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DEVELOPMENT OF OMEPRAZOLE LOADED NANOSPONGES FOR GASTRIC ULCER

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ABSTRACT

Nanosponges are tiny mesh-like nanoporous particular structure in which a large variety of substances can be encapsulated or suspended, and then be incorporated into a dosage form. They have a proven spherical colloidal nature, reported to have a very high solubilization capacity for poorly soluble drugs. Omeprazole is proton pump inhibitor which is extensively degraded in acidic pH conditions. Omeprazole loaded nanosponges for gastric ulcer were prepared by Emulsion solvent diffusion method by using ethylcellulose, PVA and pluronic F-68 and dichloromethane as a solvent. The prepared nanosponges were evaluated for percentage yield, entrapment efficiency, particle size, drug polymer compatibility, scanning electron microscopy, and *in-vitro* drug release. SEM studies confirmed their porous structure with number of nanochannels. The FTIR spectra showed stable character of omeprazole in mixture of polymers and revealed the absence of drug polymer interactions. The average particle size of omeprazole nanoparticle was found to be 83.4 to 190.69 nm. The negative zeta potential values were attained to ensure a good stability of nanosponges. The drug release from nanosponges was found to extent upto 7h. The optimized nanosponges were formulated into enteric coated tablet and evaluated for weight variation, friability, hardness, and dissolution studies. In-vitro release of drug from enteric coated tablet follows zero order and showed controlled release behavior for a period of 22 h. The data obtained in this study suggests that nanosponges of omeprazole are promising for controlled drug delivery. This can reduce the dosing frequency.

KEYWORDS: Controlled drug delivery, Nanosponges, Omeprazole, dissolution.

INTRODUCTION

Drug delivery technology definitely has a new interest in drugs by giving them new life through its therapeutic goals. Targeting the distribution of drug is the major problem that the researchers face. Target-oriented drug improvements in therapeutic efficacy, reduction in side effects, and improved dosing regimen are the leading therapeutic patterns. Targeted drug delivery means the precise and efficient localization of pharmacologically motherhood at a pre-identified (preselected) target in therapeutic concentration, thus limiting access to non-target normal cell linings, thereby minimizing toxic effects and optimizing the drugs therapeutic index. They have excellent topical drug delivery. These include nanotechnology that is applied as nano-materials to medicine, diagnosing and targeting the right place in the body, and regulating drug release.[1-3]

Nanosponges are tiny mesh-like nanoporous particular structure in which a large variety of substances can be encapsulated or suspended, and then be incorporated into a dosage form. They have a proven spherical colloidal nature, reported to have a very high solubilization capacity for poorly soluble drugs by their inclusion and non-inclusion behavior. Nanosponges have recently been developed and proposed for drug delivery. Nanosponges can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability. Nanosponges are able to load both hydrophilic and hydrophobic drug molecules because of their inner hydrophobic cavities and external hydrophilic branching, thereby offering unparalleled flexibility. Nanosponges are more like a three-diamontional network or scaffold. The backbone is long length polyester which is mixed in solution with small molecules called crosslinkers that act like tiny grappling hooks to fasten different parts of the polymer together. The nano sponges 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 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 in to topical hydro gel.[3-5]

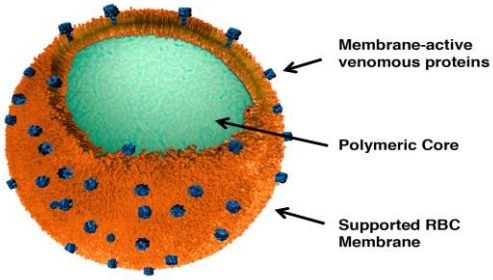

Fig 1: Structure of nanosponges.

A group called proton pump inhibitor is a class of drug whose main therapeutic effect is reduction effect is reduction of production of gastric juice in the stomach. These active substances are used in the treatment of much such disease such as zollinger-Ellison syndrome, gastroesophageal reflux disease, laryngopharyngeal reflux disease, Dispepsia. The class called proton pump inhibitors acts by irreversible blockage of Hydrogen/Potassium ATPase these proton pump inhibitor bind to these ATPase at the final stage and hampers the gastric acid secretion.[6-8] Oral route is preferable than other routes with respect to safety, comfort and reliability. Hence controlled delivery of omeprazole by oral route is ideal. Controlled release of omeprazole will reduce the frequency of dosing and dose size and may increase in patient convenience. The irritant effect of proton pump inhibitor such as omeprazole, esomeprazole, pantoprazole, etc have an irritant effect in the gastric environment and unstable at the gastric P^H. Due to these reason enteric coating is require to such active content to provide its proper therapeutic effect and its pharmacological action.[9- 12]

The present study is aimed at formulate enteric coated tablet of omeprazole nanosponges to protect it from acidic environment and delivery at controlled rate to its absorption site so that its oral bioavailability can be enhanced.

