RESEARCH PAPER

Enhancement of buoyant properties of gastroretentive dosage forms through nanosponge-based formulations

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ABSTRACT

Objective(s): This study aimed to develop floating tablets of an insoluble weak acidic drug. The study protocol objective was to prepare the tablets using two forms of active pharmaceutical ingredient (API): the pure form and the modified nanosponge form.

Materials and Methods: Lamotrigine was used as API and other ingredients used were HPMC, Xanthan gum, Magnesium stearate etc. The physicochemical properties of all the prepared tablets were tested, and the results were found to comply with the standards. Gastroretentive (GR) characteristics, such as floating lag time and duration, were recorded and compared.

Results: The formulations containing the pure form of the drug (F1 to F4) exhibited longer floating lag times and shorter floating durations, whereas the tablets containing the nanosponge form of the drug (F5 to F8) showed improved buoyant properties, evidenced by shorter lag times and longer floating durations. All formulations were evaluated for in-vitro drug release, with a higher percentage of drug dissolution observed in the nanosponge-based formulations.

Conclusion: These results highlight the importance of modifying the physical form of an insoluble drug to enhance both buoyancy and drug release properties in gastroretentive tablet dosage forms.

Keywords: *Floating; Gastric residence; Lamotrigine; Sponge meshes; Xanthan gum*

How to cite this article

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INTRODUCTION

The oral route, being the most convenient for patients, faces a significant challenge due to the dynamic and complex environment of the gastrointestinal tract (GIT), which is influenced by various factors. Two significant issues in oral drug delivery are gastric emptying and intestinal drug metabolism. Gastric retention is crucial for drugs with a favorable absorption window in the stomach or those that undergo extensive metabolism in the lower GIT. This highlights the need for formulators to design gastroretentive (GR) dosage forms to address these challenges [1]. Gastric residence time can be prolonged using various strategies, such as mucoadhesion, floating, sedimentation, and expansion. Among these, hydrodynamically balanced dosage forms (floating systems) are promising for improving gastric retention [2].

Nanosponges (NS) are tiny structures where a medicament can be encapsulated in a mesh-like consistency. They enhance the solubilization of drugs in both aqueous and lipid phases due to their spherical colloidal nature and amphiphilic properties (with an internal hydrophobic chamber and an exterior hydrophilic branching). Nanosponges offer advantages over other nanoparticles in terms of reproducibility in various treatments, such as washing with eco-friendly solvents, stripping with safe hot gases, mold heating, and altering pH or ionic strength. The core structure of nanosponges contains several voids, which allow for the free movement of the drug component. Selective attachment of nanosponges to specific targets can be achieved using chemical linkers. These structures are valuable for transforming liquid materials into solid forms. Due to their microscopic size, nanosponges act as effective drug-delivery vehicles in lung and oral

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delivery [3]. They can also be successfully incorporated into topical hydrogels [3,4].

The best therapeutic benefits can be derived from drugs with a gastric absorption window if their residence time in the stomach is prolonged. Several approaches have been discussed in the literature to achieve this objective. However, drugs belonging to BCS class II, which have low solubility and high permeability in the gastric region, present a challenge. If the issue of poor solubility for these drugs is addressed, it may result in enhanced bioavailability and improved therapeutic effects. Drugs embedded in sponge-like structures can benefit from increased solubility due to the larger voids in the network mesh [5,6]. This research aims to enhance the dissolution of the drug through its entrapment in nanosponge structures, and the modified nanosponge form of the drug was then used in the formulation development of floating tablets.

MATERIALS AND METHODS

Materials used in research

Lamotrigine (gifted by Divis Labs, Hyderabad), HPMC K4M, microcrystalline cellulose (MCC), talc, magnesium stearate, sodium bicarbonate, citric acid, hydrochloric acid, ethyl cellulose, dichloromethane, ethanol, and polyvinyl alcohol were purchased from Swavan International Drugs, Hyderabad. All chemicals procured were of analytical reagent (AR) grade.

Experimental methodology

Drug compatibility

The possible interactions of lamotrigine with other selected excipients were assessed in the preformulation studies. Drug compatibility was confirmed using Fourier Transform Infrared (FTIR) spectroscopy. FTIR spectra of both the pure drug and its physical blend with other formulation ingredients were generated. Any deviations in the characteristic peaks (observed in the pure drug spectrum) in the physical blend spectrum were noted to determine the drug's compatibility.

