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FORMULATION AND EVALUATION OF PANTOPRAZOLE LIPOSOMES BY THIN FILM HYDRATION FOR GERD MANAGEMENT

Sneha N.R.*, Krishna K.R., Parthiban S.

Department of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagara, Mandya-571422.

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***Corresponding Author**

Sneha N.R.

Department of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagara, Mandya-571422.

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ABSTRACT

The present study aimed to develop and evaluate a liposomal drug delivery system of Pantoprazole sodium for effective management of Gastroesophageal Reflux Disease (GERD). Liposomes were prepared by the thin film hydration method using soy lecithin and cholesterol as lipid components. The formulations were characterized for particle size, zeta potential, morphology, entrapment efficiency, and *in-vitro* drug release. FTIR confirmed no chemical interaction between the drug and excipients, indicating compatibility. SEM analysis showed spherical, smooth, and uniform vesicles, confirming successful liposome formation. The optimized formulation exhibited uniform particle distribution, good stability, and high drug entrapment. *In-vitro* release showed a biphasic pattern with an initial burst followed by sustained release, influenced by lipid composition. Overall, the developed liposomal system provided stable sustained delivery of Pantoprazole sodium, suggesting potential for improved therapeutic efficacy and patient compliance in GERD management.

KEYWORDS: Gastroesophageal Reflux Disease, Proton pump inhibitors, Liposomes, Drug Delivery system, thin film hydration.

INTRODUCTION

According to the American College of Gastroenterology (ACG) Gastroesophageal Reflux Disease (GERD) is defined as the reflux of gastric contents into the esophagus causing symptoms and/or complications, with objective evidence of mucosal injury on endoscopy or abnormal acid exposure on reflux monitoring.[1] GERD typically presents with heartburn and regurgitation, but may also involve chest pain, dysphagia, bloating, and nausea, along with extra-esophageal symptoms such as cough, throat irritation, hoarseness, and sleep disturbances.[2,3] Risk factors include advancing age, obesity, smoking, anxiety, sedentary lifestyle and the use of NSAIDs or corticosteroids.[4] The disease manifests in three phenotypes-non-erosive reflux disease (NERD), erosive esophagitis (EE), and Barrett's esophagus-which usually persist throughout a patient's lifetime. Symptoms are considered significant when they adversely affect quality of life, typically occurring two or more times per week.[5,6]

Pharmacologic management primarily relies on Proton Pump Inhibitors (PPIs), which are the mainstay of GERD therapy due to their potent and sustained acid suppression. PPIs act by irreversibly inhibiting the H^+–K^+ ATPase enzyme in gastric parietal cells, providing superior mucosal healing and symptom relief compared with H_2 receptor antagonists (H_2RAs). Among available PPIs, Pantoprazole is widely preferred for its high efficacy, favorable pharmacokinetic profile, and minimal drug interactions.[7,8]

However, despite their effectiveness, oral PPIs like Pantoprazole present significant formulation challenges. Being acid-labile, they undergo degradation in the gastric environment, leading to variable absorption and reduced bioavailability. Furthermore, first-pass metabolism and poor patient adherence limit therapeutic success, with noncompliance contributing to substantial healthcare costs. These issues highlight the need for innovative oral delivery systems capable of protecting PPIs from gastric acid and ensuring sustained drug release.[9,10]

In this liposomal drug delivery offers a promising approach. Liposomes, first described by Alec D. Bangham in 1961, are spherical vesicles composed of phospholipid bilayers enclosing an aqueous core. They can encapsulate both hydrophilic and lipophilic drugs, providing protection from degradation, improving stability, and enabling controlled or targeted release. The amphiphilic nature of phospholipids allows liposomes to self-assemble

in aqueous environments, making them biocompatible and highly suitable for oral delivery of acid-labile drugs such as Pantoprazole.[11]

Thus, formulating Pantoprazole into a liposomal delivery system could overcome the limitations of conventional oral PPIs by enhancing stability in acidic media, prolonging drug release, and improving therapeutic efficacy in the management of GERD.

MATERIALS AND METHODS

Materials

Pantoprazole was purchased by the Dham tech Pharma, Mumbai. Cholesterol was obtained from S D Fine Chem limited, Mumbai. Soya lecithin was obtained from Sonic Bio-chem Extraction Ltd., Indore. Chloroform and methanol solvents were obtained from S D Fine Chem limited, Mumbai.

