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DEVELOPMENT AND CHARACTERIZATION OF ESOMEPRAZOLE LOADED NANOSPONGES FOR TREATMENT OF GASTRIC ULCER

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Abstract:
Ulcers are sores or eroded areas that form in the lining of the digestive (gastrointestinal) tract. They usually occur in the stomach (gastric ulcer) or in the duodenum (duodenal ulcer). Proton pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion available, and they are effective for treating all acid-related disorders Esomeprazole is indicated for the treatment of gastroesophageal reflux disease in adults and children, risk reduction of NSAIDs-associated gastric ulcer, Helicobacter pylori eradication and control of pathological hypersecretory conditions associated with Zollinger–Ellison syndrome. Nowadays, targeting drug delivery is the major problem which is being faced by the researchers. Target oriented drug administration with improvements in therapeutic efficacy, reduction in side effects and optimized dosing regimen, shall be the leading trends in the area of therapeutics. Nanosponges are a new class of materials and made of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules. The aim of this study is to formulate & evaluate nanosponge loaded with Esomeprazole. The nanosponge was prepared by standard methods & evaluated for various parameters.
The result showed that the bulk density and the tapped density for all the formulations varied from 0.345 to 0.385gm/cm^3 and 0.458 to 0.492gm/cm^3 respectively. The result of Hausner's ratio of all formulations ranges from 1.278 to 1.328. Compressibility index of all the formulations ranges from 21.75% to 24.67%. The kinetics study revealed that formulations was found to follow Zero order of drug release kinetics. The actual drug content of prepared nanosponge's formulation F1, F2, F3, F4, F5 and F6 was found to be 94.45±0.32, 92.23±0.25, 97.74±0.15, 99.45±0.26, 98.85±0.36 and 92.23±0.14 respectively. The maximum drug content was found in formulation F3 (99.45±0.26). The Encapsulation efficiency of formulation F1, F2, F3, F4, F5, and F6 was found 74.56±0.22, 73.36±0.25, 85.45±0.36, 78.85±0.14, 82.23±0.25 and 81.14±0.35. The maximum encapsulation efficiency was also found maximum in formulation F3 (85.45±0.36). It can be concluded that F3 nanosponge of Esomeprazole can be used for treating gastric ulcer as it exhibits all ideal characteristics.

Keywords: *Nanosponge, Gastric ulcer, Esomeprazole, Targeted drug delivery*

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INTRODUCTION:

Ulcers are sores or eroded areas that form in the lining of the digestive (gastrointestinal) tract. They usually occur in the stomach (gastric ulcer) or in the duodenum (duodenal ulcer). The stomach and duodenal lining have several mechanisms that help prevent ulcers from developing, like coating of mucus (mucous layer) protects the stomach lining from the effects of acidic digestive juices, Food and other substances in the stomach neutralize acid and Certain chemicals produced by the stomach protect the cells lining the stomach. If the mucous layer is damaged or if acid neutralizing substances are not present in normal amounts, digestive juices can cause irritation and breakdown of the stomach or duodenal lining this further causes many disorders related to digestion [1,2].

Proton pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion available, and they are effective for treating all acid-related disorders. Esomeprazole is one of several most recent PPIs that became available to the market in 2001. Esomeprazole is indicated for the treatment of gastroesophageal reflux disease in adults and children, risk reduction of NSAIDs-associated gastric ulcer, *Helicobacter pylori* eradication and control of pathological hypersecretory conditions associated with Zollinger–Ellison syndrome. Esomeprazole is available in both oral and intravenous formulations [3].

Nowadays, targeting drug delivery is the major problem which is being faced by the researchers. Target oriented drug administration with improvements in therapeutic efficacy, reduction 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 preidentified 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 [4,5].

Nanosponges are a new class of materials and made of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules. 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 crosslinker to polymer. The main limitation of nanosponges is their ability to include only small molecule. 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 capsules or tablets are reduction of total dose, retention of dosage form, reduction in toxicity and improving patient compliance by prolonged release. For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solution. For topical administration, they can be effectively incorporated into topical hydrogel [6-10]. This study deals with formulation & evaluation of Nanosponge loaded with Esomeprazole for its effective role in treating gastric ulcer.