Formulation of Nanosponges for drug:

This study used the 'Emulsion Solvent Diffusion' method to prepare drug-loaded nanosponges. In this method, controlled and dropwise addition of the internal (dispersed) phase to the external (aqueous) phase resulted in the formation of nanosponge structures. The literature suggests a 1:5 drug-to-ethyl cellulose polymer ratio as the best optimization. An organic solvent blend (20 mL) containing dichloromethane and ethanol in a 1:1 ratio was used to dissolve the drug (50 mg) and ethyl cellulose (250 mg) [7]. The practice of complete dissolution was followed to prepare the dispersed phase. The external phase was prepared by dissolving 500 mg of polyvinyl alcohol in 100 mL of distilled water. Using a magnetic stirrer, the dispersed phase was slowly added to the external phase under stirring at 1000 rpm. Complete homogenization of the resultant mixture was performed for 2 hours, followed by filtration to obtain the wet product. Dried drug-loaded nanosponges were obtained by placing the filtration residue in an oven at 40°C for 24 hours. The resulting nanosponges were then placed in a vacuum desiccator to remove any solvent traces, if present [7,8].

Characterization of Lamotrigine-loaded Nanosponges

A) Practical yield

Equation 1 was applied to calculate production yield:

$$\text{Production Yield} = \frac{\text{Practical weight of NS}}{\text{Theoretical weight of NS}} \times 100$$

Equation (1)

Completely dried granules were weighed to get practical weight, and the total mass of the drug and polymer was considered theoretical weight [7,8].

B) Drug entrapment efficiency

The drug-loaded nanosponges (weighing equivalent to the dose) were crushed in a mortar using a pestle. The resulting crushed mixture was suspended in 50 ml of ethanol for 24 hours and then filtered to collect the filtrate. The filtrate was appropriately diluted with ethanol before scanning in a UV-visible spectrophotometer. The drug loaded in the sponge formulation was calculated using the drug's standard calibration curve. The entrapment efficiency of lamotrigine in the prepared nanosponges was estimated using the following equation 2 [7,8]:

$$\text{Drug Entrapment Efficiency} = \frac{\text{Practical amount of drug loaded in NS}}{\text{Theoretical drug loading amount as per formula}} \times 100$$

Equation (2)

C) FTIR spectroscopic analysis

The FTIR spectrum of the nanosponge dosage form was obtained, and the characteristic peak regions were compared with those in the lamotrigine spectrum. This analysis was performed to predict potential interactions between the drug and the other excipients used in the formulation of the nanosponges. KBr was mixed with the formulation product to form a disc-shaped pellet, which was then placed in the spectrophotometer to obtain the spectrum [8].

D) Particle size

The dynamic light scattering (DLS) method was used to determine the mean size of the drug-loaded nanosponges. Particle sizes were analyzed using a Brookhaven instrument. The prepared nanosponge product was dispersed in distilled water and then scanned using the instrument [7-9].

Table 1. Formulation composition of Lamotrigine floating tablets

Formulative Ingredients (mg)	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Lamotrigine (pure)	50	50	50	50	-	-	-	-
Lamotrigine (as NS forms)	-	-	-	-	50	50	50	50
HPMC K4M	100	150	-	-	100	150	-	-
Xanthan Gum	-	-	100	150	-	-	100	150
MCC	176	176	176	176	176	176	176	176
Citric acid	40	40	40	40	40	40	40	40
$NaHCO_3$	110	110	110	110	110	110	110	110
Mg. Stearate	12	12	12	12	12	12	12	12
Talc	12	12	12	12	12	12	12	12

Formulation of floating tablets

In this research, floating matrix tablets were developed separately for pure lamotrigine and the nanosponge form of the drug. The tablets were formulated using the direct compression method. To ensure homogeneous mixing, a polybag was used to blend the pure drug or nanosponge form, microcrystalline cellulose (MCC), the rate-controlling polymer, and effervescent materials (sodium bicarbonate and citric acid). The resulting blend was lubricated with magnesium stearate and talc (Table 1) [10].

Evaluation of floating tablets

A) Physicochemical characterization

The prepared dosage forms were tested for variations in weight, hardness, thickness, friability, and drug content according to the methodology outlined in the literature [10]. The obtained results were reviewed and compared to ensure compliance with pharmacopoeial limits.

