



A Prospective Review on Novel Strategies for Preparation and Evaluation of Nanosponge Tablets

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ABSTRACT:

Nanosponges are small sponges where they reach the target site and stick to that surface and initiate to release in a controlled manner they can also be loaded with the various types of medications. Drugs loaded with Nanosponges improves their dissolution rate, solubility, rate of release, stability, reduces the frequency of dosing and improves bioavailability. Nanosponges are mostly used in targeted drug delivery system. Drug delivery is the major problem faced in the pharmaceutical field from a long time by the invention of Nanosponge technology has become important step so that we can minimize some problems like poor solubility, poor stability and dosing frequency. The main advantage of this Nanosponge is it can be loaded by both hydrophilic and lipophilic drugs. The present review article is to discuss about the general introduction, composition of Nanosponges, drugs loaded with Nanosponges, different preparation techniques and evaluations methods for the Nanosponge tablets. Zeta potential, Fourier transform-infrared spectroscopy, determination of percentage yield, particle size analysis, porosity, invitro dissolution studies and entrapment efficiency by these characterizations we can know the inclusion complexes formed in between drug and Nanosponges, mainly lansoprazole loaded Nanosponges characterization parameters and

evaluations are presented in this article. Nanosponges can deliver the drug through various routes like oral, topical, aerosol and parenteral administration.

INTRODUCTION:

Nanosponges are minute particles that may enclose a wide range of chemicals, including volatile oils, volatile proteins and peptides, DNA, and anti-cancer medications. Because their diameter is smaller than 1 μm compared to micro sponges 10–25 μm and 5-300 μm void size, Nanosponges have an advantage over micro sponges. While micro sponges are frail and only stable at temperatures of 130 $^{\circ}\text{C}$, Nanosponges are powerful and stable up to 300 $^{\circ}\text{C}$ (1).

Drugs that are poorly water soluble can be made more stable by using Nanosponges, which are having the capability to carry both water soluble and oil soluble drugs. The Nanosponges which are made from three-dimensional scaffold (or) network are made from the polymers, these Nanosponges have the capability to degrade spontaneously. To create Nanosponges, the polymers are combined with a cross linker in a solution. Here, the polyester degrades in the body moderately because it is normally biodegradable. Drug molecules that were put onto the Nanosponges scaffold are released in a damaging manner when the scaffold collapses (2). This technique is thought to be a unique method that enables a regulated delivery of the drug for topical usage. It effectively provides the trapping of substances with less side effects, increased stability, improves appearance, and higher formulation mouldability. Majorly the Nanosponges are solid, but they can also be prepared in different dosage forms for oral, parenteral, topical, or inhalation use(3).

NANOSPONGES' SUBSTANCE COMPOSITION:

1) Polymer - The choice of polymer can affect how well Nano sponges operate as well as how they form. The polymer which is used can be determined by the medication to be enclosed and exact release. The selected polymer should have the ability to bind to particular ligands. Examples include cyclodextrin and their derivatives, such as methyl β -cyclodextrin, and copolymers, such as ethyl cellulose and PVA.

2) Cross-linking agent: Depending on the polymer's structure and the medicine being developed, the choice of a cross-linking agent can be made. Diphenyl carbonate, dichloromethane, dialyl carbonates, and diisocyanates are a few examples.

3) Drug substance:

Molecular weight of the drug substance is between 100 and 400 Daltons. The average drug molecule has four to five closed rings. Solubility is less than 10 mg/ml in water. The drug substance's melting point is lower than 250 $^{\circ}\text{C}$ (4).