Preformulation Studies

The drug was characterized for melting point (capillary method), λ max in phosphate buffer pH 7.4 (UV scan 200–400 nm), and calibration curve (0–35 µg/ml at 289 nm). Drug–excipient compatibility was assessed using FTIR spectra (4000–500 cm^{-1}) of pure drug and physical mixtures with excipients.

Preparation of liposomes

Thin film hydration method was used to prepare liposomes. Lipids such as phosphatidylcholine and cholesterol are first dissolved in a volatile organic solvent or a mixture of solvents chloroform and methanol. Upon evaporation of the solvent under reduced pressure, a thin lipid film is formed on the inner surface of a round-bottom flask. This dry lipid film is then hydrated with an aqueous buffer typically phosphate-buffered saline (PBS) at physiological pH (7.4) to form multilamellar vesicles (MLVs). During hydration, the lipid bilayers swell and detach from the glass surface, spontaneously forming vesicular structures that trap part of the aqueous phase containing the drug.[12] For this study the eight batches were prepared and formula and their composition are shown in the below table:

Table 1: Formulation code of Liposomes.

Formulation code	Drug (mg)	Soya Lecithin: Cholesterol Ratio
F1	40	4:1
F2	40	4:2
F3	40	4:3
F4	40	4:4
F5	40	10:1
F6	40	10:2
F7	40	10:3
F8	40	10:4

Characterization of Pantoprazole sodium liposome[13-15]

Surface morphology by scanning electron microscopy (SEM)

The surface morphology of Pantoprazole sodium liposomes was determined by Scanning Electron Microscopy (SEM). Liposomes were coated with Gold-palladium alloy coating done by sputter coater (Polaron SEM coating system). Then the samples were observed under the scanning electron microscopy (JSMT330A, JEOL) at a beam voltage of 15 KV.

Vesicle size analysis

A drop of liposome with distilled water formulation is added on glass slide without cover slip to observe the formation of liposome. Vesicle size analysis was carried out using an optical microscope with a calibrated eye piece micrometer. About 300 liposomes were measured individually, average was taken and their size distribution range and mean diameter were calculated.

Particle size

The particle size of the vesicle after hydration of liposomes was also determined by Microtac Zeta potential Analyzer optimized formulation. Particle size measurements were carried at 25 ºC by photon correlation spectroscopy on Malvern Zetasizer Nano Z® instrument (Malvern, Model ZEN3600) armed with a 4 mW He-Ne laser (633 nm). Samples were put in transparent disposable cuvette and the dispersant viscosity and refractive index was set to 0.8872 cP and 1.330 at 25 ºC. Particle size was analyzed by the Dispersion Technology Software provided by Malvern Instruments. All samples were kept in refrigerator at 4 °C prior to characterization.

Zeta potential

The surface charge of Pantoprazole sodium-loaded liposomes prepared with soya lecithin and cholesterol was determined to evaluate their stability. Zeta potential of the liposomal vesicles

was measured using a Microtrac instrument. The obtained values reflected the electrostatic repulsion between vesicles, which plays a critical role in preventing aggregation and ensuring colloidal stability of the liposomal dispersion.

Entrapment Efficiency

The entrapment efficiency of Pantoprazole sodium liposomes was determined after hydration with distilled water. 2 ml of distilled water was added to the liposome equivalent to 2 mg of drug then the mixture was shaken manually for 2 min. For the separation of unentrapped Pantoprazole sodium, the liposomal suspension was subjected to centrifugation on a cooling centrifuge (REMI TR-01) at 25000 rpm for 1hr. For the separation of un entrapped drug. The clear supernatant (0.1 ml) was taken and diluted to 10ml with methanol and water solution and absorbance was recorded at 289 nm using UV visible spectrophotometer then calculates the percentage drug in each formulation.

***In-vitro* diffusion study**

The release of drug was determined by using the treated cellophane membrane mounted on the one end of open tube, containing formulations. The dialysis tube was suspended in 500 ml beaker, containing 150 ml pH 7.4 buffer. The solution was stirred at 100 rpm with the help of magnetic stirrer at 37 ± 0.5 ℃. Perfect sink conditions were maintained during the drug release testing. The samples were withdrawn at suitable time interval (at 1, 2, 4, 6, 8, 12, hrs). The diffusion medium was replaced with same amount of fresh pH 7.4 buffer solutions to maintain the volume 150 ml throughout the experiment. The drug content in the withdrawn samples (1ml) were analyzed by UV spectrophotometer at λ max 289 nm after making the volume up to 10 ml with pH 7.4 buffer and cumulative % of drug released was calculated and plotted against time (t). The rate and release mechanism of Pantoprazole sodium from the formulations were analyzed by fitting the release data in to various kinetic model.

