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FORMULATION AND CHARACTERIZATION OF GASTRORETENTIVE NANOSPONGES OF DEXLANSOPRAZOLE

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ABSTRACT

Gastro-oesophageal reflux disease is a common disorder characterised by the reflux of stomach contents into the oesophagus, resulting in unpleasant symptoms and problems. The prevalence of this illness is rising, and this rise has been connected to population ageing and the global obesity crisis. Numerous efforts have been made over the last three decades to develop a dose form that can be kept in the upper part of the GIT which will increase the bioavailibilty of anti-ulcer medication. Thus this study aims at formulation and characterization of gastroretentive nanosponges of dexlansoprazole. The Nnosponges were prepared by emulsion solvent diffusion technique & evaluated for various parameters. Results revealed that the maximum percentage yield was noticed to be 80.32±0.22 in F3 formulation. Further, the highest entrapment efficiency was observed in F3 formulation which is 74.45±0.45%. The results of measurement of mean particle size & zeta potential of optimized formulation F3 nanosponges were found 136.65 nm & -35.65 mV respectively. Also, it was observed that upto 97.74% drug release was achieved in nansponge within 12 hours. The plain drug release was noticed to be 48.87% in 2 hours. Thus this results showed that nanosponge have sustained release drug delivery over conventional formualtions. From regression analysis data it was clear that nanosponge follow first order kinetics with R^2 value of 0.982. The stability study of optimized formulation of nanosponges F3 was performed for duration of 3 months. The % EE for at 4.0 ±0. 2°C was observed to be 72.14±0.36 with normal physical appearance within 3 months. Thus it can be interpreted that formulated nanosponges of dexlansoprazole possess all ideal parameters & can be used for treatment of GERD.

Keywords: Gastro-oesophageal reflux disease (GERD), Nanosponges, Dexlansoprazole, Gastro retentive drug delivery (GRDD)

INTRODUCTION

GERD is defined as a "condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications." The most frequent symptom of GERD is heartburn, which is believed to affect 7% of the US population on a daily basis. Between 20 and 40% of people who experience frequent heartburn are likely to have GERD. GERD symptoms include heartburn, regurgitation, and difficulty swallowing. Non-erosive esophageal reflux disease (NERD) and the other pathologies that result when GERD progresses, such as esophageal ulcer, esophageal stricture,

Barrett's oesophagus, and Barrett's carcinoma (esophageal adenocarcinoma), are also subcategories of diagnosis (Kahrilas, 1996; Savarino *et al.,* 2017).

GERD is associated with several risk factors, including Nonsteroidal Anti-inflammatory Drugs (NSAIDs), type of food, beverages, smoking, family history, high body mass index (BMI), physical activity, salt, or consuming pickles with meals and fast food, which are more associated with the patient's lifestyle. It has also been demonstrated that age, gender, pregnancy, and geographical variance are all associated with GERD. Furthermore, it has been proposed that vertebral fractures and/or spinal malalignment may influence the occurrence of GERD. According to Iranian studies, NASID and pickle eating, as well as smoking, are more dangerous factors (Ness-Jensen *et al.,* 2016).

According to a systematic analysis of longitudinal research, the prevalence of GERD has grown in recent decades. If this trend continues, major GERD problems may become more common, patients' quality of life may suffer, and health-care costs would rise. Increasing GERD awareness may be crucial to enhance Iranian people's health. Much information in Western cultures can be generalised to an Iranian person but cannot perfectly match. Understanding the epidemiological effects of GERD in Iranian society might thus assist healthcare practitioners and policymakers in developing a list of disease management goals (Kinoshita *et al.,* 2011).

Numerous efforts have been made over the last three decades to develop a dose form that can be kept in the upper part of the GIT. Scientists design gastro retentive dosage forms (GRDF) after multiple attempts, which have the potential to retain in the stomach for a longer period of time and produce the best therapeutic benefits against peptic ulcer (Kavitt *et al.,* 2019).