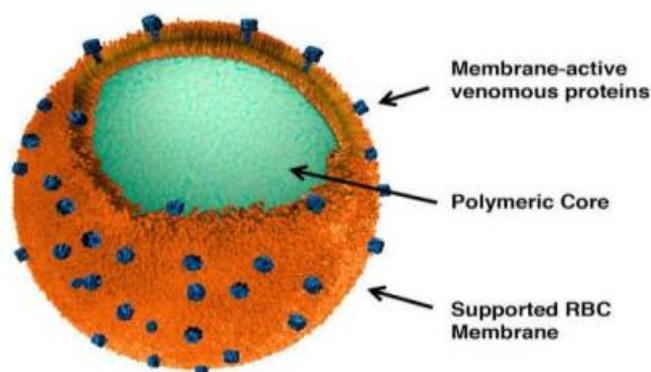


Figure 1. Structure of Nanosponges

Advantages of Nanosponge:

- Increased formulation mouldability, elegance, and stability.
- Non-toxic, Non-irritating, and biodegradable
- Offers 12-hour prolonged release.
- Prevents deterioration of the active component.
- The substance utilised in this approach can act as a shield to prevent the medicine from being prematurely destroyed inside the body.
- This type of formulation can increase the bioavailability of drug.
- These are free flowing and can be worthwhile.
- These formulations change the release of the drug.
- They enhance the solubility of badly soluble drug.

Disadvantages of Nanosponge:

- They include only small molecules encapsulating.
- Dose dumping may occur.
- They depend only upon the loading capacities.
- May retard the release.

Applications:

- A large number of approved drugs based on Nanosponges are so far in the market including drugs for tumour.
- Use of Nanosponge as a topical agent, in enhancing solubility, in synthetic detectors, in wastewater remediation, as a protein carrier and also in farming(5).
- Used in biomedical Engineering.
- Used in the Anti-viral and Anti-Cancer Therapy(19).