Stability Studies

Stability testing studies was performed at refrigerated condition for 6 months as per ICH guidelines. The optimized formulation was kept at 4 ± 2℃ and 75 ± 5 % RH in stability chamber. At the end of 0, 3, 6 months intervals regularly tested for % entrapment and drug release were fixed as physical parameters for stability testing.

RESULT AND DISCUSSION

The melting point of Pantoprazole sodium was determined to be 159.23°C by DSC, confirming drug purity as per IP standards. The UV spectrum of Pantoprazole sodium in pH 7.4 buffer showed a λ max at 289 nm, and the calibration curve obeyed Beer's law in the range of 0–35 µg/ml with a correlation coefficient (r^2) of 0.9996, indicating good linearity. FTIR spectra of the pure drug and its physical mixture with soy lecithin and cholesterol showed all characteristic peaks without major shifts, indicating no interaction and confirming compatibility between the drug and excipients. Liposomes prepared by thin film hydration appeared spherical, uniform, and smooth under SEM, confirming successful vesicle formation and drug encapsulation. The vesicle size distribution varied with lipid composition; formulation F1 exhibited the smallest vesicle size, while higher lipid formulations (F4 and F8) showed larger vesicles due to increased bilayer rigidity. The mean particle size of the optimized formulation F1 was 165.04 nm, and the zeta potential was found to be –22.9 mV, indicating good physical stability. The entrapment efficiency ranged from 90.9% (F1) to 76.9% (F4), showing that increasing cholesterol concentration reduced drug entrapment by decreasing bilayer fluidity. In-vitro release studies revealed a biphasic release profile with an initial burst followed by sustained release for 12 hours. The cumulative drug release of F1 was 85.11%, while F4 and F8 showed 64.93% and 70.31% respectively, indicating that higher lipid concentration decreased drug diffusion due to enhanced vesicle packing and rigidity. The formulation F1 exhibited desirable physicochemical characteristics, higher entrapment, good stability, suggesting its potential as an effective liposomal drug delivery system for Pantoprazole sodium in the treatment of (GERD).

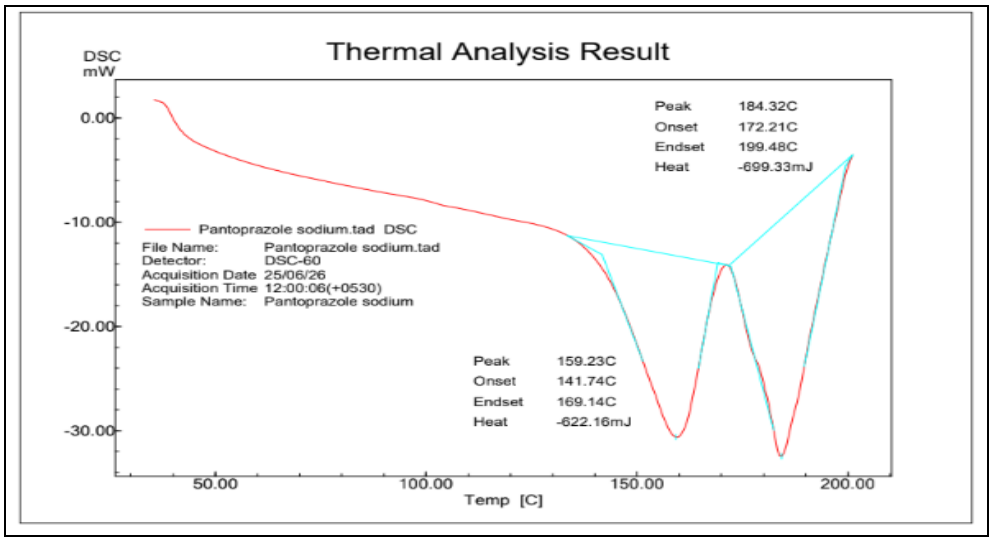

Fig. 1: Thermal analysis of Pantoprazole sodium.

