ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

A COMPARATIVE STUDY OF NATURAL AND SYNTHETIC POLYMERS ON LANSOPRAZOLE NANOSPONGES

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ARTICLE INFO

Key words:
Lansoprazole, Eudragit, Guar gum, first order, Nanosponges, Fickian release

Access this article online
Website: https://www.jgtps.com
Quick Response Code:

ABSTRACT

Lansoprazole is proton pump inhibitor which extensively degraded in acidic pH conditions. Lansoprazole loaded nanosponges were prepared by Quassi Emulsion solvent diffusion method using Eudragit RS 100 and Guar gum and dichloromethane as a solvent. The prepared nanosponges were evaluated for percentage yield, entrapment efficiency, particle size, , scanning electron microscopy and *invitro* drug release. SEM studies confirmed their porous structure with number of nanochannels. The FTIR spectra showed stable character of lansoprazole in mixture of polymers and revealed the absence of drug polymer interactions. The average particle size of lansoprazole nanoparticles was found to be in the range of 115. 7 nm and 121.9 nm .The negative zeta potential values were attained to ensure a good stability of nanosponges. The drug release from nanosponges was found to extended upto 12 h. The prepared nanosponges were formulated in enteric coated tablets and evaluated for weight variation, hardness,friability and dissolution studies. *In-vitro* release of drug from enteric coated tablet follows zero order and showed controlled release behaviour for a period of 12 h. The data obtained in this study suggests that nanosponges of lansoprazole are promising for controlled drug delivery, which can reduce dosing frequency.

INTRODUCTION

The drug delivery technology has certainly a new interest for drugs by providing them new life through their therapeutic targets. Nowadays, targeting drug delivery is the major problem which is being faced by the researchers. Target oriented drug administration with improvements in therapeutic efficacyreduction in side effects and optimized dosing regimen, shall be the leading trends in the area of therapeutics. Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at pre identified target in therapeutic Concentration, while restricting its access to non-target normal cellular linings and thus minimizing toxic effects and maximizing therapeutic index of the drug [(1).] Nanosponges have emerged as one of the most promising fields of science because of their perceived application in controlled drug delivery. Nanosponge delivery system can precisely control the release rates or target drugs to a specific body site and have an enormous impact on the health care system. This nanosized delivery system has definite advantages for the purpose of drug delivery because of its high stability, high

carrier capacity and feasibility of incorporation of both hydrophilic and hydrophobic substances. The application of nanosponges for targeted and localized delivery of therapeutic agents is the driving force for the research in this area [2]. The sponge acts as a three-dimensional network or scaffold. The backbone is long-length polyester. It is mixed in solution with cross-linkers to form the polymer. The net effect is to form spherically shaped particles filled with cavities where drug molecules can be stored. The polyester is biodegradable, so it breaks down gradually in the body. As it breaks down,it releases its drug payload in a predictable fashion. The nanosponges can be synthesized to be specific size and to release drugs over time by varying proportions of crosslinkerto polymer. The main limitation of nanosponges is their ability to include only small molecules [3]. Nanosponges are solid in nature and are small particles with porous surface can be formulated as oral, parenteral, topical or inhalational dosage forms. For oral administration, these may be dispersed in a matrix of excipients, diluents, lubricants and anti caking agents which is suitable for the preparation of tablets or capsules and the major benefits of these capsulesor tablets are reduction of total dose, retention of dosage form, reduction in toxicity and improving patient compliance by prolonged release [3,4]. For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions [4] . For topical administration, they can be effectively incorporated into topical hydrogel [5].Lansoprazole is a proton pump inhibitor commonly used in thetreatment of gastric ulcer, gastro oesophageal reflux disease (GERD), duodenal ulcer, ulcers associated with usage of Nonsteroidal anti-inflammatory drug (NSAID) and long term management Zollinger-Ellison syndrome [6]. Lansoprazole is primarily metabolized by liver. Hence it is a need to reduce the dose to the hepatic failure patients. But reduction of dose in conventional dosage systems may not show sufficient pharmacological effect [7] . Regular usage of lansoprazole causes various adverse effects like abdominal pain, diarrhoea, skin rashes, thrombocytopenia, impotence etc. So, controlled delivery of lansoprazole at optimal concentration may be required [8]. Oral route is preferable than other routes with respect to safety, comfort and reliability. Hence controlled delivery of lansoprazole by oral route is ideal. Controlled release of lansoprazole will reduce the frequency of dosing and dose size and may increase patient convenience [7,8] . More over lansoprazole is highly acid labile and represents many formulation challenges to protect it from acidic environment of the stomach [9] . So the aim of the present investigation was to formulate enteric coated tablets of lansoprazole nanosponges to protect it from acidic environment and deliver at controlled rate to its absorptive site so that its oral bioavailability can be enhanced [8,9] .