B) Buoyant properties

0.1 N HCl medium was used to evaluate these properties. Buoyancy characterization of the prepared formulations was performed by measuring the floating lag time and floating log time. A 1-liter beaker was filled with 900 mL of the medium, and a tablet that sinks immediately to the bottom was placed in the beaker. The time the tablet floated to the surface was recorded as the floating lag time. The duration for which the tablet remained buoyant after the lag time was recorded as the floating log time [10].

C) In-vitro drug release

The percentage of drug released from the floating matrix was estimated using a USP type-II (paddle) apparatus, with 900 mL of 0.1N HCl (pH 1.2) at 37°C. No sinker was used during the dissolution testing. Throughout the study, the tablets were allowed to float freely in the medium. Drug release was monitored for up to 12 hours, with 5 mL samples withdrawn periodically at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12-hour time points. The collected samples were scanned in a UV-visible spectrophotometer at a λmax of 210 nm. The cumulative percentage of drug release at each time point was calculated using the calibration curve [11].

D) Drug release kinetics and mechanism

The release kinetics and mechanism of drug release from the polymer matrix were determined by fitting the obtained dissolution data into the equations of different models, including zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. The resulting regression values (R^2) of the straight line in each model were recorded and compared to confirm the drug release kinetics and mechanism [10, 11].

E) Drug compatibility in formulation

The compatibility of the drug with other ingredients in the selected best formulation was assessed using the FTIR method. The ground tablet powder was placed in the IR instrument along with KBr and scanned to obtain the spectrum. The resulting spectrum was compared with the characteristic peaks of the pure drug, and any peak deviations were observed to confirm the compatibility status [10-12].

RESULTS AND DISCUSSION

Drug compatibility in preformulation study

The characteristic peaks present in pure Lamotrigine spectrum at 1520.25cm^{-1} (-N-N-stretching), 1227.45, 1378.16 cm^{-1} (-C-N-stretching), 3094.16, 3277.31 cm^{-1} (-N-H-stretching), 1586.14 cm^{-1} (>C=N stretching) were unaltered in the spectrum of physical formulation blend (Fig. 1), indicating the absence drug interaction with other formulative ingredients.

