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PREPARATION AND EVALUATION OF LANSOPRAZOLE NANOSPONGES

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ABSTRACT

The objective of present study is to formulate and evaluate nanosponges of Lansoprazole for controlled release application. Lansoprazole nanosponges were prepared by Quassi emulsionsolvent diffusion method employing Eudragit Rs 100as a polymer and dichloromethane as crosslinker. The formulated nansoponges were evaluated for Average particle size distribution,Entrapment efficiency, Estimation of drug content and Drug release study. All the lansoprazole nansoponges prepared were found to be spongy and good . The size of nanosponges was 12/16 mesh (1435µm). The drug content and entrapment efficiency of nanopsonges prepared are given in table. 3. Low c. v. values (< 2.25 %) in the drug content ensured uniformity of the drug content in the nanosponges prepared. The entrapment efficiency was in the range 73.6 % with prepared nanosponges. Lansoprazole release from the nanosponges prepared was studied in 0. 1 N Hcl. The drug release profile of nanospongesprepared is shown in Table 4 and in Figs.3-6. The drug release parameters are given in Table 5. Lansoprazole release from all the nanosponges prepared was slow and spread for 7 h. The relationship could be expressed by the linear equation, Y= -0.007X+0.807 (R2=0.981), whereY is release rate (K1) and X is percent coat in the nanosponges. As such drug release rate from the nanosponges can be controlled by varying the percent coat. The drug release data were analyzed as per zero order, first order, Higuchi and Korsmeyer-Peppas kinetic equation models to assess the release kinetics and mechanism. The coefficient of determination values (R2) observed in the analysis of release data as per various kinetic models are shown in Table 4. The R^2 values were higher in the first order model than those in the zero order model indicating that the drug release from the nanosponges prepared followed first order kinetics. The first order drug release profiles of nanopsonges prepared are shown in Fig. 4. Drug release data also obeyed Higuchi and Korsmeyer-Peppas equation models with $R^2 > 0.930$. The Higuchi plot (Fig.5), were found to be linear indicating diffusion controlled drug release from the nansoponges prepared. When the release data were analyzed as per Korsmeyer- Peppas (Fig.6) equation, the release exponent 'n' was 0.937 indicating non-fickian diffusion as the release mechanism from the lansoprazole nanosponges prepared. **Novelty of the work:** Nanosponges of Lansoprazole were prepared by employing eudragit RS 100 as a polymer by using Quassi emulsion solvent diffusion method.

INTRODUCTION

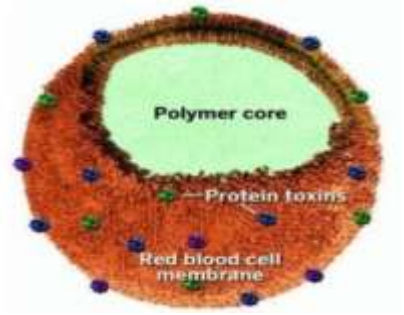
The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. Based on the method of associating with drugs, the nanoparticles are classified into encapsulating nanoparticles, conjugating nanoparticles and complexing nanoparticles. The encapsulating nanoparticle is represented By nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are sponge like nanoparticles contains many holes that carry the drug molecules. The second category isconjugating nanoparticle, which links to drugs through covalent bonds. The third type is complexing nanoparticle, which attracts the molecules by electrostatic charges. The nanosponges are

solid in nature and 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 anticaking agents which is suitable for the preparation of tablets or capsules. For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions. For topical administration, they can be effectively incorporated into topical hydrogel. When compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non-toxic and stable at high temperatures up to 300°C. They are capable of capturing, transporting and selectively releasing a huge variety of substances because of their specific 3D structure containing cavities of nanometric size and tunable polarity. Furthermore, nanosponges show a notable advantage in comparison with the common nanoparticles that is, they can be easily regenerated by different treatments, such as washing with eco-compatible solvents, mild heating, stripping with moderately inert hot gases or changing ionic strength or pH. The simple chemistry of polymers and cross linkers poses no problems in the preparation and this technology can be easily ramped up to commercial production levels. They can be mixed with water and used as a transport fluid. They are also used to mask unpleasant flavours, to convert liquid substances to solids. The chemical linkers allow the nanosponges to bind preferentially to the target site. The nanosponges could be either in crystalline or in paracrystalline form. The loading capacity of nanosponges depends mainly on the degree of crystallisation. Paracrystalline nanosponges show Different load capacities. The nanosponges can be formulated to be of specific size and to release drugs over time by varying the proportion of cross linker to polymer. These nanosponges can be magnetized when they are synthesised in the presence of compounds having magnetic properties. The tiny shape of nanosponges enables the pulmonary and venous delivery of drug in a controlled manner.