MATERIAL AND METHOD

Lansoprazole was gift sample from Dr. Reddy's Labs limited, Hyderabad. Eudragit Rs 100, Polyvinyl Alcohol and Guar gum were purchased from Inception Source Pvt Ld, Hyderabad. All other ingredients used were analytical grade.

Methodology

Preparation of lansoprazole nanosponges [5,10]

Lansoprazole nanosponges were prepared by using of synthetic and natural polymer like Eudragit Rs 100 and guar gum, polyvinyl alcohol by quassi emulsion solvent diffusion technique. The disperse phase consisting of 100 mg lansoprazole and specified quantity of eudragit and guar gum (Table 1) dissolved in 30 mL of dichloromethane was slowly added to a definite amount of PVA in 100 mL of aqueous continuous phase. The mixture was stirred at 1000 rpm on a magnetic stirrer for two hours. The formed lansoprazole nanosponges were collected by vacuum filtration and dried in an oven at 40°C for 24 h.

Percentage yield

The lansoprazole nanosponges obtained after drying was weighed. Percentage yield value was calculated as follows [11]

% yield = Weight of nanosponges×100/Total solids weight

Entrapment efficiency [11]

UV spectrophotometric method was used to estimate entrapment efficiency of lansoprazole nanosponges. A calibration curve was plotted for lansoprazole in methanolic HCl in the range of 2-10 µg/mL (Beer's Lambert's range) at 284nm. A good linear relationship was observed between the concentration of lansoprazole and its absorbance . 100 mg of lansoprazole nanosponges of were selected, powdered in a mortar and placed in 100 mL of methanolic HCl. Lansoprazole was extracted by centrifuging at 1000 rpm for 30 min, filtered and analyzed concentration from calibration curve data after necessary dilution. Percentage entrapment was calculated as follows:

% Entrapment efficiency= Actual drug content in the nanosponge×100/Theoritical drug content

Particle size measurement [5,11]

The average particle size of lansoprazole nanosponges were determined by photon correlation spectroscopy (PCS) using a Nano ZS-90 (Malvern Instruments limited, UK) at a fixed

angle at 25°. Sample was diluted 10 times with distilled water and then it was analyzed for particle size.

Zeta potential [5,11] The zeta potential was measured for the determination of the movement velocity of the particles in an electric field and the particle charge. In the present work, the nanosponges was diluted 10 times with distilled water and analyzed by Zetasizer using Laser Doppler Micro electrophoresis (Zetasizer nano ZS, Malvern instruments Ltd., UK).

Particle shape and morphology [12]

The shape and morphology of nanosponges was examined using Scanning Electron Microscopy (LEO 440I). Sample was deposited on a glass slide, and was kept under vacuum. The samples were coated with a thin gold/palladium layer using a sputter coater unit. The scanning electron microscope was operated at an acceleration voltage of 15 kV.

Fourier transform infrared spectroscopy studies [12] The FTIR spectral measurements were taken at ambient temperature using a Perkin Elmer Model 1600 (USA). Samples were dispersed in KBr powder and the pellets were made

by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

Porosity

Bulk volume was obtained by pouring the nanosponges in to a grated cylinder and is noted. It is then under gone for 100 tappings and the volume is noted as true volume.

% Porosity= (Bulk Volume-True Volume/Bulk volume)×100

Preparation of lansoprazole tablets

Lansoprazole tablets were prepared by direct compression method. The prescribed quantity of lansoprazole nanosponges, polymers and excipients (Table 2) were mixed homogeneously

and the mixture was then compressed into tablets (100 mg) using an 8 mm, biconcave punches on a 'Rimek mini press 16 station rotary compression machine

Evaluation of lansoprazole tablets

Weight variation

The weight variation test was performed according to specifications given in the Indian Pharmacopoeia on 20 tablets. The maximum acceptable limit is ±7.5% deviation of an individual weight from average weight.