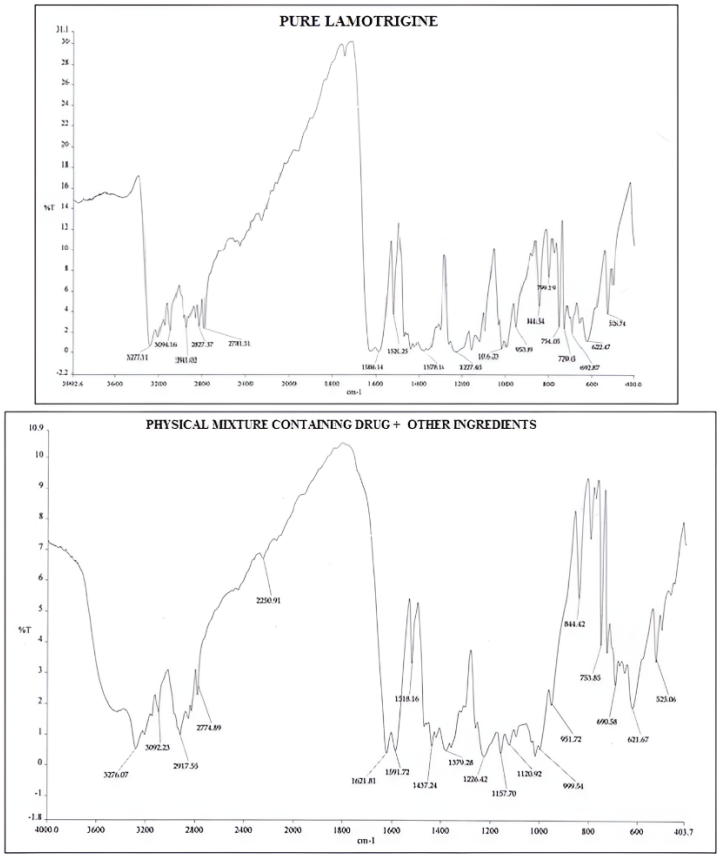

Fig. 1. FTIR spectra of pure Lamotrigine and physical blend

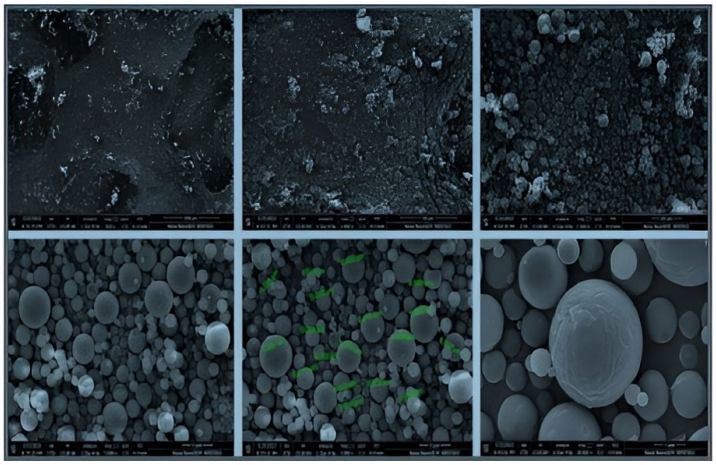

Fig. 2. SEM photographs of Nanosponges

Characterization of Lamotrigine-loaded Nanosponges

A) Practical yield, Drug entrapment efficiency, and Particle size of Nanosponges

Approximately 8% of practical wastage was observed after obtaining the product. The practical yield of the nanosponges was found to be 91.84% w/w.

The drug loading in the resulting nanosponges was observed to be 94.11% w/w. This result indicates good entrapment within the porous matrix of the polymeric material used in the formulation. Size and surface analysis revealed that the nanosponges were individual, spherical, and had smooth surfaces, with a size of less than 1 µm (Fig. 2).

B) FTIR spectroscopic analysis

The spectrum of the nanosponge formulation exhibited characteristic peaks in the same wavenumber regions as those present in the Lamotrigine spectral graph. This confirmed the absence of drug interactions with the other ingredients in the nanosponges (Fig. 3).

Evaluation of floating tablets

A) Physicochemical characterization

Table 2 represents the mean ± SD values of weight, thickness, friability, and drug content of all formulations. All these results complied with pharmacopoeial standards. All the tablets are complex in the 4-5 kg/cm2 range.

B) Floating lag time and duration

Better buoyancy was observed in the tablets containing the nanosponge (NS) form of the drug (F5-F8) compared to the formulations with pure lamotrigine (F1-F4). Conventional formulations with pure drugs showed more lag time and shorter floating duration when compared to the same parameters in NS-loaded tablets (Table 3). This could be attributed to the enriched porous matrix formation, which led to more significant entrapment of CO_2 in formulations F5-F8. The results also revealed enhanced buoyancy (shorter lag time) was observed in formulations with a 1:2 drug-to-polymer ratio compared to a 1:3 ratio. This observation may be due to the quicker formation of a hydrodynamically balanced layer after polymer swelling in the tablets [8]. However, the floating duration was longer in tablets with a 1:3 drug-to-polymer ratio. This could be due to the compact porous polymer matrix formation, which retains CO_2 for extended periods, thus enhancing buoyancy in formulations F2, F4, and F6 [8, 10]. Nonetheless, formulations F7 and F8 demonstrated extended buoyancy (>12 hours) regardless of the polymer ratio. This could be attributed to the increased cross-linking of xanthan gum chains with the NS matrix components [9, 10].

C) In-vitro drug release

Maximum drug release was observed with all formulations at the end of 12 hours (Fig. 4). The lower amount of polymer (1:2 drug-to-polymer ratio) in the tablets enabled faster and more efficient drug release. Results demonstrated that xanthan gum showed a greater ability to control drug release from the dosage units (F3, F4, F7, F8) compared to HPMC K4M (F1, F2, F5, F6) (Table 4). The more significant swelling and porous matrix-forming ability of xanthan gum, a natural hydrophilic polymer, may have contributed to the delayed release of the drug [10-12]. Moreover, both polymers exhibited enhanced control over drug release from the nanosponge matrices (F5-F8). According to the literature, this increased controlled drug release could be due to the interlocking of polymeric chains facilitated by the nanosponge components [7,8]. The best and most controlled release was achieved with formulation F7, containing the drug in nanosponge form with a 1:2 drug-to-xanthan gum ratio.