Nanosponge is a novel kind of material composed of microscopic particles with new few nanometres broad cavities into which a wide range of compounds can be enclosed. These particles may transport both lipophilic and hydrophilic compounds and improve the solubility of poorly water-soluble molecules. Nano sponges are microscopic mesh-like structures that may revolutionise the treatment of numerous diseases. Early trials indicate that this technology is up to five times more successful than current methods at delivering drugs for breast cancer. These are solids in nature and can be administered orally, parenterally, topically, or inhalationally. For oral delivery, nanosponges can be disseminated in a matrix of excipients, dilutes, lubricants, and anti-caking agents suited for tablet or capsule production. Nanosponges can dramatically minimise medication irritability while maintaining efficacy (Mishra and Jain, 2021; Vishwakarma et al; 2014).

Dexlansoprazole is a proton pump inhibitor (PPI) of newer generation used to treat symptoms of gastroesophageal reflux disease (GERD) and erosive esophagitis. Dexlansoprazole is a proton pump inhibitor (PPI) that belongs to the antisecretory medication class. It prevents stomach acid secretion by specifically inhibiting (H+, K+)-ATPase at the secretory surface of parietal cells on the gastrointestinal mucosa. The unusual pharmacokinetics of dexlansoprazole address the disadvantages of older generation

PPIs such as short plasma half-life, breakthrough symptoms, and the need for meal-associated dosage. Dexlansoprazole is an excellent choice for persons who struggle with adherence and strict medication scheduling before meals (Behm and Peura, 2011; Vakily *et al.,* 2019). Thus this study aims at formulation and characterization of gastroretentive nanosponges of dexlansoprazole.

MATERIALS AND METHODS

Chemicals & Reagents

Polyvinyl alcohol, Eudragit S-100, Pluronic F68, Dichloromethane, Distilled water (ml) were obtained from S.D. Fine chemicals, Mumbai. All chemicals & reagent used were of standard laboratory grade.

Formulation Development of Nanosponges

Dexlansoprazole nanosponges were prepared by different proportions of Eudragit S-100, polyvinyl alcohol and Pluronic F68 by emulsion solvent diffusion technique (Singh, 2021). The disperse phase consisting of 100 mg Dexlansoprazole and specified quantity of Eudragit S-100 (Table 1) dissolved in 30 mL 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 Dexlansoprazole nanosponges were collected by vacuum filtration and dried in an oven at 40ºC for 24 hrs.

Table 1: Composition of Dexlansoprazole nanosponges

Ingredients	F1	F2	F3	F4	F5	F6
Dexlansoprazole (mg)	60	60	60	60	60	60
Polyvinyl alcohol (mg)	200	300	400	500	600	800
Eudragit S-100 (mg)	100	150	200	250	300	350
Pluronic F68 (mg)	100	100	100	100	100	100
Dichloromethane	15	15	15	15	15	15
Distilled water (ml)	100	100	100	100	100	100

Characterization of Nanosponges

Percentage yield

The Dexlansoprazole nanosponges obtained after drying was weighed. Percentage yield value was calculated as follows:

% yield = Weight of nanosponges×100/Total solids weight

Entrapment efficiency

UV spectrophotometric method was used to estimate entrapment efficiency of Dexlansoprazole nanosponges (Srinivas and Reddy, 2015). A calibration curve was plotted for Dexlansoprazole in 0.1 N HCl in the range of 5-25 µg/mL (Beer's Lambert's range) at 282nm. A good linear relationship was observed between the concentration of Dexlansoprazole and its absorbance (r2=0.999, m=0.020, n=3). 10 mg of Dexlansoprazole nanosponges of each batch were selected, powdered in a mortar and placed in 10 mL of 0.1 N HCl.

Dexlansoprazole 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

Particle size, polydispersity index

Average particles size, polydispersity index (PDI) of prepared nanosponges was determined using zetasizer (DTS were 4.10, Horriba instrument, India). The nanosponges formulation was diluted with deionized water (1:9 v/v) and analysed for average size and PDI (Tamkhane and Sharma, 2014).

Shape and surface morphology

The shape and surface morphology of the nanospongess were investigated using scanning electron microscopy (IISER, Bhopal) (Kaur *et al.,* 2013). The nanospongess were fixed on supports with carbon-glue, and coated with gold using a gold sputter module in a high-vacuum evaporator. Samples were then observed with the Scanning Electron Microscope at 10 kV.

***In vitro* drug release from nanosponges**

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. It is a dynamic property that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. The test determines the time required for formulation to release percentage of drug under specified conditions.

Table 2: Dissolution Parameters

Medium	900ml, pH 1.2 0.1 N HCl
Apparatus	Paddle (USP-II)
RPM	55
Temperature	37ºC±0.5
Time Points	0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs.