Thickness The thickness of 20 randomly selected tablets from each formulation was determined in mm using a vernier calliper (Pico India).

Hardness Six tablets were randomly selected from each formulation and measured hardness in kg/cm^2 using Monsanto type hardness tester.

Friability Tablet friability was measured using the Roche Friabilator. Randomly selected twenty pre-weighed tablets were

placed in the apparatus and operated for 100 revolutions and then the
tablets were reweighed. The friability was determined as the mass loss in percent according to following to Equation
F= (WA-WB/WA)×100
Where F: Friability, WA: Initial weight (gm), WB: Final weight (gm); the acceptable limits of the weight loss should not be more than 1%.

Assay

Ten tablets were randomly selected from each formulation and crushed to a fine powder in mortar with pestle. Weigh accurately equivalent to 10 mg of lansoprazole from fine powder then transfer in 100 mL volumetric flask, 100 mL of methanolic HCL was added to dissolve and sonicated for 20 minutes. Lansoprazole was extracted by centrifuging at 1000 rpm for 30 min. The samples were filtered, diluted and analyzed UV spectrophotometrically at 284 nm.

Enteric coating of lansoprazole tablets [14]

Enteric coating of optimized lansoprazole tablets was done to protect the drug in acidic environment. Coating solution was prepared by dissolving 5% w/v of cellulose acetate phthalate and 1.5% w/v of propylene glycol 400 in acetone. Coating solution was applied by dip coating technique using pipette (10 mL) attached to vacuum pump. Vacuum pump produced suction force that allowed tablet to adhere to pipette mouth. This adhered tablet was then partially dipped in coating solution to allow coat formation at one side of tablet. The
other side was coated when other side dried.

***In vitro* release studies [15,16]**

A calibration curve was plotted for lansoprazole in methanol in the range of 2-10 µg/mL (Beer's Lambert's range) at 284 nm respectively. A good linear relationship was observed between the concentration of lansoprazole and its absorbance in methanol
The dissolution test for optimized lansoprazole nanosponges and coated tablets was carried out according to USP 27 NF 22 by adapting the method B in pH 1.2 and pH 6.8 buffers.

Dissolution test was carried out using USP apparatus 2 (Model Labindia) at 100 rpm. To reproduce digestive physiological phases, dissolution medium (900 mL) with different pH environments at 37±0.5°C was used. Six tablets were introduced into the apparatus and the apparatus was run for 2 h in pH 1.2 buffer and 5 mL sample was withdrawn at various time intervals and the same volume of fresh dissolution medium was replaced to maintain sink condition. The samples were filtered, diluted and analyzed UV spectrophotometrically (Shimadzu, Japan) at 306 nm. After 2 h the dissolution medium with the pH of 1.2 was replaced with 6.8 buffer and continued for up to 24 h. Five millilitre samples were withdrawn at regular intervals and the same volume of fresh dissolution medium was replaced to maintain sink condition. The samples were filtered, diluted and analyzed UV spectrophotometrically at 284 nm. Dissolution studies were performed and the mean cumulative percentage of lansoprazole was calculated and plotted against time.

Evaluation of release kinetics [17-20]

To investigate the mechanism of lansoprazole release from nanosponges and enteric coated tablets, the release data was analyzed for zero order, first order, Higuchi model and Korsmeyer-Peppas model. The data was presented in the following graphical representation and regression analysis was performed. Mt versus t (zero order) Log cumulative % of drug remained versus t (first order) Mt versus square root of t (Higuchi) Log Mt versus log t (Korsmeyer-Peppas) Mt is the cumulative % of drug released/permeated at time t. Korsmeyer et al [20] derived a simple relationship which described drug release from a polymeric system. $Mt/M\infty = ktn$
Where, $Mt/M\infty$ is the fraction of drug released at time t, k is the rate constant and n is the release exponent. Release curve where $Mt/M\infty < 0.6$ was used to determine the exponent

'n' value. The n value was used to characterize different release mechanisms. For example, n = 0.45 for Case I or Fickian diffusion, 0.45 < n < 0.89 for anomalous behaviour or non-Fickian transport, n=0.89 for Case II transport, and n > 0.89 for Super Case II transport. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. The rate constant 'k', coefficients of correlation (r^2) and 'n' of each model were calculated by linear regression analysis.