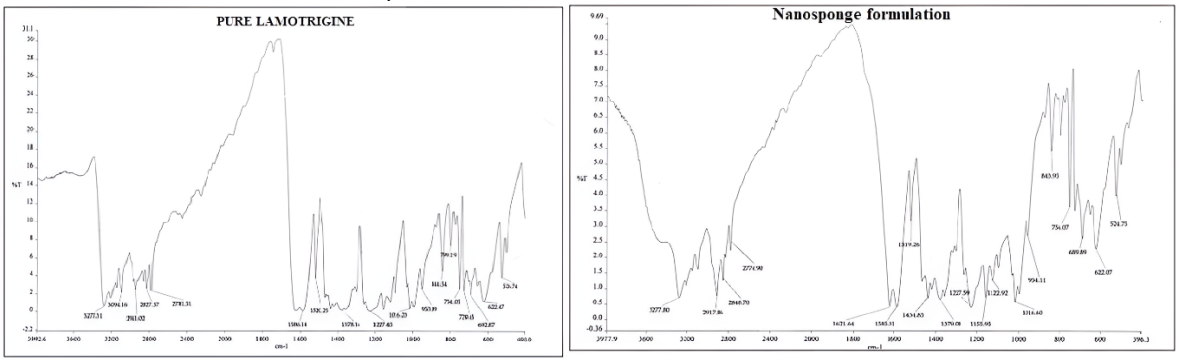

Fig. 3. FTIR spectra of pure Lamotrigine and Nanosponge formulation

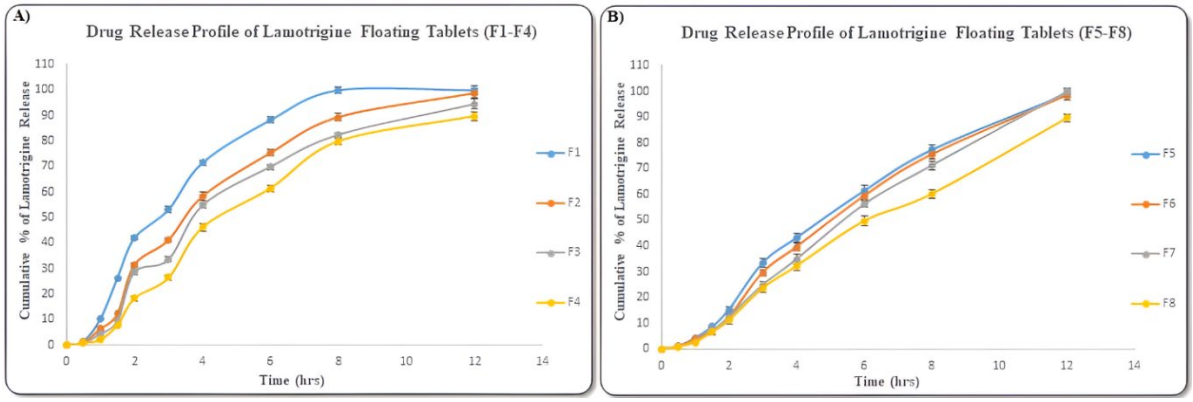

Fig. 4: In-vitro Drug Release Profile of Floating Tablets of A) F1 to F4 & B) F5 to F8

D) Drug release kinetics and mechanism

The drug release from tablets containing pure lamotrigine (F1-F4) followed first-order kinetics, whereas the formulations containing the nanosponge (NS) form of the API exhibited zero-order release kinetics (Table 5). The surface erosion mechanism (Hixson-Crowell model) was observed in the F1-F4 formulations. This could be attributed to the lack of drug entrapment in the sponges and the mere presence of polymeric chains [10]. In contrast, the drug release from the NS-based formulations followed a diffusion mechanism (Higuchi model). This suggests that the combination of both sponge and polymeric matrices allowed the drug to diffuse in a more predictable and controlled manner [7,8]. Since the dissolution data for F8 fit well with both the Higuchi and Hixson-Crowell models, it was concluded that the API in these dosage forms diffused from the polymeric matrix while simultaneously undergoing surface erosion due to the enhanced swelling of xanthan gum in a higher proportion [11]. Due to its more controlled drug release pattern with a diffusion mechanism, formulation F7, which showed more than 99% cumulative lamotrigine release, was selected as the best formulation. The related kinetic and mechanism model graphs for F7 are shown below (Fig. 5).

E) Drug compatibility in formulation

The characteristic peaks observed in the spectrum of the selected best formulation (F7) were compared with those in the pure drug spectrum (Fig. 6). All the peak regions in the formulation corresponded to the wave numbers of the characteristic stretching vibrations in the pure lamotrigine spectrum. This observation confirms the absence of drug incompatibility with the excipients used in the prepared tablet dosage forms.