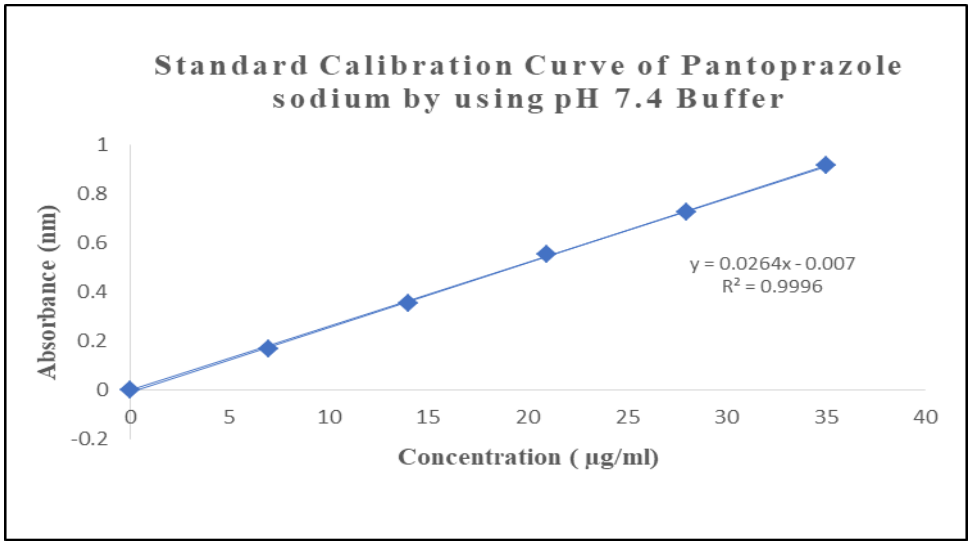

Fig. 2: Plot of Standard Calibration urve of Pantoprazole sodium.

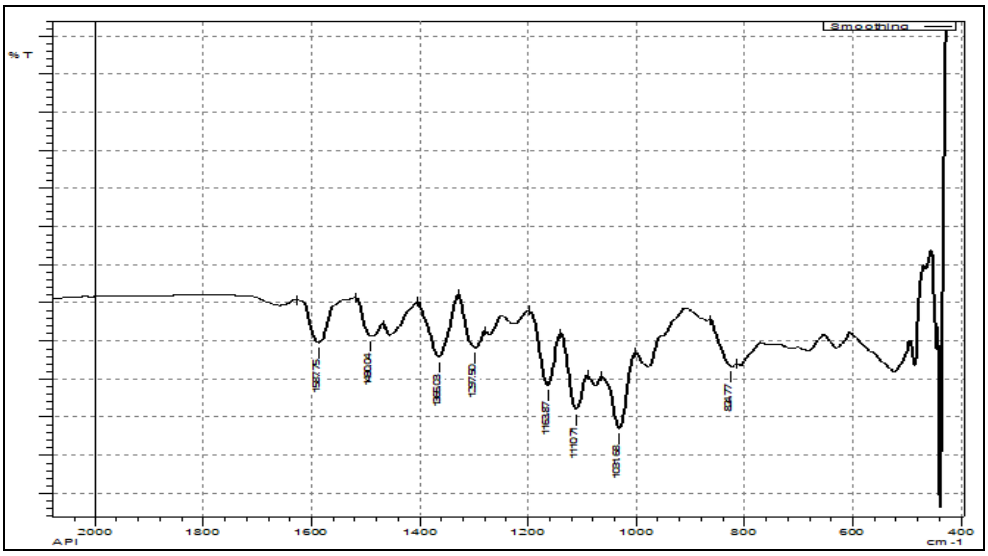

Fig. 3: FT-IR Spectra of Pantoprazole sodium.