RESULTS AND DISCUSSION:

Percentage yield value, drug entrapment efficiency, particle size and zeta potential of lansoprazole nanosponges were shown in Table 3. Percentage yield value of nanosponges was found to be best for F2. The entrapment efficiency of nanosponges was found to be best for formulation F2. The size of the nanosponges prepared by using eudargit RS 100 was found to be to 121.9 nm prepared by using Guar gum was found to be to 115.7 nm (Table 3 and Figure 1&3). The zeta potential of the nanosponges was found to be in the range -23.4 mV to -25.1mV (Table 3 and Figure 2&4). The negative sign indicates the stability of nanosponges. The SEM images of the lansoprazole nanosponges were shown in Figure 8 &9. SEM analysis revealed that Nanosized spherical particles with numerous pores on surface (lansoprazole nanosponges). The pores are tunneled inwards which may be due to diffusion of dichloromethane from the surface of the nanosponges [(5).] Surace of nanosponges prepared by using guar gum is smooth compared to Eudragit RS 100.

The FTIR spectra of pure lansoprazole and lansoprazole with polymers are shown in Figure 5, 6 &7. FTIR spectra of pure lansoprazole demonstrated the characteristic absorption peaks for O-H stretching , N-O stretching and C=C stretching . Lansoprazole nanosponges also showed almost similar absorption peaks indicates good compatibility with polymers [(12).] Lansoprazole nanosponge showed a similar endothermic peak at 180.8°C which confirms no polymer drug interaction [(12).]

Porosity study is performed to check the extent of nanochannels and nanocavities formed. Porosity of the nanosponges can also be assessed by the use of density of nanosponges. Owing to their porous nature, nanosponges prepared by using guar gum exhibit higher porosity compared to the Eudragit used to fabricate the system. Porosity of the nanosponges was found to be 60% and the bulk volume of the nanosponges was found to be 80 mL and true volume was found to be 32 mL. The concentration of dichloromethane was found to be 298 ppm. According to Guidelines for residual solvents Q3C (ICH), dichloromethane is class II solvent (solvents to be limited) thus the limits of 600 ppm is acceptable without justification. Lansoprazole tablets were evaluated for weight variation, thickness, hardness, friability and assay. The results of the evaluation are given in Table 4. *In vitro* release studies of lansoprazole nanosponges were carried out in triplicate. After 12 h the release was found to be 83.83 For F1 and 90.78 for F2 formulations (Figure 10).To study the release kinetics of optimized formulation, obtained *in vitro* release data was fitted in various kinetic models such as zero order, first order, Higuchi model and Korsmeyer-Peppas model. The *in vitro* release profile of F1 & F2 could be best expressed by first order kinetic model, as the plot showed highest linearity (r^2= 0.980 & 0.956). The release exponent (n) value 0.708 &0.957 (Table 5) indicates that the release from nanosponges followed non fickian release i.e., by swelling and erosion which is always associated with diffusion and dissolution mechanism. Preapred nanosponges were formulated in to tablet by direct compression and coated by dipping the tablets in coating solution (5%

w/v cellulose acetate phthalate and 1.5% w/v polyethylene glycol 400 in acetone). After 10 min the tablets were removed and air dried. The enteric coated tablets were subjected to weight variation, hardness, friability, thickness and *in vitro* dissolution studies. The average weight of all tablets was found to be 101.27±2.78. The deviation of all tablets was found to be within the limit. So, all formulations passed the test for uniformity of weight as per official requirements. Thickness of the tablets was found to be 3.18 &3.23 mm. Hardness of tablets was found to be 5.65 & 0. 5.66 kg/cm^2. Percentage friability of tablets was found to be 0.752 & 0.886 i.e., less than 1%, indicating that the friability was within the prescribed limits. All the tablets showed acceptable properties and complied with the I.P specifications for weight variation, hardness, and friability. Lansoprazole enteric coated tablet showed no release of drug in acidic medium which is desirable and showed 89.15% for nanosponges prepared using Eudragit RS100 and 98.8% for nanopsonges prepared using Guar gum at the end of 12 h (Figure 10). The *in vitro* release profile of lansoprazole enteric coated tablets could be best expressed by first order kinetic model, as the plot showed highest linearity (r^2=0.976& 0.974). The release exponent (n) value 0.879 &0.881 (Table 5) indicates that the release from coated tablets followed non fickian release [(20).] The drug release from enteric coated tablets prepared by using natural polymer (guar gum) is high ie, 98.8% compared to nanosponges prepared by using synthetic polymer (Eudragit RS 100) ie, 89.15%