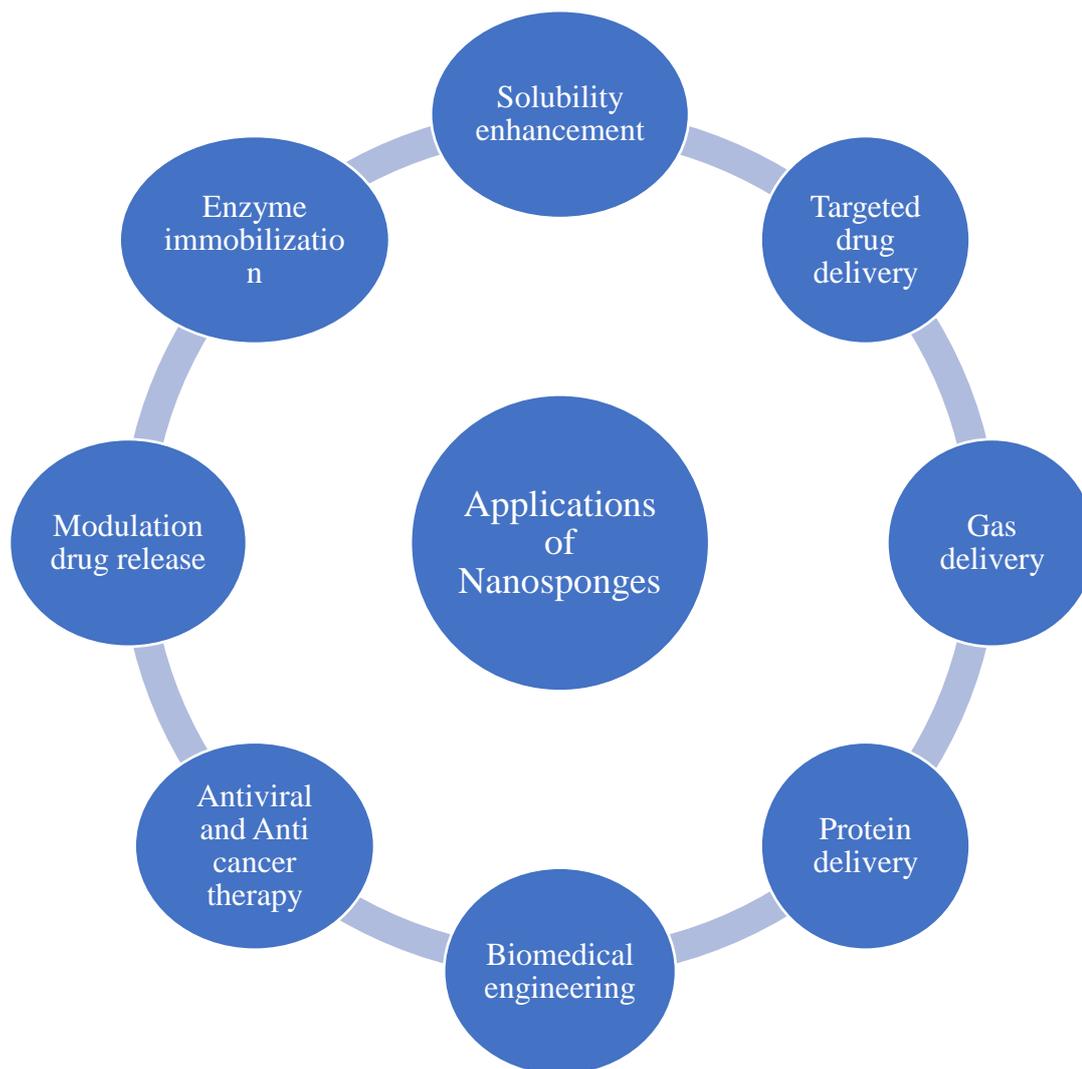


Figure 2. Applications of Nanosponges

Drugs used in Nanosponge drug delivery

Taking into account the small therapeutic indices, large doses, and repeated administrations required for so many antiviral drugs because of their less aqueous solubility, low penetrability, insufficient bio distribution, and short span, Nano medicine formulations can provide certain benefits that can make better antiviral treatments.

Cyclodextrin-based polymers are used because of various reasons:

The ability of cyclodextrin to combine materials whose size and polarity match those of their cavities. Antiviral medications can be combined with β -cyclodextrin to produce inclusion complexes, increasing their effectiveness. Nanosponges made of cyclodextrin (β CD-NS) are intended to increase the capacity for drug complexation. These are solid, strongly cross-linked β -cyclodextrin nanoparticles with Nano cavities(6).

Tamoxifen(anti-estrogen class)

Tamoxifen has a liquefaction point of 100°C and is a weak base with low level of aqueous solubility. Nolvadex base is commercially changed to the citrate salt to improve the drug's solubility & potency in water. Tamoxifen citrate has a higher melting point than water (146°C), which slows down the rate of dissolution, limiting the amount of solubility increase that may be achieved through salt formation. Tamoxifen is used to treat breast tumor in premenopausal and postmenopausal women and is administered to sick person over an extended period of time. It causes serious, dose- and concentration-dependent adverse effects such as uterine cancer, hepatocellular carcinoma, deep vein thrombosis, pulmonary emboli, and eye damage. This will restrict the use of Tamoxifen. Thus, it is necessary to create a prolonged release. Tamoxifen formulation can reduce the negative effects. Nanosponges with tamoxifen loaded on them make the drug more soluble and release it gradually(7).

Resveratrol

Resveratrol is a group of compounds known as polyphenols that is utilized to treat a variety of illnesses, including hyperlipidemic, dermatitis, gonorrhoea, inflammation, and cardiovascular problems. Since hydrophobicity makes dissolution as a rate-determining step for in vivo absorption, oral bioavailability is hampered. Resveratrol is loaded into Nanosponges to help with this issue by improving solubility and dissolution rate(7).

Camptothecin(Topoisomerase Inhibitor-Antineoplastic)

An effective anti-cancer agent, camptothecin is a plant alkaloid that works by inhibiting topoisomerase-1 throughout the S-phase of the cell division cycle. The anticancer effects of camptothecin and its derivatives were demonstrated in a variety of human cancers including pleura, prostate, breast, large bowel, abdomen, ovarian carcinomas, malignant melanoma, lymphomas, and sarcomas. In spite of its great action, it only offers a modest amount of beneficial value. This is due to its low solubility in water, harmful side effects, and opening of the lactone ring with respect to physiological pH, which results in the indolent carboxylate form. Furthermore, the ring-opening causes charged medication type to only partially pass through a phospholipid bilayer with a low dielectric constant, changing the molecular diffusivity. To create delivery systems for the insoluble lactone form of camptothecin and its derivatives, extensive study has been done. They include making macromolecular prodrugs and entrapment in liposomes, microparticles, Nano spheres, by forming a complex with triglycerides or cyclodextrin. For the sake to increase the storage life and rate of release of the medication, a novel formulation for camptothecin has been created. As a result of complexation and potential lactone ring protection provided by the Nanosponges strong inclusion abilities, the drug's stability may be increased(7).