MATERIAL AND METHODS:

Materials:

Esomeprazole was obtained as gift sample from Pharmaceutical Company. Eudragit S-100, dibutyl phthalate, dichloromethane, methanol were provided by Scan research laboratories Bhopal.

Methods:

Preparation of Nanosponges:

The nano-sponges containing Esomeprazole were formulated by a method called the quasi-emulsion solvent diffusion [10]. The accurately weighed amount of polymethyl-methacrylate (PMMA), Eudragit S-100 in different ratios with dibutyl phthalate (1% w/v) was dissolved in 10 mL of dichloromethane: methanol (50:50). Dibutyl phthalate was incorporated to increase the polymer plasticity. Esomeprazole was dissolved in this mixture. At the next, 0.5-1.5% w/v solution with distilled water was prepared as dispersing media. The previously prepared solution of polymers and drug was added gradually in PVA solution and stirring was kept constant for 2 hours. After complete evaporation of solvent from polymer droplets, nano-sponges were formed, which were centrifuged at 4000 rpm for collection and followed by 3 times washing. The solvent was slowly removed to form the nano-sponges. The aqueous suspension of nano-sponges

was lyophilized and stored in a tightly sealed container until further analysis.

Table 1: Composition of nanosponges formulations

Components	Formulation code/amount					
	F1	F2	F3	F4	F5	F6
Esomeprazole (mg)	40	40	40	40	40	40
Eudragit S-100 (mg)	10	20	30	10	20	30
PMMA (mg)	10	10	10	20	20	20
PVA (%)	0.5	1.0	1.5	0.5	1.0	1.5
Dibutyl phthalate (%)	1	1	1	1	1	1
Dichloromethane: methanol (50:50) (ml)	10	10	10	10	10	10
Distilled water	20	20	20	20	20	20

Characterization of nanosponges:

Carr's Index and Hausners ratio:

Tapped density was calculated by placing 5 gm of the nanosponges in a graduated cylinder tapping it for 100 times. Poured density was calculated by placing 5 gm of nanosponges into a graduated cylinder and measuring the volume [11].

Determination of production yield:

The production yield of the nanosponges was determined by calculating the initial weight of the raw materials and the final weight of the nanosponges obtained [12]. All the experiments were performed in triplicate and the mean of the each value was reported.

Actual drug content and encapsulation efficiency:

The weighed amount of drug loaded nanosponges (100 mg) was suspended in 100 ml 7.2 pH Phosphate Buffer and subjected to intermittent stirring [13]. The sample was filtered using 0.45_m membrane filter and analyzed at 282.0 nm against blank using UV spectrophotometer (Labindia, 3000+). All analyses were carried out in triplicate.

Surface charge and vesicle size:

The Particle size and size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (SAIF RGPV Bhopal, Malvern Zetamaster, ZEM 5002, Malvern, UK). Zeta potential measurement of the nanosponges was located on the zeta potential that was determined according to Helmholtz–Smoluchowsky from their electrophoretic mobility. For measurement of zeta potential, a zetasizer was used with field strength of 20 V/cm on a large bore measures cell [14,15]. Samples were diluted with 0.9% NaCl adjusted to a conductivity of 50 lS/cm.

***In-vitro* release studies:**

***In vitro* drug release in gastrointestinal fluids of different pH:**

The prepared nanoparticles were evaluated for *in vitro* drug release. The drug release studies were carried out using USP I Basket type dissolution test apparatus [16-18]. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 100 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows:

- *1st hour:* Simulated gastric fluid (SGF) of pH 1.2.
- *2nd and 3rd hour:* Mixture of simulated gastric and Intestinal fluid of pH 4.5.
- *4th to 5th hour:* Simulated intestinal fluid (SIF) of pH 6.8.
- *6th hour and onward:* SIF pH 7.2

A weighed quantity of formulation (equivalent to 30mg) was filled in capsule and kept in basket of dissolution apparatus with dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 5ml by media. The

samples withdrawn were assayed spectrophotometrically at 282.0 nm for percent of release Esomeprazole using UV visible spectrophotometer. The release of Esomeprazole was calculated with the help of Standard curve of Esomeprazole.

Drug release kinetic data analysis:
Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time).