Targeting Sites by Nanosponges "Tagging" drug-loaded nanosponges ensures desired pharmacological response by targeting only disease affected cells and leaving the healthy ones unharmed. Drugs encapsulated within the nanosponge pores are shielded from premature destruction and stability of drug is enhanced. This tiny sponge circulates around the tumour cell until they encounter the surface to release their drug cargo in a sustained manner. Nanosponge is three to five times more effective at decreasing tumour growth than direct injection. The targeted delivery systems of nanosponge have several basic advantages like, the drug is released at the tumour instead of circulating widely through the body, and it is more effective for a given dosage. The nanosponges have basic features such as fewer harmful side effects as smaller amounts of the drug will come into contact with healthy tissue .

Difference between Nanoparticles and Nanosponges

The thin line of distinction among nanoparticles and nanosponges is the difference in porosity and size. Nanoparticles have size in nanometer whereas nanosponges have pores in nanometers while their overall size can extend up to micrometers, and are usually smaller than 5µm. Many times nanosponges have been reported as nanoporous nanoparticles / microparticles. Nanosponges show diverse domains in their structure, since they have both hydrophobic and hydrophilic groups.



ADVANTAGES OF NANOSPONGES

1. Being amphiphilic in nature, nanosponges can carry both hydrophobic molecules in the hydrophobic cavity and hydrophilic molecules in the spaces between the hydrophobic moieties simultaneously. Hydrophobic drugs can be loaded into the nanosponge structure to consequently increase their solubility.
2. The superior properties of nanosponges have been attributed to 'tunability', that is the

ability to control the structure of particles and control the nature and size of aperture.

3. Nanosponges have the ability to produce predictable/controlled drug release.
4. Nanosponges can be tagged with specific linkers to target diseased cells hence achieving greater efficacy while reducing side-effects, decreasing dose and dosing frequency and in turn increasing patient compliance.
5. Nanosponges can significantly reduce the irritation of drugs without reducing their efficacy.
6. Biodegradable in nature and easy scale up for commercial production
7. They mix with water and are used as a transport fluid. They can be used to mask unpleasant flavours.

DISADVANTAGE:

The only disadvantage of this nanosponges is their ability to include onlysmall molecules.

CHARACTERISTIC FEATURES OF NANOSPONGES

- ✓ Nanosponges of specific size can be synthesized by changing the crosslinker topolymer ratio.
- ✓ They are nontoxic, porous particles, insoluble in most organic solvents and stable up to 300^0C. They are stable at the pH range of 1-11.
- ✓ They form clear and opalescent suspension in water.
- ✓ They can be reproduced by simple thermal desorption, extraction with solvents, byusing microwaves and ultrasounds.
- ✓ Their three-dimensional structure allows capture, transportation and selective release of a variety of substances.
- ✓ Chemical linkers permit nanosponges to bind preferably to the target site.
- ✓ By complexing with different drugs nanosponges can form inclusion and non- inclusion complexes.
- ✓ By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges.

POLYMERS USED IN NANOSPONGES PREPARATION:

There are various polymers and cross linkers are used in the preparation of nanosponges.

Polymers: Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives

like Alkyloxycarbonyl Cyclodextrins, Methyl β-Cyclodextrin, Hydroxy Propyl β- Cyclodextrins.
Copolymers:
Poly(valerolactoneallylvalerolactone), Poly(valerolactoneallylvalero -lactone oxepanedione), Ethyl Cellulose, Poly vinyl alcohol.
Cross linker: Carbonyl diimidazoles, Carboxylic acid dianhydrides, Diarylcarbonates, Dichloromethane, Diisocyanates, Diphenyl Carbonate, Epichloridine, Gluteraldehyde, Pyromellitic anhydride, 2,2-bis (acrylamido)Acetic acid.