Econazole nitrate(Anti-fungal medication)

In order to treat the signs of superficial candidosis, tinea, dermatosis, and topical infections, dermatologists often prescribe the imidazole antifungal drug econazole topically. Commercially, econazole nitrate is offered as a 150 mg vaginal tablet, 1% cream, 1% ointment, lotion, powder, and solution. Due to their poor delivery system efficacy, these delivery methods need to be combined with a high concentration of active drugs for effective therapy. A delivery mechanism is required to lengthen the time of an active substance remains on the dermis during the time of reducing its absorption into the torso. As econazole

Author name	Published year	Title of work	Class of drug	Drug used	Nanosponge vehicle	Reference number
Torne SJ, Ansari KA, Vavia PR, Trotta F, Cavalli R	2010	Enhanced oral Paclitaxel bioavailability after	Anticancer	Paclitaxel	B-cyclodextrin	10

nitrate is slightly digested by the skin, regulating the drug's discharge will increase formulation effectiveness and reduce the need for frequent application. Consequently, topical delivery systems based on Nanosponges will be able to get around these restrictions. In order to overcome the drawbacks of current formulations and lessen adverse effects like burning, stinging, and contact dermatitis, topical delivery systems based on Nanosponges are needed. By employing the emulsion solvent diffusion method, econazole nitrate Nanosponges were generated, and the particular Nanosponges were then placed into hydrogel as a local depot for constant drug release. Nanosponges loaded with econazole nitrate exhibit extended drug release, which results in several advantages such as a depletion in overall dose, frequency of administration, and dose-related systemic adverse-effects(8).

Paclitaxel(Antimicrotubule agent-stops growth of cancer cells)

An anti-cancer substance called Paclitaxel is originated from the bark of the Pacific yew tree (*Taxus brevifolia*). The liver is a primary site of metabolism and biliary excretion for paclitaxel. Paclitaxel which is used orally have some disadvantages because of their limited bioavailability caused by poor solubility, dissolution, high presystemic hepatic metabolism, and intestinal wall P-glycoprotein transport mechanisms. Paclitaxel's oral bioavailability could be increased by comprising it in the Nanosponges, a Novel drug delivery system. When paclitaxel-filled cyclodextrin Nanosponges are administered, gastrointestinal fluids develop a matrix-like structure, solubilizing the water-insoluble paclitaxel by creating a Nano suspension. The AUC of 20 mg of paclitaxel-loaded Nanosponges is greater than the AUC of 10 mg of paclitaxel alone. Paclitaxel-loaded Nanosponges had a mean unadulterated bioavailability that was 2.5 times greater than paclitaxel(9).

SOME DRUGS LOADED WITH NANOSPONGES:

In the following table some class of drugs are loaded with Nanosponge to increase stability and solubility.

		administration of Paclitaxel loaded Nanosponges. Drug Delivery				
Palminteri et al.	2021	Cyclodextrin Nanosponge for the GSH mediated delivery of resveratrol in human cancer cells	polyphenolic compound with anti-cancer activity	Resveratrol	Cyclodextrin	11
Selvamuthukumar Subramanian, Anandam Singireddy, Kannan Krishnamoorthy and Manavalan Rajappan	2012	Nanosponges: A Novel Class of Drug Delivery System	Antineoplastic and antiestrogen.	Camptothecin And Tamoxifen	Cyclodextrin	12
Renuka S, Kamla P.	2010	Polymeric Nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation	Antifungal	Econazole nitrate	Ethyl cellulose and Polyvinyl alcohol	8

Methods of preparation of Nanosponge

1.Quasi-emulsion solvent diffusion

By using various polymer quantities and a quasi-emulsion solvent diffusion technique, the Nanosponges can be created. An appropriate solvent was used to dissolve eudragit RS100 in order to prepare the inner phase. later, medication or active ingredient can be incorporated into the solution and broken down at 350°C using ultrasonic. The inner phase was poured into the PVA.

