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RESEARCH ARTICLE

DEVELOPMENT AND EVALUATION OF NANOSPONGES LOADED EXTENDED RELEASE TABLETS OF LANSOPRAZOLE

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ABSTRACT
Nanosponges are tiny sponges with an average diameter below 1µm and consist of cavities filled with drug molecules. Lansoprazole is one of the classes of proton pump inhibitors, it reduces gastric acidity, and used in disorders such as gastric ulcer, duodenal ulcer and reflux oesophagitis. In present study for extended delivery of lansoprazole at optimal concentration and to reduce the frequency of dosing and thus to increase patient convenience nanosponges loaded extended release tablets were prepared. Initially four different nanosponges formulations were prepared by solvent evaporation method and evaluated on various parameters. Ethyl cellulose was used as entrapping agent and dichloromethane as cross linking agent in various proportions and evaluated for powder flow properties, % yield, zeta potential, and *in-vitro* drug release characteristics. Based on the evaluation results, formulation NS1 was selected to prepare five extended release tablets formulations by using HPMC K30 and chitosan as extended release polymers. All five formulations were evaluated for thickness, hardness, friability, % drug content and *in-vitro* drug release. From the results, it was found that all the evaluation results are within pharmacopoeial limits. From this study, we concluded feasibility of extended release of Lansoprazole through nanosponge loaded extended release tablets. Formulation of batch NT1, containing HPMC K30 was found to be optimum formulation.
Keywords: Entrapment efficiency, ethyl cellulose, HPMC, *in-vitro* drug release, lansoprazole, nanosponges.

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INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of action in the body and also to achieve and it maintain the valuable plasma concentration of the drug for a particular period of time[1]. Nanosponge drug delivery can provide increased efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient and novel manner[2].

Nanosponges are those porous polymeric delivery systems that contain small spherical particles with large porous surface. Nanosponge is play vital role in targeting drug delivery in a controlled manner[3]. Lipophilic and hydrophilic drugs are incorporated in Nanosponge[4]. These are tiny sponges with a size of about a virus. These sponges circulate around the body until they encounter the specific target site, stick onto the surface and begin to release the drug in a controlled and predictable manner[5].

Nanosponges can be formulated as parenteral, oral, topical or inhalational dosage forms. For oral administration, Nanosponge can be easily dispersed in the matrix of excipients, diluents, lubricants and anti caking agents which is used for the preparation of tablets or capsules formulation[6].

Lansoprazole is a proton pump inhibitor; it is used in the treatment 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[7]. Lansoprazole also exhibits antibacterial activity against Helicobacter pylori. Lansoprazole comes under the BCS II classification drug which has poor aqueous solubility and bioavailability. Regular usage of lansoprazole causes various adverse effects like abdominal pain, diarrhoea, skin rashes,

thrombocytopenia, impotence etc[8]. So, controlled delivery of lansoprazole at optimal concentration may be required. Controlled release of lansoprazole will reduce the frequency of dosing and dose size and may increase patient convenience[9].

Since oral route is preferred than other routes with respect to safety, comfort and reliability.

So the aim of the present study was to develop extended release tablets of lansoprazole nanosponges to deliver at controlled rate to its absorptive site, to reduce the frequency of administration and thus to improve patient compliance.

MATERIALS AND METHODS

Lansoprazole was obtained from Abumec Pharmaceuticals Ltd, Kaduna State. Ethyl cellulose, Polyvinyl alcohol, was obtained from AC Drugs Limited, Enugu State and Dichloromethane, HPMC K30, chitosan were obtained from Afrik Pharmaceuticals Plc, Awo-Omamma. Magnesium stearate, Talc and MCC pH 102 were procured from Avro Pharma Limited, Lagos Nigeria.

Drug-excipient compatibility studies

Fourier transform infrared analysis was conducted to verify the possibility of interaction of chemical bonds between drug and polymers. Samples were scanned in the range from 400-4000 cm^{-1} and carbon black reference. The detector was purged carefully by clean dry helium gas to increase the signal level and reduce moisture[10].

Preparation of Lansoprazole nanosponges

Lansoprazole nanosponges were prepared by the emulsion solvent evaporation method by the use of different proportions of polymers and polyvinyl alcohol[11]. Ethyl cellulose was used as entrapping agent and dichloromethane as cross linking agent in various proportions. The disperse phase containing Lansoprazole as a dispersing medium and polymer in 20ml of dichloromethane was added slowly to a definite amount of Poly vinyl alcohol in100mL of aqueous continuous phase with 1000 rpm stirring speed using magnetic stirrer for 2hrs. The formed nanosponges were collected by filtration and dried in oven at 40ºC for 24hrs and packed in vials. The prepared Nanosponges formulations with three different polymers are listed in Table 1.