RESULTS AND DISCUSSION

In total six formulations were created & subjected for evaluation of various parameters. The maximum percentage yield was noticed to be 80.32±0.22 in F3 formulation while the minimum yield was found to be associated with F5 formulation which is 68.85±0.35. Other formulations percentage yield was observed in between these two formulations.

Further, the highest entrapment efficiency was observed in F3 formulation which is 74.45±0.45%. The results of measurement of mean particle size of optimized formulation F3 nanosponges were found 136.65 nm. Results of zeta potential of optimized formulation F3 nanosponges were found to be -35.65 mV.

The *In vitro* drug release study of Dexlansoprazole loaded nanosponges is then carried out in comparison to plain drug. It was observed that upto 97.74% drug release was achieved in nansponge within 12 hours. The plain drug release was noticed to be 48.87% in 2 hours. Thus these results showed that nanosponge have sustained release drug delivery over conventional formulations. The obtained in vitro release data was fitted in various kinetic models such as zero order, first order, Higuchi model, and Korsmeyer-Peppas model to evaluate the release kinetics of optimized formulation.

The regression analysis data revealed that the R^2 value for zero order & first order kinetics estimated to be 0.865 & 0.982 respectively. The R^2 value for Higuchi Korsmeyer & Peppas model observed to be 0.963 & 0.964 respectively. From these obtained value it is clear that nanosponge follow first order kinetics. The stability study of optimized formulation of nanosponges F3 was performed for duration of 3 months. The % EE for at 4.0 ±0. 2°C was observed to be 72.14±0.36 with normal physical appearance.

Table 3: Percentage yield for different formulation

Formulation	Percentage Yield*
F1	75.58±0.15
F2	69.98±0.23
F3	80.32±0.22
F4	70.26±0.15
F5	68.85±0.35
F6	72.23±0.12

***Average of three determinations (n=3)**

Table 4: Entrapment efficiency for different formulation

Formulation	Entrapment Efficiency of prepared nanosponges
F1	68.85±0.32
F2	69.98±0.25
F3	74.45±0.45
F4	69.98±0.36
F5	65.58±0.14
F6	66.98±0.20

Table 5: *In vitro* drug release study of Dexlansoprazole loaded nanosponges

S. No.	Time (hrs.)	Plain Drug	Nanosponges
1.	0.5	14.52	20.23
2.	1	26.65	35.65
3.	1.5	39.87	41.12
4.	2	48.87	52.23
5.	3	-	63.32
6.	4	-	65.56
7.	6	-	78.85
8.	8	-	89.98
9.	12	-	97.74

Table 6: *In-vitro* drug release data for optimized formulation F3

Time (h)	Root Time	Log Time	% Drug Release	Log % Drug Release	% Drug Remaining	Log % Drug Remaining
0.5	0.707	-0.301	20.23	1.306	79.77	1.902
1	1	0	35.65	1.552	64.35	1.809
1.5	1.225	0.176	41.12	1.614	58.88	1.770
2	1.414	0.301	52.23	1.718	47.77	1.679
3	1.732	0.477	63.32	1.802	36.68	1.564
4	2	0.602	65.56	1.817	34.44	1.537
6	2.449	0.778	78.85	1.897	21.15	1.325
8	2.828	0.903	89.98	1.954	10.02	1.001
12	3.464	1.079	97.74	1.990	2.26	0.354

Table 7: Regression analysis data of Dexlansoprazole loaded nanosponges

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
F3	0.865	0.982	0.963	0.964

CONCLUSION

The Nanosponge was made by solvent diffusion technique utilising Eudragit S-100, polyvinyl alcohol and Pluronic F68 and was tested for its various properties, which provided several intriguing results for efficient nanosponge preparation. The formulation F3 outperforms the other. Based on the results of various evaluation parameters, it is concluded that Eudragit S-100, polyvinyl alcohol when used as a copolymer different concentrations, nanosponge drug delivery system has shown increased drug entrapment, drug release, and dosage form yield. The nanosponge systems have been reported to have a high potential for sustained drug release, which can lead to benefits such as dose reduction, reduced frequency of administration, and avoidance of associated systemic side effects. As a result, the created oral enteric coated tablet - nanosponges of dexlansoprazole are regarded as excellent and successful in the treatment of GERD and related disorders.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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