MATERIAL AND METHODS

Omeprazole, Ethyl cellulose, Polyvinyl alcohol and Pluronic F68, Microcrystalline cellulose, Magnesium stearate.

Methodology

Preparation of omeprazole nanosponges [13-14]

Omeprazole nanosponges were prepared by different proportion of ethyl cellulose, polyvinyl alcohol, pluronic F68 by emulsion solvent diffusion method. The disperse phase consisting of 100 mg omeprazole and specified quantity of ethyl cellulose (Table 1) dissolved in 30ml 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 omeprazole nanosponges were collected by vacuum filtration and dried in an oven at 40°C for 24 h.

Entrapment efficiency[15]

UV spectrophotometric method was used to estimate entrapment efficiency of omeprazole nanosponges. A calibration curve was plotted for omeprazole in methanolic HCl in the range of 3-18 µg/mL (Beer's Lambert's range) at 302 nm. A good linear relationship was observed between the concentration of lansoprazole and its absorbance (r^2=0.9993, m=0.0469, n=3). 100 mg of omeprazole nanosponges of each batch were selected, powdered in a mortar and placed in 100 mL of methanolic HCl. omeprazole 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

The average particle size of omeprazole nanosponges were determined by photon correlation spectroscopy (PCS) using a Nano ZS-90 (Malvern Instruments limited, UK) at a fixed angle at 25°C. Sample was diluted 10 times with distilled water and then it was analyzed for particle size.[15]

Zeta Potential

Zeta sizer can be used to measure zeta potential, which is the measure of surface charge of nanosponges. In the present work, the nanosponges was diluted to 10 times with distilled water and analyzed by zetasizer using laser Doppler micro electrophoresis. More than 30mv zeta potential value in water indicates good stability of nanospoges.[15]

Particle shape and morphology

The shape and morphology of nanosponges was examined using Scanning Electron Microscopy (LEO 440I).

Preparation of omeprazole 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 'Karnavathi' 10 station rotary compression machine.

Preparation of Enteric coating of Omeprazole Tablet

Enteric coating of 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 sectional 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.

Fourier transform infrared spectroscopy studies

The drug-polymer and polymer-polymer interactions were studied by FTIR spectrometer, Jasco-FTIR-4100 using the KBr disk method. The FTIR spectra was recorded over the wavelength range of 400-4000 cm^{-1} using FTIR spectrometer. FTIR spectral analysis of pure drug and polymers was carried out individually and also in combination, observation was made whether changes in the chemical constitution of drug after combining it with the polymers occurred.

Table 1: Formulation of Omeprazole nanosponges.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Omeprazole (mg)	100	100	100	100	100	100
Polyvinyl alcohol (mg)	600	800	900	1000	1100	1200
Ethyl cellulose (mg)	400	600	800	1000	800	600
Pluronic F68 (mg)	200	200	200	200	200	200
Dichloromethane (ml)	30	30	30	30	30	30
Distilled water to (ml)	100	100	100	100	100	100

Table 2: Formulation of omeprazole tablet.

Ingredient	Quantity (mg)
Nanosponges	25 (equivalent to 20 mg of omeprazole)
Microcrystalline cellulose	66
Magnesium stearate	9

Evaluation of omeprazole tablets[16-20]

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 caliper (Pico India).

Hardness

Twenty tablets were randomly selected from each formulation and measured hardness in kg/cm2 using Monsanto type hardness tester.

Friability

The friability of tablets was determined by using Dolphin Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100$$

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 omeprazole from fine powder then transfer in 100 mL volumetric flask, 100 mL of methanolic HCL was added to dissolve and sonicated for 20 minutes. omeprazole was extracted by centrifuging at 1000 rpm for 30 min. the samples were filtered, diluted and analyzed UV spectrophotometrically at 302 nm.