EVALUATION OF NANOSPONGES MICROMETRIC PROPERTIES

Angle of repose, Bulk density, Tapped density, Hausner's ratio and Carr's index were determined to assess the flow ability of the prepared nanosponges powder.

Determination of percentage yield

It was calculated accurately by using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of nanosponges[12].

$$\% \text{ yield} = \frac{\text{Practical weight of nanosponges obtained}}{\text{Theoretical weight (drug + polymers)}}$$

Determination of entrapment efficiency

Nanosponges equivalent to 100 mg of the drug were taken and then crushed into powder followed by transferred into a 100 ml volumetric flask consist of 10ml of methanol and the volume was made up with simulated gastric fluid of pH 1.2. After 24 h, the solution was filtered through Whatmann filter paper and the absorbance was measured spectrophotometrically after suitable dilutions[13].

Zeta Potential determination

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)[14].

***In-vitro* dissolution studies**

In vitro drug release was carried out by diffusion method using phosphate buffer pH 6.8 as dissolution media. Required quantity of sample (100 mg) was taken and then suspended in required media and then kept in the open ended apparatus. One end of the tube was kept open and the dialysis bag was tied (molecular weight cut off: 12–14kDa, surface area of 22.5cm^2) at the other end which was then submerged in a beaker containing 100ml of the phosphate buffer pH 7.2. Temperature of the media was kept at 37±2°C and 100 rpm speed. The samples were withdrawn at predetermined intervals and replaced by fresh medium simultaneously. Aliquots withdrawn were assayed at each time interval for the drug released at λ max of 236 nm using UV-Visible spectrophotometer[15].

Formulation of Lansoprazole nanosponges loaded extended release tablets

From the results of evaluation studies of nanosponges, the formulation NS1 was selected and Optimized for preparation of nanosponges loaded extended release tablets. Five different extended release tablets formulations were prepared with varying concentrations of polymers by direct compression method[16]. HPMC K30 and chitosan were used as polymers, talc as lubricant and magnesium stearate acts as glidant and microcrystalline cellulose was used as a directly compressible binder. Compositions of different formulations were given in Table 3.

Lansoprazole nanosponges and all other ingredients were individually passed through sieve number #60 and all the ingredients were mixed thoroughly by triturating up to 15 min followed by lubricated with talc. Finally the lubricated mixture was subjected to direct compression by using RIMEK rotary tablet punching machine.

EVALUATION OF TABLETS

Post compression studies

The manufactured nanosponges loaded tablets were subjected to weight variation, hardness (Pfizer hardness tester), thickness (vernier Calipers) and friability (Roche) studies according to the standard procedures.

Drug content

Ten tablets were weighed, finely powdered and triturate equivalent to 10 mg of the drug was

accurately weighed, dissolved in pH 1.2 buffer and volume was made up to 100 ml with the same buffer. Further dilutions were done to get concentration of 10µg/ml and absorbance was read at 236 nm against blank by UV Visible spectrophotometer[17].

***In-vitro* drug release studies of tablets**

900ml of 0.1N HCl was placed in vessel and the USP apparatus-II (Paddle Method) was assembled. The medium was allowed to equilibrate to temperature of 37±0.5°C. Nanosponge loaded tablet was placed in the vessel and operated at 50 rpm. Then the medium was replaced with pH 6.8 phosphate buffer and continued up to 10 h at 50 rpm. At definite time intervals, 5 ml of the receptor fluid was withdrawn and same volume was replaced with fresh medium. The withdrawn fluid was filtered, suitably diluted and analyzed using UV-spectrophotometer[18].

RESULTS AND DISCUSSION

The present study was aimed for developing Lansoprazole nanosponges loaded extended release tablets using various polymers and excipients. In present study four nanosponges formulations were prepared. Excipients compatibility studies were performed by FT-IR spectroscopy (Figure 1). No significant shifting of the peaks, so polymers used in the study are suitable for the development of Lansoprazole nanosponges formulations.

Percentage yield value of nanosponges was found to be the best for NS1 i.e. 97.35±0.08. It was observed that as the polymer ratio in the formulation increases, the percentage yield also increases. The low percentage yield in some formulations may be due to wastage of the drug-polymer solution.