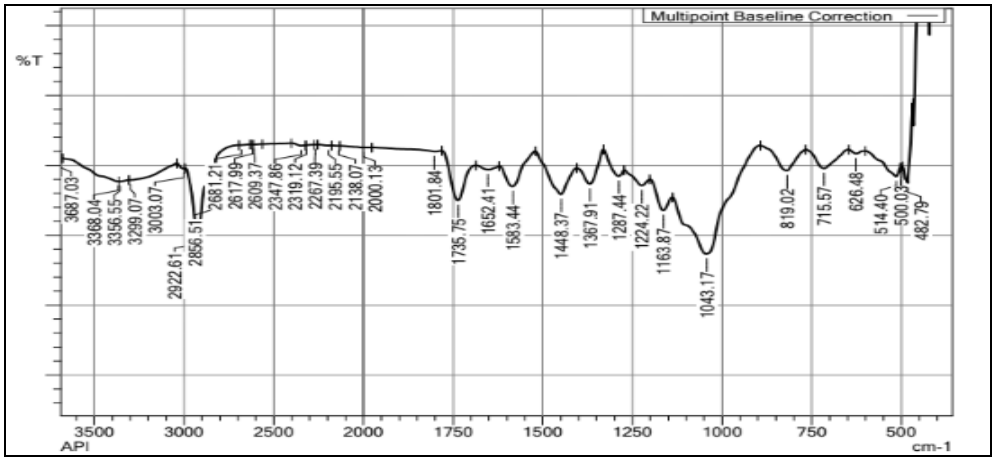

Fig. 4: FT-IR Spectra of Physical mixture of Soyalechithin + cholesterol+ Pantoprazole sodium.

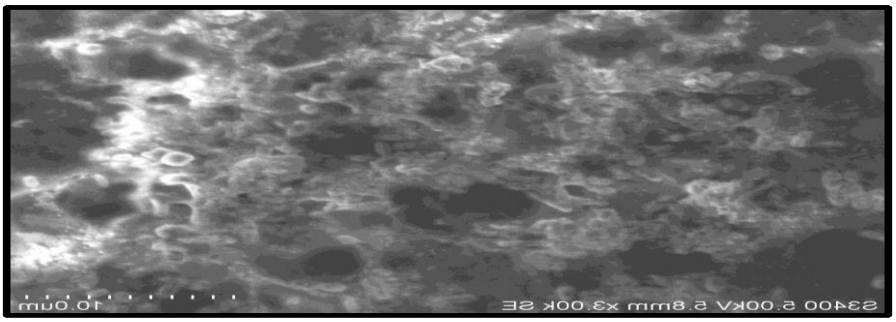

Fig. 5: SEM image of Pantoprazole loaded liposome.

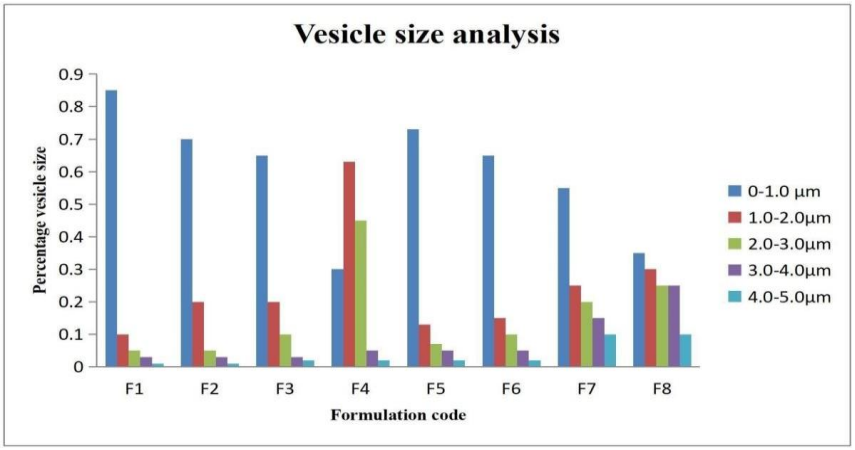

Fig. 6: Vesicle size analysis of F1-F8.

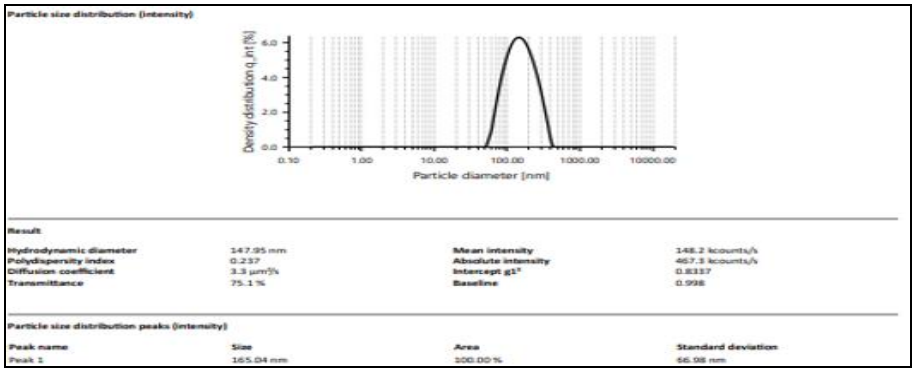

Fig. 7: Particle size analysis of F1 formulation.