***In-vitro* dissolution study of preliminary formulation**

The *In-vitro* dissolution test was carried out using USP apparatus-II at 100 rpm using 900ml of pH 6.8 phosphate buffer maintained at 37±0.5°C as the dissolution medium. Six tablets were introduced into the apparatus. 5 ml sample were withdrawn at predetermined time intervals and same volume of fresh medium was replaced into the basket to maintain sink condition. The sample were filtered, diluted and analyzed UV spectrophotometrically at 302 nm .The percent of drug released at various time intervals was calculated and plotted against time.

***In vitro* dissolution study of enteric coated tablet**

The *in vitro* dissolution test was carried out using USP apparatus-II at 100 rpm. To reproduce the digestive physiological phase, dissolution medium, (900ml) with different pH environment at 37°C was used . six tablet were introduced into the apparatus and the apparatus was run dor 2 hr in 0.5 N methanolic HCl. 5ml sample were withdrawn at predetermined time intervals and the same volume of fresh medium was replaced into the basket to maintain sink condition.the sample were filtered, diluted and analyzed UV spectrophotometrically at 302 nm. After 2h the dissolution medium with the 0.5 N methanolic HCl relaced with pH 6.8 phosphate buffer and continued for upto 24 hr. 5 ml sample withdrawn at regular intervals and the same volume of fresh medium was replaced to maintain the sink condition. The sample were filtered, diluted and analyzed UV spectrophotometrically at 302 nm. The percent of drug released at various time intervals was calculated and plotted against time.

Table 3: Evaluation parameters of omeprazole nanosponges.

Formulation	Percentage yield	Entrapment efficiency	Particle size (nm)	Zeta potential (-mv)
F1	38.35±1.27	50.71±0.73	190.69	-15.5
F2	52.57±1.09	86.93±0.65	83.40	-14.2
F3	34.68±1.17	79.57±1.01	103.26	-16.7
F4	30.32±0.98	78.04±1.62	114.91	-14.5
F5	35.32±2.20	70.31±0.94	135.33	-15.1
F6	24.80±1.73	69.47±1.20	173.27	-14.2

Table 4: Evaluation of Nanosponge loaded Omeprazole tablets.

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	98±0.31	3.17±0.13	2.66±0.28	0.886	96.93±1.16
F2	100±0.61	3.23±0.11	2.25±0.20	0.752	99.47±1.81
F3	99±0.23	3.08±0.16	2.71±0.14	0.890	95.18±1.43
F4	98±0.47	3.11±0.09	2.82±0.10	0.821	94.97±1.97
F5	99±0.48	3.27±0.21	3.54±0.21	0.812	92.01±2.13
F6	100±0.32	3.14±0.12	3.03±0.06	0.778	95.43±1.73

Omeprazole loaded nanosponges

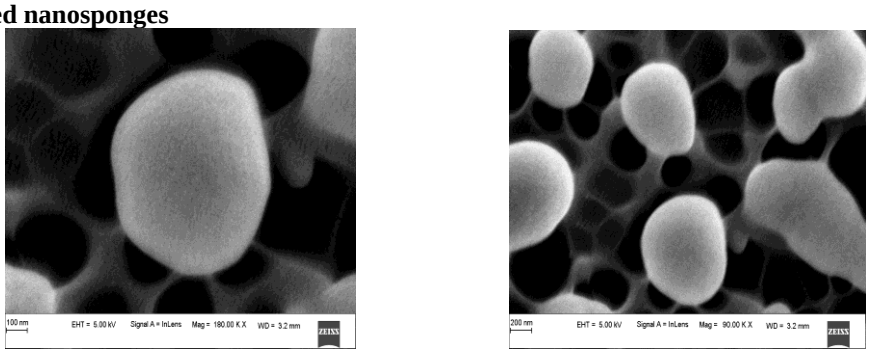

Fig 4: Scanninng electron micrograph of omeprazole nanosponges (F2)