The liquid is filtered to remove the Nanosponges after 60 minutes of stirring. During 12 hours, the Nanosponges are drained at 40°C in an air-heated oven(13).

2.Solvent method

With a suitable solvent, dissolve the polymer. After that, include this with extra cross-linker. Reflux the mixture for 2 days at 10 degrees. After that, let the mixture cool to room temperature. This should be mixed with extra bidistilled water before filtering the result. Thereafter, purify using an extended ethanol Soxhlet extraction. Dry the product before grinding it in a mechanical mill to produce uniform powder(14).

3.Nanosponge prepared from hyper cross-linked β -cyclodextrin

Hyper-cross-linked β -cyclodextrin is used to make Nanosponge. To completely dissolve 100 mL of anhydrous dimethylformamide (DMF), 17.42 g of anhydrous β -cyclodextrin (15.34 mmol) was put to a flask with a round bottom. 9.96 g of carbonyl di imidazole (61.42 mmol) were then added, and the solution was allowed to react at 100°C for 4 hours. The translucent block of hyper-cross-linked cyclodextrin was partially crushed after condensation polymerization was finished, & more deionized water was mixed up to get rid of DMF. Lastly, ethanol-based Soxhlet extraction was used to totally eliminate any remaining by-products or unreachable reagents. The resulting white powder was pulverised in a mortar after being dried for the night at 60°C in an oven. The obtained fine powder was dissolved in water. The colloidal component that persisted in suspension in water was retrieved and lyophilized. The Nanosponges that were found are spherical in shape and have sub-micron dimensions. It is possible for the cyclodextrin:cross-linker molar ratio to change (i.e. 1:2, 1:4, and 1:8). According to the molar proportion of a cross-linker utilised in their synthesis, Nanosponge can be categorised (i.e. Nanosponge, 1:4)(15).

4.Ultrasound-assisted method

The polymer ultrasonic junction is used in the ultrasound-assisted method of synthesis. Without the use of a solvent, polymer crosslinking takes place and polymer crosslinking takes place because of ultrasonic vibrations. A suitable molar ratio of polymer and cross linker was mixed in a flask. The flask was placed in an ultrasound bath during the ultra-sonication process, which lasted for five hours at a temperature of 90 °C. After sonication, the temperature of the collected mixture was lowered, and the result was severely divided and washed to remove non-reacted polymer and reagents using an abundance of water [46]. Soxhlet extraction was used to purify the washed solid using ethyl alcohol. Before further drug loading, the filtered NSs collected were correctly processed and vacuum dried. (16)

5.Melt method

In this technique, the cross linker & CD are homogenised and melted together with three to five hours of continuous stirring at 100°C. In order to remove the reaction byproducts, the

mixer was cool down to normal room temperature, and the finished product was smashed up and repeatedly cleaned with a acceptable solvent(17).

6. Microwave assisted synthesis

Microwave irradiation is the easiest way for synthesising CDNS, and it considerably slows down reaction time. The NS that is produced has more crystallisation. Microwave aided manufacturing revealed a four-fold reduction in reaction time in contrast to typical melt technique. The procedure produced crystallinity and a homogenous distribution of the particle size(18,19).