MATERIALS AND METHODS

Chemicals required for the formulation include

Lansoprazole , Eudragit RS 100, Dichloromethane and Polyvinyl Alcohol

Estimation of Lansoprazole

UV Spectrophotometric method based on the measurement of absorbance at 284nm in methanol was used for estimation of Lansoprazole. The method was validated for Linearity, Accuracy, Precision and Interference. The method obeyed Beer's law in the concentration range of 2-10µg/ml. Low RSD values ensured reproducibility of the method. When the standard solution was repeatedly assayed, the Regression was found to be 0.9996. No interference by the excipients used in the study was observed.

Preparation of Lansoprazole nanopsonges by quasi emulsion solvent diffusion technique:

The dispersed phase containing polymer

(eudragit RS 100) and Lansoprazole were dissolved in appropriate concentration of cross-linkers (dichloromethane) and which was slowly added to a definite amount of stabilizers (polyvinyl alcohol) of aqueous continuous phase. The reaction mixture was stirred at 1000 rpm for 2 hrs. The nanosponges formed were collected by filtration and dried in oven at 40^0c for 24 hrs. The dried NSGs were store up in vacuum desiccators to make sure the deletion of residual solvent

Evaluation of Lansoprazole nanosponges Drug-Excipient compatibility: FTIR was used o check drug excipient compatibility

Vesicular Size distribution and average particle size determination: Particle size analysis was carried out using an optical microscope (compound microscope) with a calibrated eyepiece micrometer. About 5o mg were measured individually, average was taken and their size distribution range, mean diameter were calculated.

Entrapment Efficiency: Entrapment efficiency (Ee) was determined by taking a weighed quantity of nanosponges (25mg) in a 25ml volumetric flask, sufficient quantity of 0.1N HCL was added to make volume 25ml. The suspension was shaken vigorously and then expose for centrifugation at 10,000 X gm for 1 hr. The supernatant of formulation after centrifugation were taken as such without further processing and filtered through 0.45 µm filter, and determined by using UV/VIS spectrophotometer at suitable wavelength (284nm). Entrapment efficiency = Amount of entrapped drug/ Amount of used drug * 100

Estimation of Drug Content in the Nanosponges: Nanosponges (50 mg) were taken in a dry mortar, finely powdered and mixed thouroughly. Powder equivalent to 20mg was taken into a 50 ml conical flask ad extracted repeatedly with methanol and the extracts were collected into 100 ml volumetric falsk and made up to volume with methanol. The solution was suitably diluted with distilled water and assayed for Lansoprazole at 284 nm.

Reproducibility: One for mulation each of nansoponges was prepared six times and studied to validate the reproducibility of formulation. The statistical analysis was avoided, as the results were reproducible each time

Drug Release Study:

Drug release from the nanoponges prepared was studied employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperatureof 37°C ± 1°C. 0.1N HCL (900 ml) was used as dissolution fluid for Lansoprazole nanopsonges respectively. Nanopsonges (100 mg) were used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for Lansoprazole at 284 nm.. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn. Each dissolution experiment was run in triplicate (n=3).

Analysis of Drug Release Data:

Drug release data were analyzed as per zero order, first order, Higuchi and Korsmeyer- Peppas kinetic equation models to assess the release kinetics and mechanism.

DISCUSSION:

Lansoprazole nanopsonges could be prepared by Quassi Emulsion Solvent Diffusion Method All the lansoprazole nanopsonges prepared were found to be good. The size of nanospongeswas 12/16 mesh (1435µm). The drug content and entrapment efficiency of nanospongesprepared are given in table.7. Low c. v. values (< 2.25 %) in the drug content ensureduniformity of the drug content in the nanoponges prepared. The entrapment efficiency was inthe range 73.6-86.7 % with various nanosponges. Lansoprazole release from thenanopsonges prepared was studied in 0.1 N HCL. The drug release profiles of nanospongesprepared are shown in Tables 8-11 and in Figs.5 – 8. The drug release parameters are given inTable 13. Lansoprazole release from all the nanosponges prepared was slow and spread over7 h.