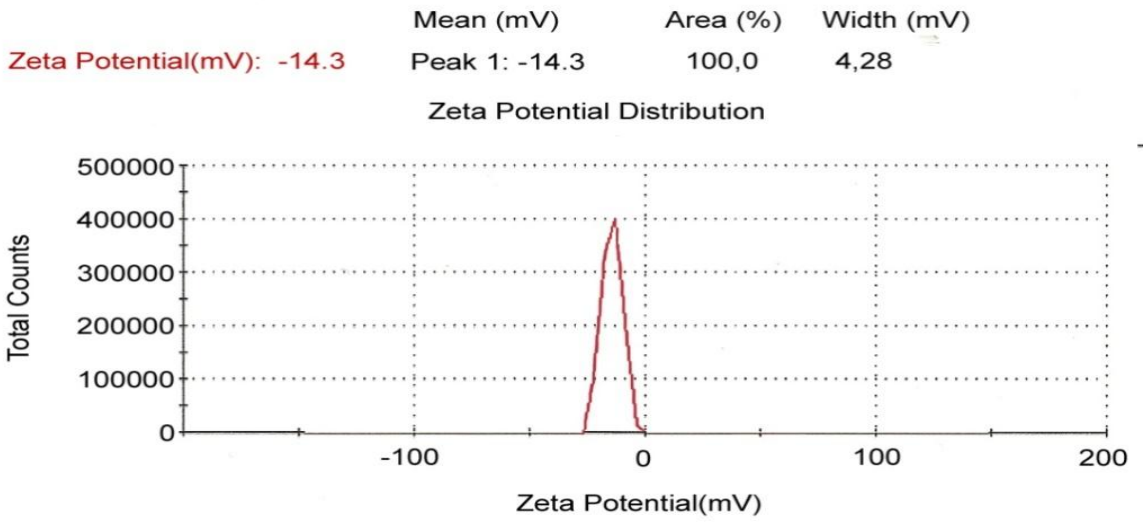

Fig 5: Zeta potential of Omeprazole nanosponges (F2).

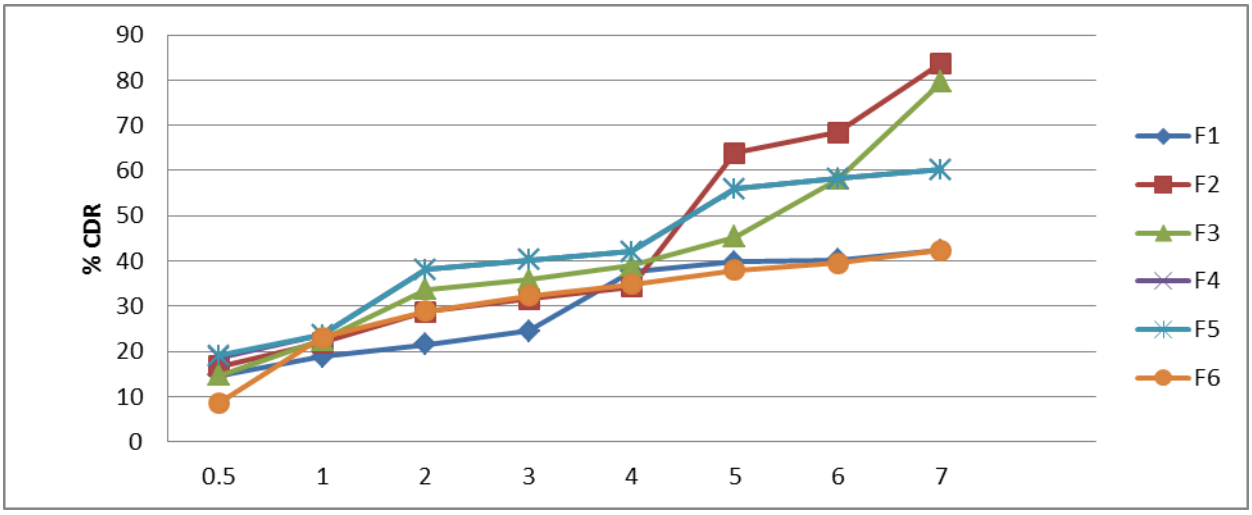

Fig. 6: *in-vitro* dissolution study of preliminary formulation.