Shape and Surface Characterization of Nanoparticless by Scanning Electron Microscopy (SEM):
From the formulated batches of nanoparticles, formulations (F3) which showed an appropriate balance between the percentage drug releases was examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator [19]. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

Stability Studies:
Stability studies were carried out with optimized formulation which was stored for a period of 45 days at 4±1°C, RT and 40±1°C. The particle size of formulation was determined by optical microscopy using a calibrated ocular micrometer. The vesicle size of the nanosponges was found to increase at RT, which may be attributed to the aggregation of nanosponges at higher temp. At 452°C the aggregate i.e. these nanosponges were unstable at higher temp like 452°C. Percent efficiency of nanosponges also decreases at higher temp like 452°C.

RESULTS & DISCUSSION:

The bulk density and the tapped density for all the formulations varied from 0.345 to 0.385gm/cm^3 and 0.458 to 0.492gm/cm^3 respectively.The values obtained lies within the acceptable range. The difference exists between the bulk density and tapped density found to be very few. This result helps in calculating the % compressibility of the powder.

The result of Hausner's ratio of all formulations ranges from 1.278 to 1.328. The results of the Compressibility index of all the formulations ranges from 21.75% to 24.67%. Results clearly showed that the flow ability of all the formulations was good and also the powder had good compressibility.

The actual drug content of prepared nanosponge's formulation F1, F2, F3, F4, F5 and F6 was found to be 94.45±0.32, 92.23±0.25, 97.74±0.15, 99.45±0.26, 98.85±0.36 and 92.23±0.14 respectively. The maximum drug content was found in formulation F3 (99.45±0.26). The Encapsulation efficiency of formulation F1, F2, F3, F4, F5, and F6 was found 74.56±0.22, 73.36±0.25, 85.45±0.36, 78.85±0.14, 82.23±0.25 and 81.14±0.35. The maximum encapsulation efficiency was also found maximum in formulation F3 (85.45±0.36).

The surface charge of optimized formulation of nanosponges F-3 was found -36.85and average particle size was found 105.56. The *in vitro* drug release data of the formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of formulation was maximum i.e 0.988 hence indicating drug release from formulations was found to follow Zero order of drug release kinetics. Maximum drug release from optimized formulation (F3) after 12 hrs.

Table 2: Characterization of nanosponges

Formulation Code	Evaluation parameters			
	Poured Density (gm/cm^3)	**Tapped Density (gm/cm^3)**	**Carr's Index (%)**	**Hausners Ratio**
F1	0.345	0.458	24.67	1.328
F2	0.365	0.472	22.67	1.293
F3	0.374	0.482	22.41	1.289
F4	0.365	0.475	23.16	1.301
F5	0.385	0.492	21.75	1.278
F6	0.375	0.483	22.36	1.288

Actual drug content and encapsulation efficiency:

Table 3: Result of actual drug content and encapsulation efficiency

Formulation code	Actual drug content (%)	Encapsulation efficiency (%)
F1	94.45±0.32	74.56±0.22
F2	92.23±0.25	73.36±0.25
F3	97.74±0.15	85.45±0.36
F4	99.45±0.26	78.85±0.14
F5	98.85±0.36	82.23±0.25
F6	92.23±0.14	81.14±0.35

Table 4: Characterization of Optimized formulation of nanosponges

Characterization	Average Particle size (nm)	% Encapsulation efficiency	Zeta Potential (mV)
F-3	105.56	85.45±0.36	-36.85

Table 5: Cumulative % drug release of Esomeprazole nanosponges at different pH

S. No.	**Dissolution medium**	**Time (hrs)**	**% Cumulative drug Release**
1	SGF (pH 1.2)	1	10.25
2		2	20.23
3	SIF (pH 7.2)	3	28.89
4		4	36.65
5		5	42.25
6		6	55.85
7		7	68.78
8		8	72.23
9		9	82.23
10		10	89.98
11		12	98.78

Table 6: *In vitro* drug release data for coated formulation

S. No.	Time (H)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.000	0.000	10.25	1.011	89.75	1.953
2	2	1.414	0.151	20.23	1.306	79.77	1.902
3	3	1.732	0.239	28.89	1.461	71.11	1.852
4	4	2.000	0.301	36.65	1.564	63.35	1.802
5	5	2.236	0.349	42.25	1.626	57.75	1.762
6	6	2.449	0.389	55.85	1.747	44.15	1.645
7	7	2.646	0.423	68.78	1.837	31.22	1.494
8	8	2.828	0.452	72.23	1.859	27.77	1.444
9	9	3.000	0.477	82.23	1.915	17.77	1.250
10	10	3.162	0.500	89.98	1.954	10.02	1.001
11	12	3.464	0.540	98.78	1.995	1.22	0.086