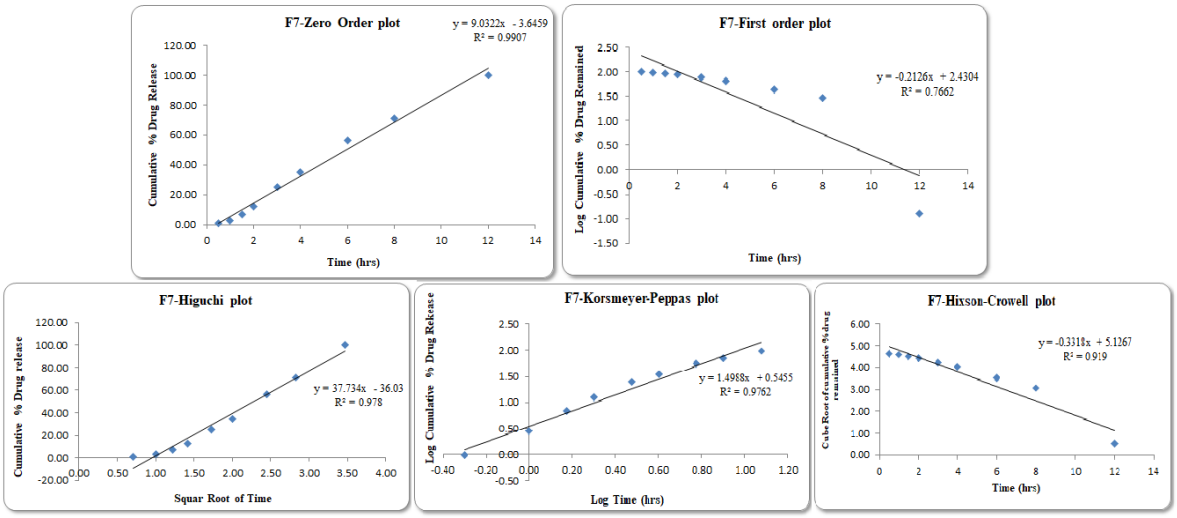

Fig. 5. Fitting of drug release data into kinetic and mechanism models (F7)

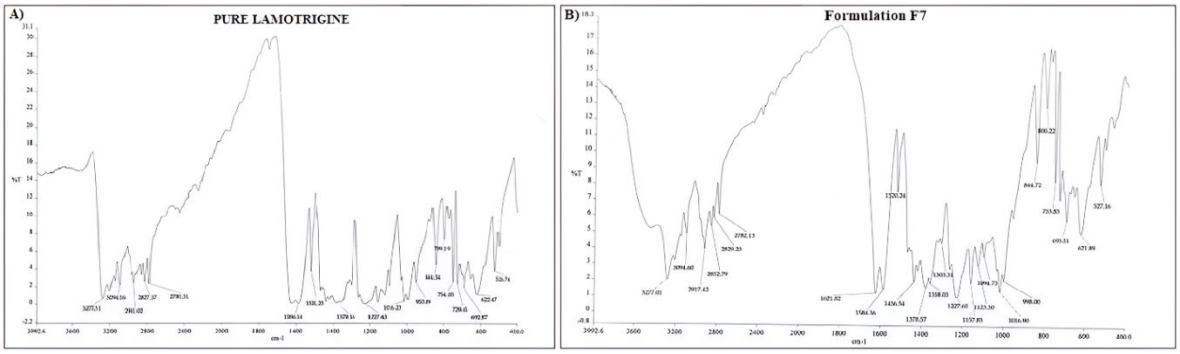

Fig. 6: FTIR spectra of A) Pure Lamotrigine and B) Formulation (F7)

CONCLUSION

Nanosponges loaded with a poorly soluble drug can significantly enhance its solubility, and the NS forms were compatible with the matrix-forming polymeric chains. The enhanced entrapment of CO_2 in the resulting porous matrix contributed to increased buoyancy in the NS-loaded floating tablets (F5-F8). Both HPMC K4M and xanthan gum polymers resulted in good floating behavior and controlled drug release when combined with the NS forms. A gastroretentive dosage form is expected to release the drug in a controlled manner during flotation. Therefore, both buoyancy and drug release were tested in this study. Among all eight tablet compositions, the best buoyancy and most controlled drug release were observed in formulation F7, which contained the NS form of the drug and xanthan gum in a 1:2 ratio. It can be concluded that a better gastroretentive dosage unit with enhanced buoyancy and controlled drug release is achieved when a poorly soluble drug is converted to the NS form and incorporated into the formulation.

CONFLICT OF INTEREST

No conflict of interest was declared.

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