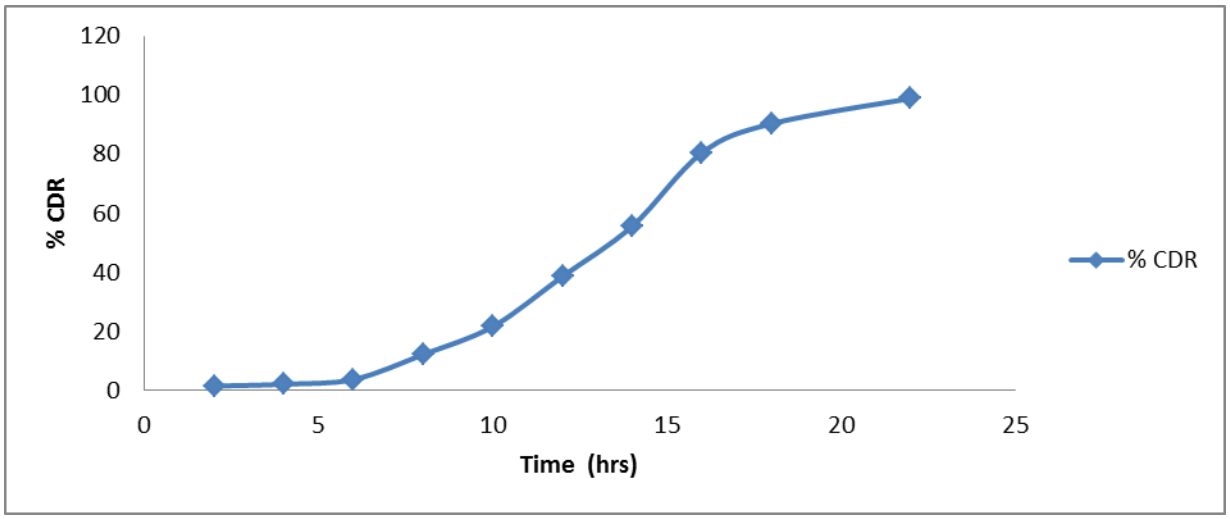

Fig. 6: *in-vitro* dissolution study of enteric coated tablet.

RESULTS AND DISCUSSION

Drug and polymers were subjected for the compatibility study using FTIR spectroscopy, which suggested that there is no interaction between the drug and polymer. Maximum wavelength (λ_{max}) was determined by using UV spectrophotometer by using methanolic HCl (0.5 N) as medium. Maximum absorbance was found at 302nm. Standard calibration curve was constructed in the concentration range of 0-25 µg/ml using 0.5N methanolic HCl as a medium and obtained slope of 0.999. Six batches of preliminary formulations are designed and the tablets were prepared by direct compression technique.

All six formulations are subjected to pre compressional like bulk density, tapped density, angle of repose and Carr's index. Bulk density of all six formulations ranges from 0.38±0.0.02 to 0.42±0.11gm/cc. Tapped density of all six formulations ranges from 0.45±0.02 to 0.48±0.41 gm/cc. It is within the acceptable limit. Angle of repose value of all formulations ranges from $26^0$43'±0.14 to $29^0$38'±0.32. The result of the Carr's consolidation index of all the formulations ranges from 12.54±0.10 to 13.22±0.15%. Results clearly showed that the flowability of all the formulations was good and also the powders had good compressibility. Evaluation on post compressional parameters, like hardness, friability, thickness, weight variation, percentage drug content conducted. The hardness value ranges from 2.25±0.2 to 3.54±0.21 kg/cm^2. The percentage friability ranges from 0.752 to 0.886% The percentage friability for all the formulations was below 1% indicating that the friability was within the prescribed limits the results of friability test indicates that the tablet possesses good mechanical strength. Weight variation value of all formulations ranges from 98±0.31% to 100±0.61%. All the tablets were passed weight variation test as the average weight variation was within the pharmacopoeial limit ±5%. Thickness of all formulations ranges from 3.08±0.16 mm to 3.27±0.21 mm. Percentage drug content of Omeprazole in all the formulated tablets were found within the range 92.01±2.13 to 99.47±1.81% indicate uniform mixing.

In-vitro dissolution studies are conducted using USP XXIII dissolution apparatus using 6.8 pH phosphate

buffers as dissolution medium. Dissolution profile of preliminary formulations i.e percentage cumulative drug release at 7 hrs of all formulations ranges from 14.69% to 83.76%.

The *In-vitro* drug release data of the optimized formulation were subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer Peppa's models in order to determine the mechanism of drug release. It is notable that the 'r' values of the linear regression for Higuchi's plot were found to be in range of 0.97 to 0.99 indicating that the data fits the Higuchi's model well and the drug release was found to be predominantly controlled by diffusion process. The slopes (n) values of Korsmeyer's Peppa's equation were found to be > 0.45 and < 0.89 indicating the drug release is governed by non-fickian diffusion mechanism.

CONCLUSION

In the present study was an attempt to develop enteric coated tablet of omeprazole nanosponges to protect it from acidic environment and delivery at controlled rate to its absorption site so that its oral bioavailability can be enhanced. Oral route is preferable than other routes with respect to safety, comfort and reliability. Hence controlled delivery of omeprazole by oral route is ideal. Controlled release of omeprazole will reduce the frequency of dosing and dose size and may increase in patient convenience.

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