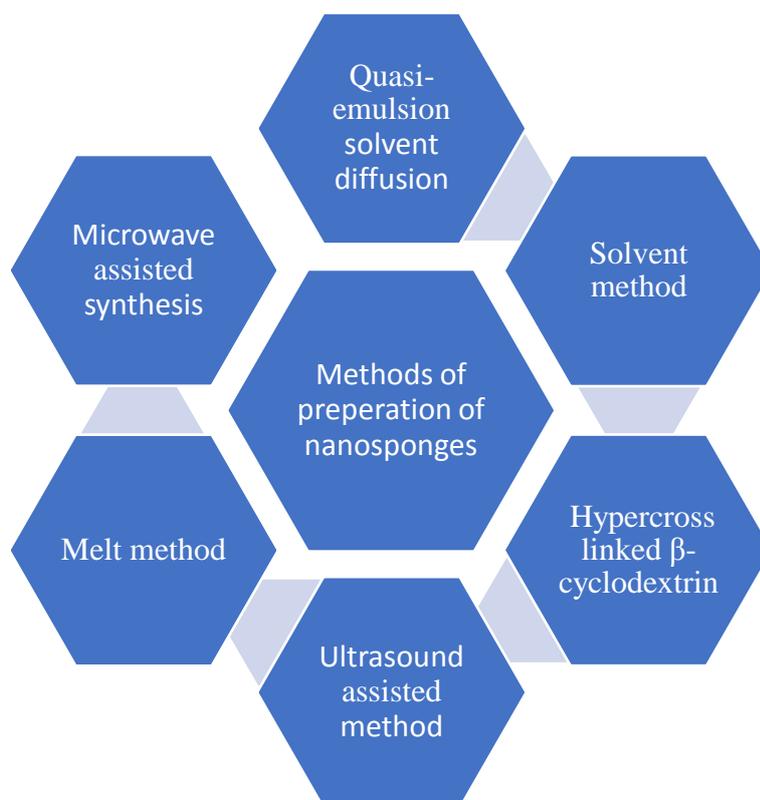


Figure 3. Methods of Preparation of Nanosponge

Characterization and assessment of a drug (Lansoprazole) loaded Nanosponge:

The emulsion solvent diffusion process was utilized to manufacture lansoprazole Nanosponges using various ratios of ethyl cellulose, polyvinyl alcohol, and Pluronic F68. A certain amount of PVA in 100 mL of an aqueous continual phase was gradually added to the dispersion phase, which was composed of 100 mg of lansoprazole and a predetermined amount of ethylcellulose dissolved in 30 mL of dichloromethane. By using a magnetic stirrer, the mixture was agitated for 120 minutes at a speed of 1000 rpm. The lansoprazole Nanosponges that had formed was taken by vacuum filtration and drained for 24 hours at 400°C in an oven(20).

In-vitro dissolution studies

Diffusion was used to test in vitro drug release, and the dissolving source was phosphate buffer pH 6.8. The required sample size (0.1g) was taken, then it is suspended in a necessary medium, in addition it can also be retained in the open-ended device. The Renal replacement therapy bag was tied (molar mass cut off: 12–14kDa, surface area of 22.5cm²) to the one end of the tube, which was then immersed in a beaker carrying of 0.1lit of the buffers pH 7.2. Another end of the tube was left open. The media was maintained at a condition of 37°C and a rate of 100 rpm. At predefined intervals, the samples were removed, and fresh medium was added at the same time. The medication released at a maximum of 236 nm was measured in withdrawn aliquots using UV-Visible spectrophotometer(20).

Studies using the Fourier transform infrared spectroscopy

The Perkin Elmer Model 1600 was utilized to perform the FTIR spectrum observations at room temperature (USA). Samples were dissolved in KBr powder, and 5 tonnes of pressure were used to form the pellets. Powder diffuse reflectance on an FTIR spectrophotometer was used to acquire FTIR spectra.

Porosity

The Nanosponges were poured into a grated cylinder to acquire the bulk volume, which is reported. Afterwards it undergoes 100 tapings and the volume is taken as actual volume(20).

$$\% \text{ Porosity} = (\text{Bulk Volume} - \text{True Volume} / \text{Bulk volume}) \times 100$$

Particle size analysis

By employing photon correlation spectroscopy (PCS), researchers were able to measure the average particle size of lansoprazole Nanosponges at a fixed angle of 25⁰ with ZS-90 Nano (Malvern Instruments limited, United Kingdom). Prior to a particle size analysis, the sample was mixed ten times with distilled water. (20).

Determination of entrapment efficiency

0.1gm of the medicament was taken which is equivalent to Nanosponges and then powdered after that it is shifted into a 100 ml measuring flask which consist of 10ml of methanol and the remaining capacity was filled with simulated gastric fluid of pH 1.2. Next day (i.e. after 24 hrs), the solution was purified by using Whatman filter paper, and after the appropriate dilutions, the absorbance was estimated spectrophotometrically(21).