Table 1: Calibration Curve for the Estimation of Lansoprazole

Concentration of Lansoprazole (µg/ml)	Absorbance	
	Mean	RSD
2	0.084	1.89
4	0.176	1.76
6	0.25	2.01
8	0.348	1.39
10	0.421	1.97

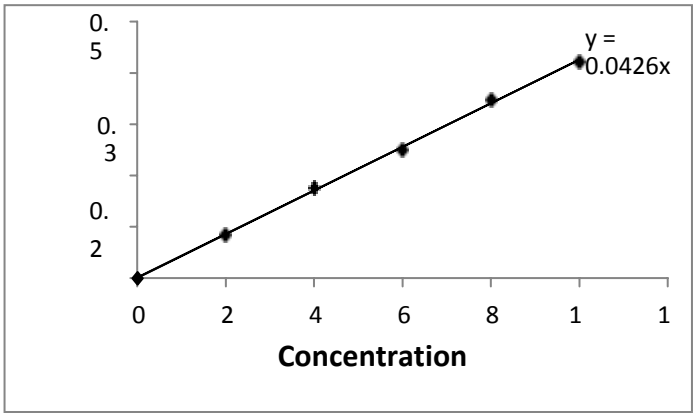


Fig-1 Calibration cuve of Lansoprazole

Table 2 - Formula of Lansoprazole Nansoponges Prepared by Quassi Emulsion Solvent Diffusion Method

S.NO	Ingredient	Quantity
1	Lansoprazole	30mg
2	Eudragit RS 100	45 mg
3	Dichloromethane	20 ml
4	Polyvinyl Alcohol	10 mg
5	Distilled water	25 ml

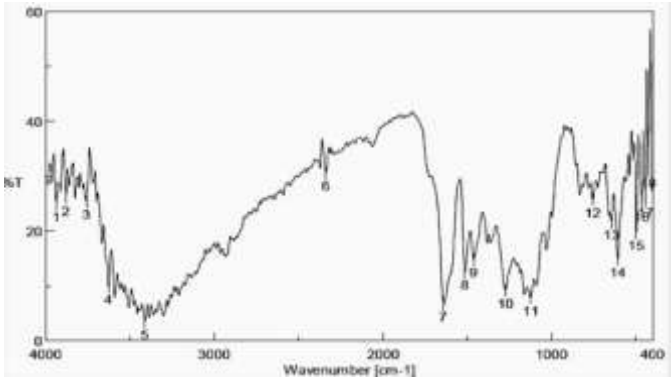


Fig-2 Drug Excipient Compatibility

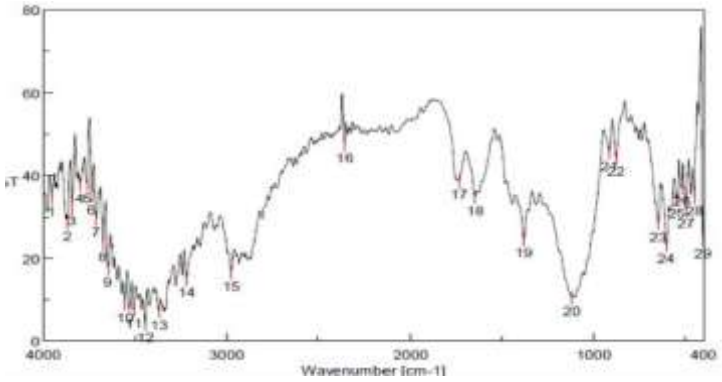


Table -3 Drug Content and Entrapment Efficiency ofLansoprazole Nanosponges Prepared

