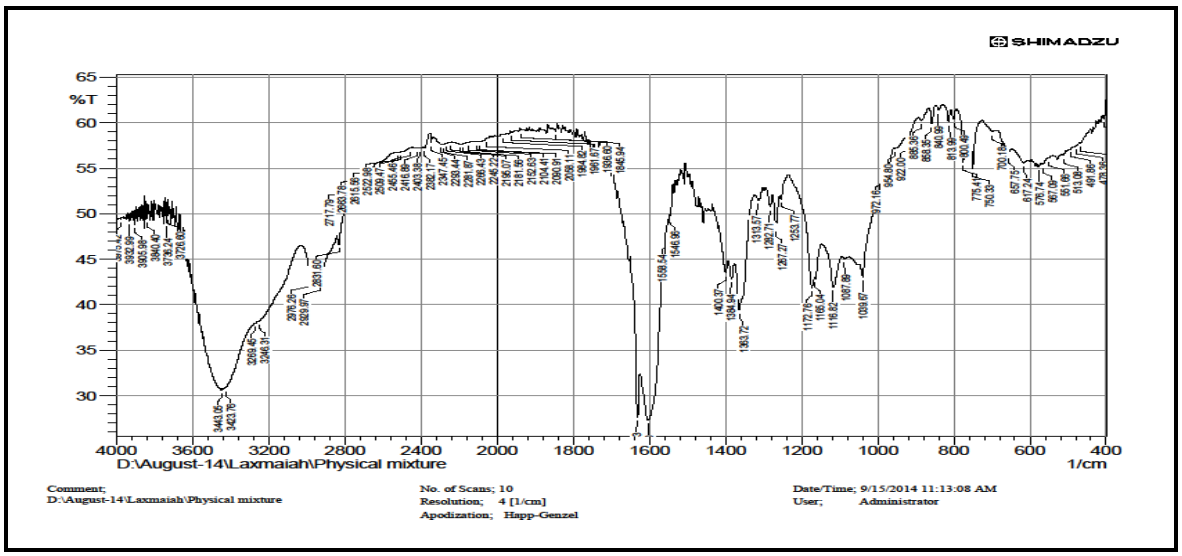


Figure No.8: FTIR Spectra of physical mixture

CONCLUSION

From the all above studies 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 prople methyle cellulose polymer.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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