The % drug entrapment efficiency of the nanosponges was found to be best for the formulation NS1 and it was ranged from 68.86±0.10 to 88.66±0.5 and the results indicated that the ethyl cellulose concentration is directly proportional to the entrapment efficiency but polyvinyl alcohol concentration is indirectly proportional to the entrapment efficiency which is due to the low solubility of polymer in aqueous phase (Table 2). The surface charge of nanosponges was determined by zeta potential and it was found to be in the range of 5.2-6.1mv (±30mv). The *in-vitro* drug release studies of Lansoprazole nanosponges were performed for all the 4 formulations by using USP Type-II i.e. paddle. All the formulations showed drug release for a period of 8 h (Figure 2). Among all the formulations NS1 has shown highest percentage of drug release i.e., 98.35% at the end of 8 h. From the results of evaluation parameters, formulation NS1 has shown acceptable results and hence, it was selected for further studies.

Five different Lansoprazole nanosponges loaded extended release tablets were prepared using HPMC K30 and chitosan and evaluated for flow properties and *in-vitro* drug release studies.

The powder blend was subjected to pre-compression studies and obtained results were complied with the pharmacopoeial limits (Table 4). The *in-vitro* drug dissolution studies of nanosponges loaded extended release tablets were performed by taking USP dissolution apparatus-II. In 10 hrs studies, the cumulative percentage drug release was found to be in the range of 42.58±0.09 to 74.81±0.12. Maximum release was shown by the formulations of batch NT1. This may be due hydrophilic nature of HPMC.

CONCLUSION

In present study nanosponges loaded extended release tablets of Lansoprazole showed extended drug release for about 10 h. On the basis of different parameters it is concluded that the nanosponges formulations of batch NS1 and nanosponges loaded extended release tablets of batch NT1 are the optimum formulations.

Study concluded that prolonged drug release and nanosponges loaded extended release tablets of Lansoprazole are suitable option for dose reduction, reduced frequency of administration and avoiding related systemic side effects. However further *in-vivo* study is needed for further estimation of importance of these formulations.

CONFLICT OF INTEREST

Authors have declared that no conflict of interest is linked with this work.

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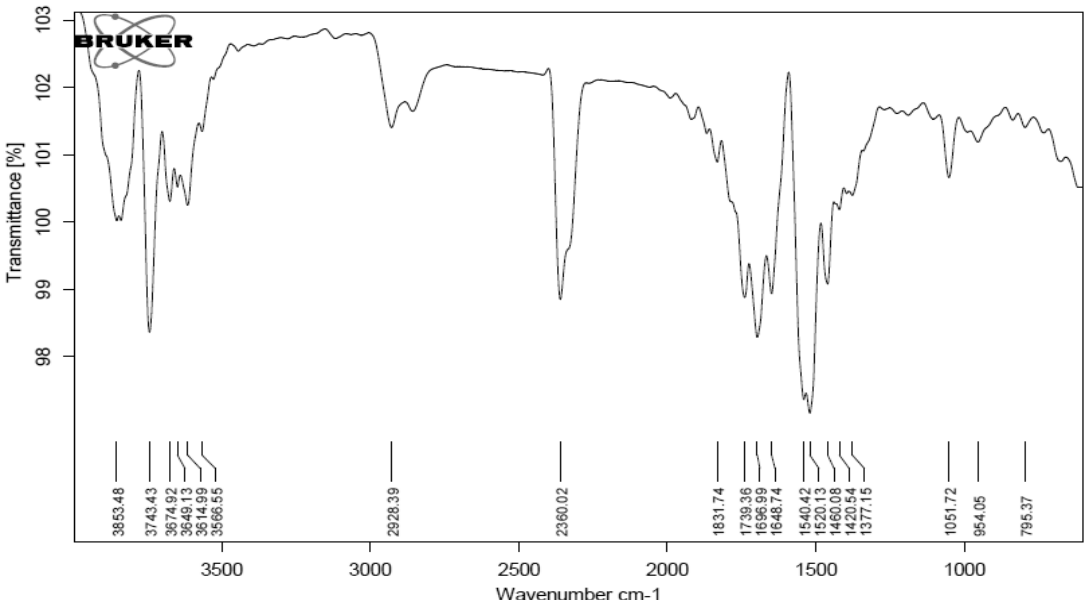

Figure 1: FTIR spectra of Lansoprazole with polymers

Table 1: Formulation of Lansoprazole nanosponges.