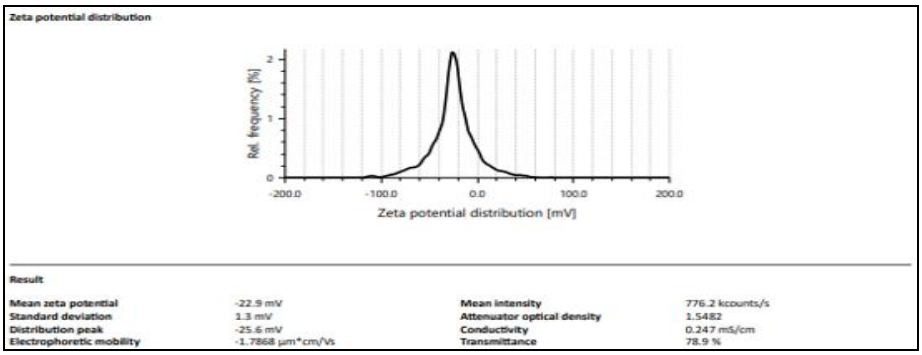

Fig. 8: Zeta potential distribution of F1 formulation.

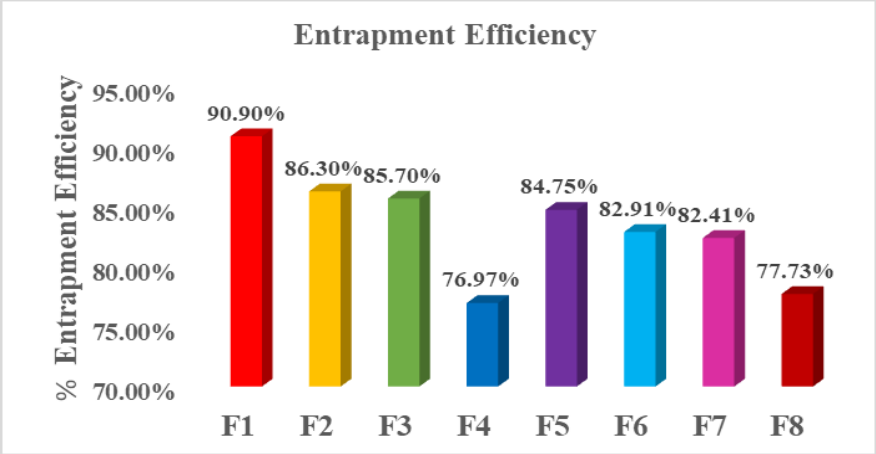

Fig. 9: Entrapment Efficiency of F1- F8.

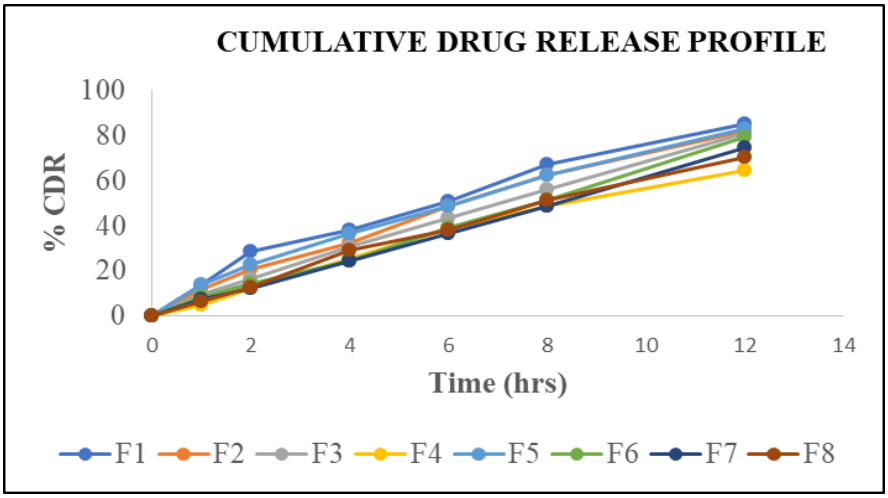

Fig. 10% Cumulative drug release of formulation F1-F8.

CONCLUSION

The study successfully developed a liposomal formulation of Pantoprazole sodium with good stability, uniform vesicle size, and high drug entrapment. The optimized formulation demonstrated effective drug incorporation and promising in-vitro performance, indicating potential for improved delivery in GERD management**.**

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