Table 7: Regression analysis data of nanosponges formulation

Formulation	Zero order	First order	Pappas plot
F3	$R^2 = 0.988$	$R^2 = 0.813$	$R^2 = 0.995$

Scanning electron microscopy image

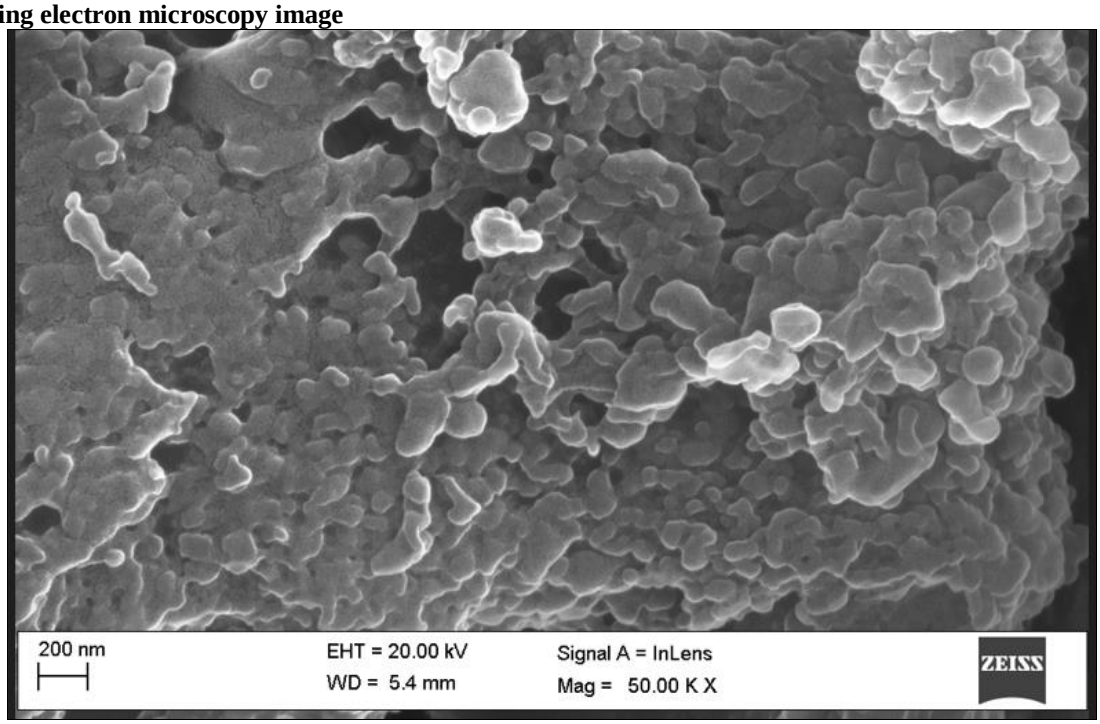

Figure 1: Scanning Electronic Microscopy of optimized formulation (F3)

Stability Studies:

Stability studies were carried out with optimized formulation which was stored for a period of 45 days at 4±1°C, RT and 40±1°C. The particle size of formulation was determined by optical microscopy using a calibrated ocular micrometer. The vesicle size of the nanosponges was found to increase at RT, which may be attributed to the aggregation of nanosponges at higher temp. At 45±2°C the aggregate i.e. these nanosponges were unstable at higher temp, like 45±2°C. Percent efficiency of nanosponges also decrease at higher temp, like 45±2°C.

CONCLUSION:

Nano-sponges based Esomeprazole system was developed successfully by using a quasi-emulsion solvent diffusion method for prolonged transport of drugs for an extended period to decrease application frequency allied to the standard marketed formulation and to enhance bioavailability and safety. The analytical characterization showed good purity of the drug. *In vitro* drug release showed a good release profile of prepared optimized-sponges formulation.

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