CONCLUSION

The nanosponges containing lansoprazole exhibited most of the ideal characters required for an oral controlled release dosage forms. The nanosponges of lower particle size 115.7 nm using Guar gum and 121.9 nm using Eudragit LS 100 aided with negatively charged surface charge has been achieved. The release profile indicated continuous controlled release up to 12 h. Lansoprazole enteric coated tablet showed less release of drug in acidic medium which is desirable and controlled release behavior for a period of 12 h. The nanopsonges prepared using Guar gum has shown high drug release ie,98.8% as compared to Eudragit RS 100 89.15%.The nanosponge systems have been found to have good potential for prolonged drug release and therefore can be beneficial such as dose reduction, reduced frequency of administration and avoiding related systemic side effects. Hence it can be concluded that the developed oral enteric coated tablet – nanosponges of lansoprazole is considered to be ideal and effective in the management of ulcer and related conditions. The nanosponge systems have been found to have good potential for prolonged drug release and therefore can be beneficial such as dose reduction, reduced frequency of administration and avoiding related systemic side effects. Hence it can be concluded that the developed oral enteric coated tablet – nanosponges of lansoprazole is considered to be ideal and effective in the management of ulcer and related conditions.

Table -1 Composition of lansoprazole nanopsonges

Ingredients	**F1**	**F2**
Lansoprazole	30 mg	30 mg
Eudragit RS 100	45 mg	-
Guar gum	-	45 mg
Dichloromethane	20 ml	20 ml
Polyvinyl Alcohol	10 mg	10 mg
Distilled water	25 ml	25 ml

Table-2 Formulation of lansoprazole tablets

Ingredients	F3	F4
Nanosponges prepared using Eudragit	30 mg	-
Nanosponges prepared using Guar gum	-	30 mg
HPMC K 100 M	30 mg	30 mg
Microcrystalline cellulose	60 mg	60 mg
Talc	5 mg	5 mg
Magnesium Stearate	5 mg	5 mg

Table-3 Evaluation parameters of Lansoprazole nanaoponges

Formulation	Percentage Yield	Entrapment efficiency	Particle size (nm)	Zeta Potential (mV)
F1	38.35	79.57	121.7	-23
F2	59.57	86.93	115.9	-25

Table-4 Evaluation parameters of Lansoprazole Tablets

Formulation	Weight variation	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Assay (%)
F3	Complies	3.18	5.66	0.886	99.47
F4	Complies	3 .23	5.65	0.752	99.93

Table-5 Comparision of correlation coeffiecient (r^2) of different kinetic models of F1,F2, F3 Aand F4

Formulation	Zero order	First order	Higuchi	Hixson crowel	N
F1	0 .914	0.980	0.966	0.766	0.475
F2	0.907	0.956	0.960	0.754	0.497
F3	0.839	0.976	0.929	0.704	0.475
F4	0.896	0.974	0.955	0.752	0.503

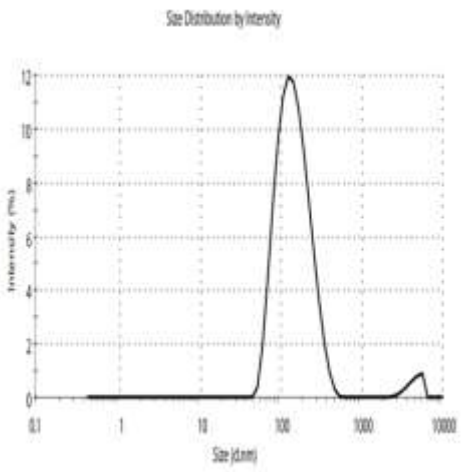

Fig 1. Particle size of lansoprazole nanosponges prepared using Eudragit RS 100 (F1)