S. No	Nanosponges	Drug Content Estimated (mg/100 mg)	Entrapment Efficiency (%)
1	Lansoprazole	7.36±0.162	73.6

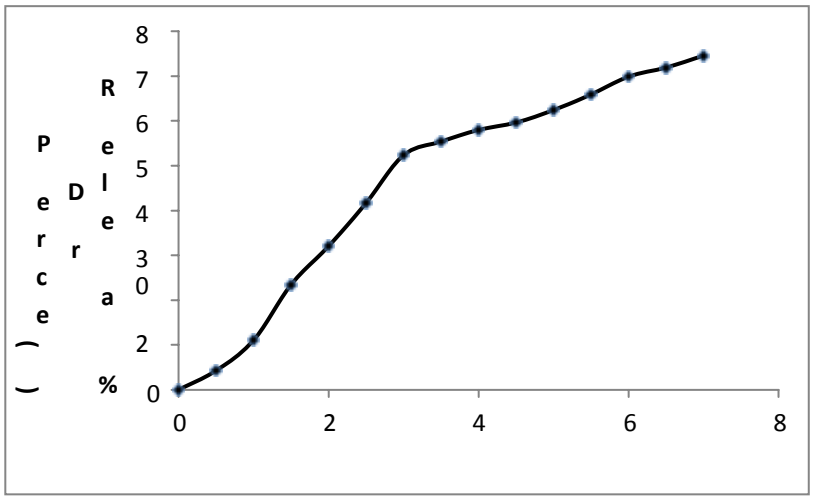


Fig 3 : Drug Release Profile of Lansoprazole nanosponges

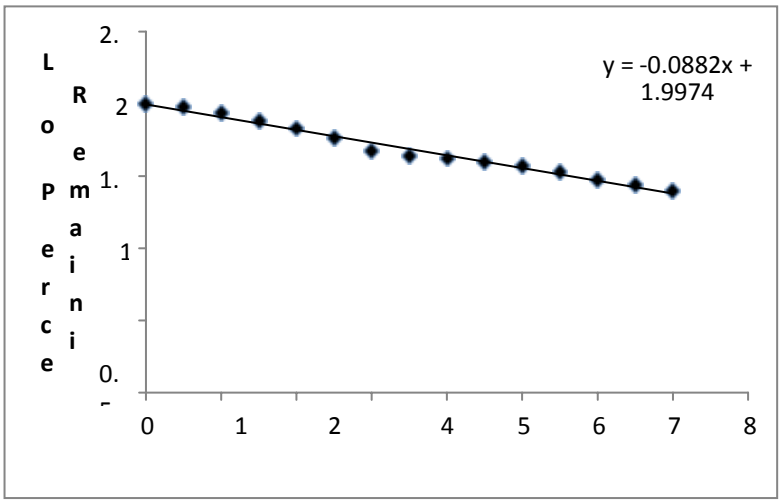


Fig 4: Log Percent Drug Remaining vs. Time Plots Lansoprazole nanosponges

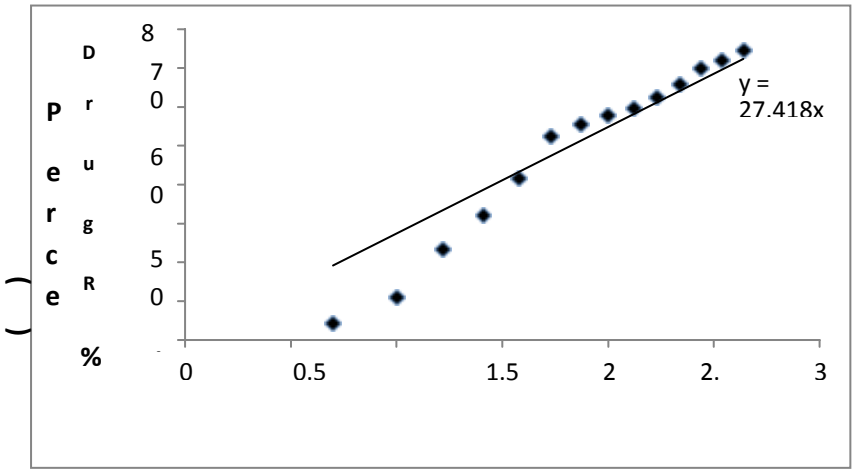


Fig 5: Percent Drug Released vs. √Time Plots of Lansoprazole NanospongesPrepared by Quassi Emulsion Solvent Diffusion Method