Batch	Lansoprazole (mg)	Ethyl cellulose (mg)	Polyvinyl alcohol (gm)	Dichloromethane (ml)	Distilled water (ml)
NS1	50	100	2	30	20
NS2	100	200	3	30	20
NS3	150	300	4	30	20
NS4	200	400	3	30	20

Table 2: Preformulation parameters of Lansoprazole nanosponges

Batch	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index	Hausner's Ratio	Angle of repose (θ)	% yield	% Drug entrapment efficiency	Zeta Potential (mV)
NS1	0.53±0.12	0.58±0.09	8.61±0.13	1.09±0.06	240.37±0.09	97.35±0.08	89.43±0.09	-6.1
NS2	0.49±0.08	0.54±0.11	9.25±0.08	1.04±0.05	245.59±0.06	81.43±0.12	86.25±0.13	-5.2
NS3	0.51±0.06	0.56±0.09	8.92±0.06	1.09±0.03	242.31±0.12	85.41±0.09	81.42±0.08	-5.6
NS4	0.55±0.04	0.60±0.06	8.33±0.14	1.08±0.04	220.43±0.31	90.37±0.06	85.43±0.05	-5.9

Table 3: Formulation of nanosponges loaded extended release tablets of Lansoprazole.

Batch	Lansoprazole Nanosponges (mg)	HPMC K30 (mg)	Chitosan (mg)	Magnesium Stearate (mg)	Talc (mg)	Microcrystalline cellulose (mg)
NT1	200	75	-	5	3	60
NT2	200	50	-	5	3	60
NT3	200	25	20	5	3	60
NT4	200	-	50	5	3	60
NT5	200	-	75	5	3	60

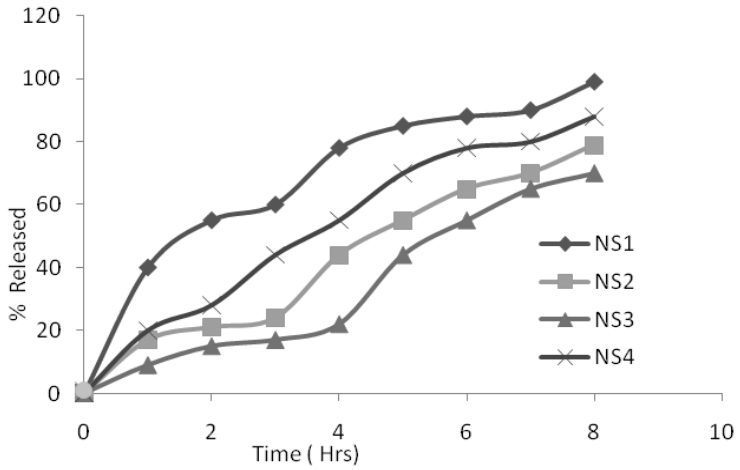

Figure 2: Dissolution profiles of nanosponges formulations

Table 4: Results of post compression parameters of nanosponges loaded extended release tablets of Lansoprazole

Batch	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability
NT1	336±0.38	4.8±0.09	3.49±0.09	0.48±0.09
NT2	318±0.45	4.7±0.12	3.28±0.11	0.33±0.12
NT3	310±0.61	4.2±0.13	3.31±0.05	0.46±0.15
NT4	318±0.28	4.9±0.25	3.48±0.18	0.42±0.08
NT5	342±0.39	4.1±0.09	3.86±0.08	0.41±0.14

Results expressed in mean (n=3) ± SD (Standard Deviation)

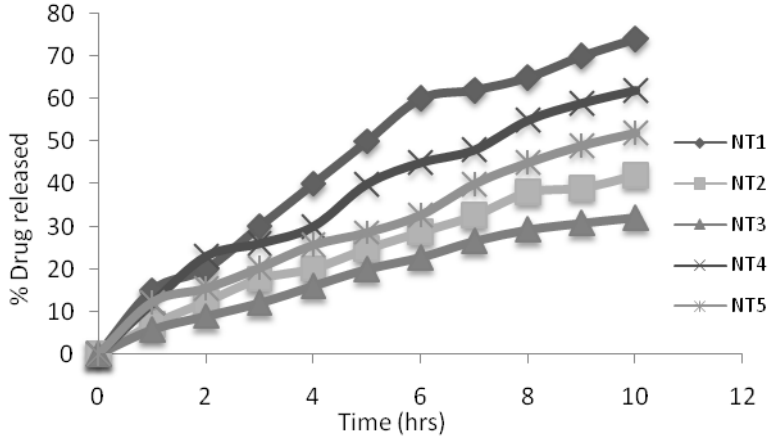

Figure 3: *In-vitro* drug release profiles of nanosponges loaded extended release tablets of Lansoprazole