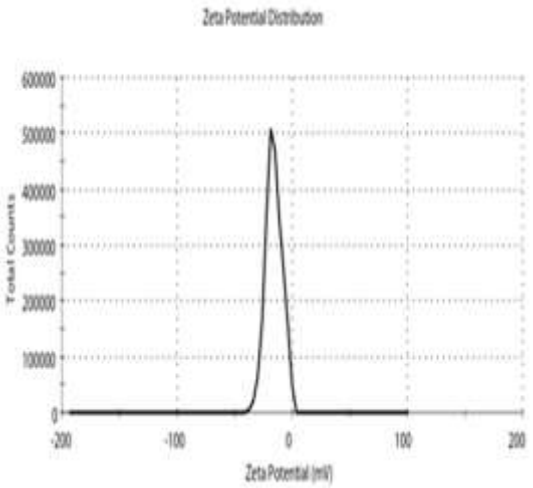

Fig 2. Zeta potential of lansoprazole nanosponges prepared using Eudragit 100 (F1)

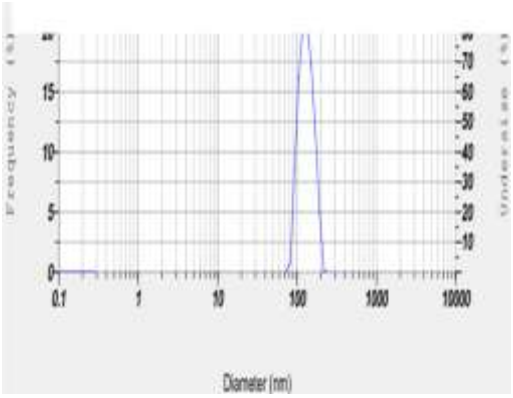

Fig 3. Particle size of lansoprazole nanosponges nanosponges prepared using Guar gum (F2)

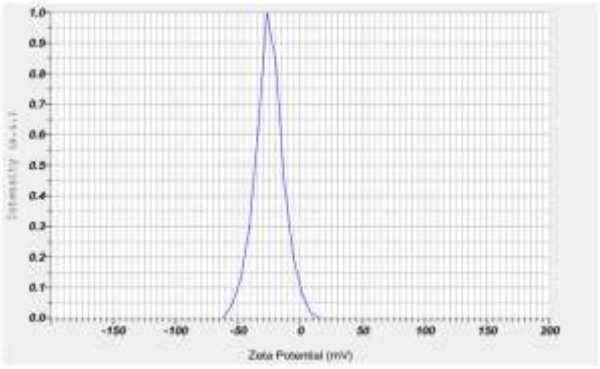

Fig 4. Zeta potential of lansoprazole nanosponges prepared using Guar gum(F2)