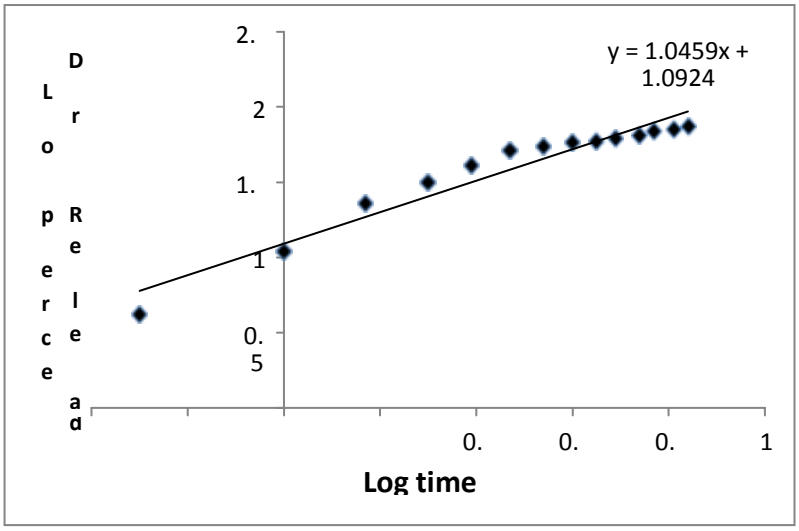


Table 4- Coefficient of Determination (R^2) Values in the Analysis of Release Data of Lansoprazole nanosponges as per Different Kinetic Models

Formulation	Coefficient of Determination (R^2)			
	Zero Order	First Order	Higuchi Model	Korsmeyer-Peppas
Lansoprazole nanopsonges	0.931	0.981	0.931	0.937

Table 5 -Drug Release Parameters of Lansoprazole Nanosponges Prepared by Quassi Emulsion Solvent Diffusion Method

Formulation	T50 (h)	T90 (h)	Dissolution Rate		Release Exponent (n)
			K0 (mg/h)	K1 (h^{-1})	
Lansoprazole	3	>7	0.587	0.124	0.75

The relationship could be expressed by the linear equation, Y= -0.007X+0.807 (R^2=0.987), where Y is release rate (K1) and X is percent coat in the niosomes. As such drug release rate from the nanosponges can be controlled by varying the percent coat. The drug release data were analyzed as per zero order, first order, Higuchi and Korsmeyer-Peppas kinetic equation models to assess the release kinetics and mechanism. The coefficient of determination values (R^2) observed in the analysis of release data as per various kinetic models are shown in Table12. The R^2 values were higher in the first order model than those in the zero order model indicating that the drug release from the nanosponges prepared followed first order kinetics. The first order drug release profiles of nanosponges prepared are shown in Fig.6. Drug release data also obeyed Higuchi and Korsmeyer-Peppas equation models with R^2 > 0.949. All the Higuchi plots (Fig.7), were found to be linear indicating diffusion controlled drug release from the nanosponges prepared. When the release data were analyzed as per Korsmeyer-Peppas (Fig 8) equation, the release exponent 'n' was in the range 0.949-0.991 indicating non-fickian diffusion as the release mechanism from the Lansoprazole nanosponges prepared.

CONCLUSIONS:

Nanosponges are a novel type of controlled/sustained release drug delivery systems to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration. The objective of the present study is to develop and evaluate Lansoprazole nanosponges for control release application. Nanosponges of Lansoprazole were prepared by Quassi Emulsion Solvent Diffusion Method. Nanopsonges were prepared by using Eudragit as a polymer and . Nanosponges prepared were evaluated for size, drug content, entrapment efficiency and drug release characteristics. From the results obtained the following conclusions are drawn

Lansoprazole Nanosponges:

1. Nanosponges containing Lansoprazole could be prepared by Quassi Emulsion Solvent Diffusion method .
2. The nanosponges prepared are good with size of (1435µm).
3. Entrapment efficiency was in the range 73.6-86.7 %.
4. Lansoprazole release from the nanosponges prepared was slow and spread over 7 h
5. Drug release from the nanosponges prepared was diffusion controlled and followedfirst order kinetics.
6. A good linear relationship was observed

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