Zeta potential determination

To determine how quickly particles, travel in an electric field, the zeta potential was calculated. Zetasizer Nano ZS, produced by Malvern Instruments Ltd. in the UK, was used to evaluate the Nanosponges after they had been diluted with distilled water 10 times(21).

Calculation of percentage yield and loading efficiency

Percentage yield was precisely determined using the finished compound weight after draining in relation to the starting mass of the polymer and medication selected to make the Nanosponges.

Percentage yield = Practical weight of Nanospongesacquired /Theoretical weight (drug + polymers)

Loading efficiency=Actual drug content in Nanosponge/Theoretical drug content×100(22).

Estimation of Drug Content in the Nanosponges:

In a dry mortar, 50 mg of Nanosponges were taken they are finely powdered, and a thoroughly blended. A 20 mg powder was put down in a 50 ml conical flask and repeatedly extracted with methanol. The extracts were then collected in a 100 ml graduated flask and diluted with methanol up to desired volume. By using appropriate amount of distilled water dilution, the solution was tested for Lansoprazole at 284 nm(23).

Angle of repose

Angle of repose is the static procedure, where it uses a funnel, to determine the Nanosponges angle of repose. The funnel was kept on a triangular platform from 2 cm height and placed on a horizontal plane. The sample powder was introduced into funnel, until the pile was formed, till the tip of the funnel. The pile's diameter was noted. The angle of repose was measured by using the formula below.

$$(\theta) = \tan^{-1}(h/r)$$

h is the height of the Nanosponges pile.

r=radius of the pile of Nanosponges

Bulk and tapped densities

Using tap density test equipment, firstly bulk density and tapped density should be calculated. Furthermore, the Hausner's ratio and the Carr's index should also calculated.

Determination of compressibility index

Carr's index

Using the formula

$$\text{Carr's Index} = (\text{tapped density} - \text{bulk density} / \text{tapped density}) \times 100$$

one can determine a powder's compressibility.

Hausner's ratio

The Hausner's ratio is a number which is correlated with the flow property. The formula is used to compute the Hausner's ratio.

$$H = \rho_T / \rho_B$$

where ρ_B is the powder's freely settled bulk density and ρ_T is the powder's tapped density(24).

EVALUATIONS OF TABLETS

Post compression

Weight differentiation tester, hardness (Pfizer hardness tester), Friability (Roche), thickness (Vernier Callipers), investigations were performed on the manufactured Nanosponges-loaded tablets in accordance with the accepted procedure (25).

Drug contents

Weigh 10 tablets carefully then powder it very finely, and triturated into a solution that contains about 10 mg of medicament. Then dissolve the solution in a buffer of PH=1.2 and 100 ml of the solution was created using the abovementioned buffer. More dilutions are also made to reach a concentration of 10 g/ml, and a UV-visible spectrophotometer was used to measure absorbance at 236 nm in comparison to a blank (26).

Invitro drug release studies of tablet:

The USP apparatus-II (Paddle type) also put together after 900ml of 0.1N HCl had been added to the vessel. The medium was given time to get equilibrium at $37\pm 0.5^\circ\text{C}$. A tablet with Nanosponge loaded in it should be placed in vessel and spun at 50 revolutions per minute. A pH 6.8 phosphate buffer media also used, then process be continued for an extra 600 minutes at 50 rpm. Five millilitres of the receptor fluid were taken out and replaced with new medium at regular intervals. Filtered, appropriately diluted, and UV spectrophotometer analysis were performed on the removed fluid(27).

CONCLUSION:

Nanosponges can effectively deliver the medicament in a controlled manner at a target site because they have the ability to enclose both hydrophilic and lipophilic drug by forming a complex. Tablets loaded with Nanosponges has less side effects, improve stability, improves solubility and increase patient compliance. Because of their small size they can be prepared into various dosage forms like parenteral, topical, capsules and aerosols etc.

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