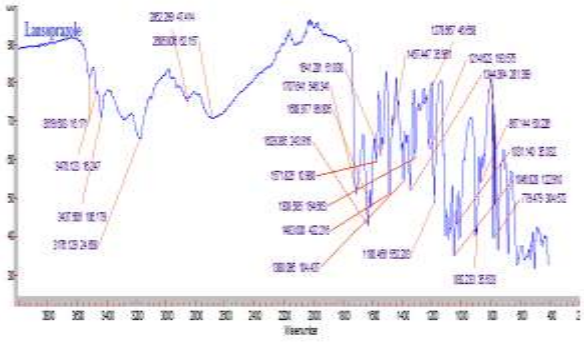

Fig 5: FTIR spectra of lansoprazole

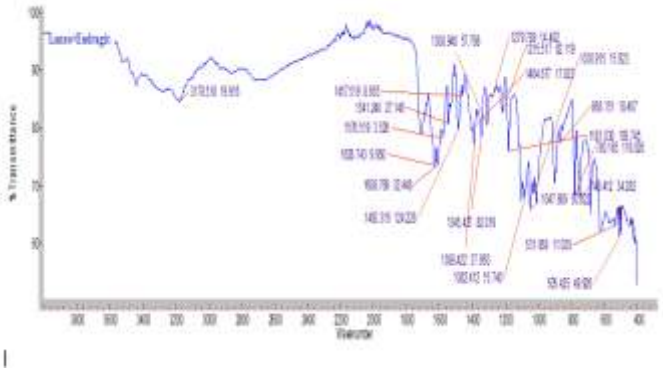

Fig 6: FTIR spectra of lansoprazole + Eudragit RS 100

Fig 7: FTIR spectra of lansoprazole + Guar gum

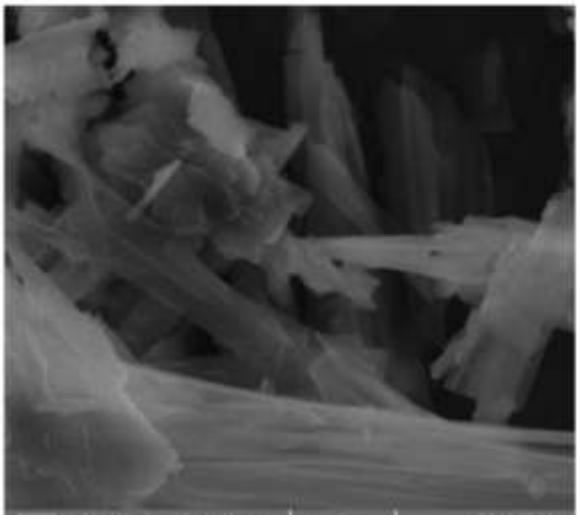

Fig 8. Scanning electron micrograph of lansoprazole nanosponges prepared using Eudragit RS 100

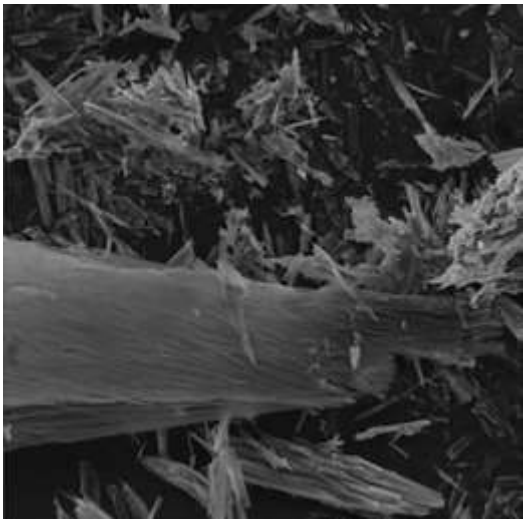

Figure 9. Scanning electron micrograph of lansoprazole nanosponges prepared using Guar gum

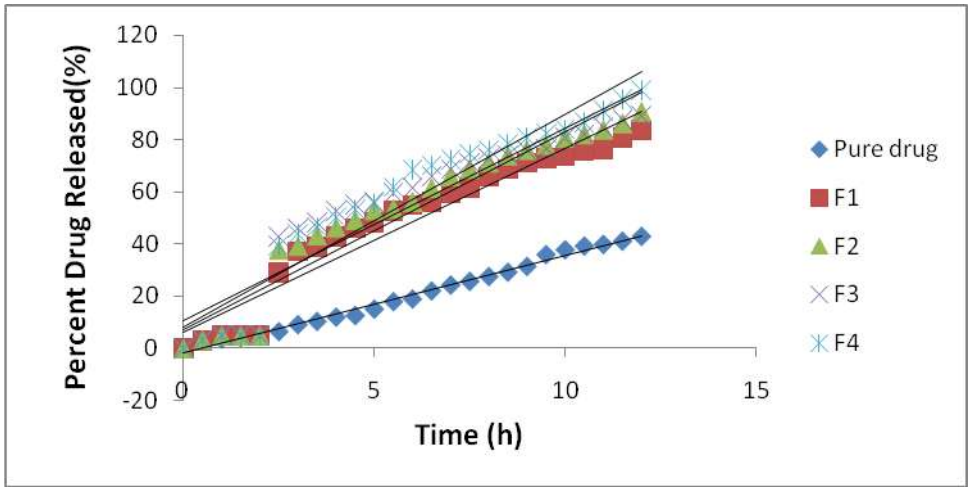

Fig 10 ***In vitro*** **release profiles of Pure drug, F1, F2, F3 and F4**

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