A Novel Gastro-Retentive Floating Microsphere of Gabapentin

G. Gunamathi, M. Pharm*[1], S. Kalaiyarasan[2], P. Jothi Mani[3], S. Jothi[4]

[1]. Assistant Professor of Sri Vijay Vidyalaya College of Pharmacy, Nallampalli, Dharmapuri.
[2, 3, 4]. B. Pharm student of Sri Vijay Vidyalaya College of Pharmacy, Nallampalli, Dharmapuri.

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ABSTRACT- *Gabapentin is a widely used antiepileptic and neuropathic pain drug that exhibits absorption mainly in the upper gastrointestinal tract and has a short biological half-life, which limits its oral bioavailability. To present research aimed at developing a novel gastro-retentive microsphere system gabapentin design to prolong gastric residence attain prolong sustained drug diffusion Floating microcapsule were formulated prepared utilizing sodium alginate and ethyl cellulose as polymeric carriers by the ionotropic gelation technique mediated by calcium chloride. The developed formulations were systematically evaluated for particle size distribution, surface morphology, drug loading, encapsulation efficiency, in vitro buoyancy, and in vitro drug dissolution behavior. FTIR analysis verified the absence of significant drug–polymer interaction, suggesting compatibility between gabapentin and selected excipients. The optimized formulation demonstrated good floating ability with prolonged buoyancy and sustained drug release over an extended period. In Vitro release studies demonstrated a controlled release pattern suitable for gastro-retentive delivery. Overall, the developed gastro-retentive floating microspheres of gabapentin may represent a promising approach to improve therapeutic efficacy, reduce dosing frequency, and enhance patient compliance in the management of neuropathic pain and epilepsy.*

KEY WORDS: Gabapentin, gastro-retentive drug delivery system, floating microspheres, sodium alginate, ethyl cellulose, sustained release.

I. INTRODUCTION:

Microspheres are small spherical particles designed for drug delivery with diameters in the range of 1-1000 micrometers. Microspheres are also known as microparticles. They consist of microcrystalline structures or are used to encapsulate medicinal compounds in various formulations. Microspheres are designed to be synthesized from a wide range of biopolymers and synthetic polymers. The role of microspheres is crucial. Improve the absorption of traditional medicines and minimize side effects. Microcapsules are spherical, freely circulating particles made up of naturally biodegradable macromolecules.

Microspheres can be classified into two main types:

- Micrometrics: In these the active substance is uniformly dispersed throughout the polymer matrix.
- Microcapsules: These consist of a core material enclosed within a well-defined capsule wall.

FLOATING MICROSPHERES:

Floating microspheres are a type of drug delivery system that has a bulk density lower than gastric fluid, allowing them to remain buoyant in the stomach regardless of the stomach emptying rate. While floating is a type of drug delivery system, they release the drug for a prolonged period of gastric fluid, minimizing side effects, increasing the bioavailability, and thereby providing a sustained therapeutic effect. While floating on the stomach contents, the drug is released gradually at a controlled rate, which prolongs gastric residence time and stabilizes plasma drug concentration. Thereby providing a sustained therapeutic effect.

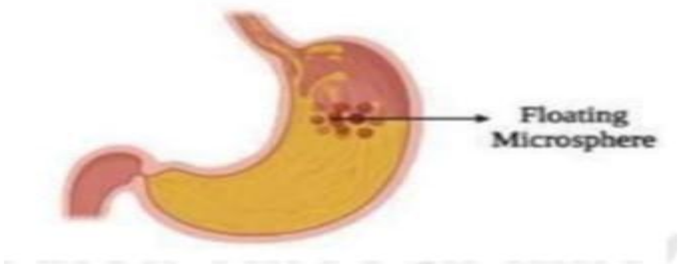

Fig 01: Floating Microspheres

Gabapentin is an anticonvulsant drug used primarily to help control a certain type of seizure in people with epilepsy and to treat nerve pain (neuropathic pain). The gabapentin mechanism of action decreases abnormal electrical activity in the brain, thus preventing seizures.

Gabapentin is now widely used for other conditions such as epilepsy, neuropathic pain, and restless neuropathic syndrome. The floating microspheres of gabapentin provide sustained release, and the sodium alginate and ethyl cellulose act as the main polymers to produce extended release of the floating tablet for 12 hrs. I will be prepared by the floating microspheres of gabapentin, which is a total of 1200 mg taken thrice in a day (TID).

The neuroprotective drug gabapentin, also known as 1-aminomethylcyclohexane acetic acid, has antiepileptic qualities. The floating systems are low density and have sufficient buoyancy to float the gastric content and remain buoyant in the stomach without affecting stomach emptying for a prolonged period of time or causing inadequate drug release in the stomach at the absorption site.

II. MATERIALS AND METHOD:

Gabapentin is procured from an approved supplier. It is used as an anticonvulsant for epilepsy and neuropathic pain. Ethyl Cellulose is prepared from a gift sample from Colorcon Asia Pvt, Ltd, Goa. It is used as a hydrophobic and controlled drug release. Sodium alginate is brought from Iso Chemicals. Calcium chloride is brought from Iso Chemicals.

FORMULATION OF GABAPENTIN FLOATING MICROSPHERES:

IONOTROPIC GELATION METHOD:

1. Accurately weigh the drug, sodium alginate, and calcium chloride.
2. Take 5% $CaCl_2$ (calcium chloride) dissolved in 100 ml water.
3. Then weighed 100 mg of drug, 350 mg of sodium alginate, and 450 mg of ethyl cellulose.
4. Then these drug mixtures and polymer are gently mixed with the use of a magnetic stirrer.
5. Calcium carbonate is added to the above mixture and mixed uniformly to impart floating property.
6. The drug-polymer dispersion is extruded dropwise through a syringe into calcium chloride solution under gentle stirring.
7. On contact with calcium ions, sodium alginate droplets undergo ionic cross-linking, forming gelled microspheres.
8. The interaction between calcium carbonate and the acidic medium generates CO_2, which becomes entrapped within the microspheres, thereby imparting buoyancy.
9. The prepared microspheres were retained in the calcium chloride solution for a predetermined duration to ensure complete cross-linking.
10. The microspheres were filtered and repeatedly washed with distilled water to eliminate excess calcium ions.
11. The microspheres are dried at room temperature or in a hot air oven at low temperature.


Fig. no. 2: Microspheres Formulation

Table NO: 01 Formulation Chart of Floating Microspheres

Formulation	Gabapentin	Sodium Alginate	Ethyl Cellulose	$CaCl_2$	Total (mg)
F1	400 mg	600 mg	200 mg	5 %	1200 mg
F2	400 mg	500 mg	300 mg	5 %	1200 mg
F3	400 mg	400 mg	400 mg	5 %	1200 mg
F4	400 mg	300 mg	500 mg	5 %	1200 mg
F5	400 mg	700 mg	100 mg	5 %	1200 mg
F6	400 mg	350 mg	450 mg	5 %	1200 mg

EVALUATION OF FLOATING MICROSPHERES OF GABAPENTIN:

1) Percentage Yield:

The dried microbeads were weighed, and the percentage yield of the prepared microspheres was calculated by using the following formula. (5)

Percentage yield = **Weight of microbeads Weight of polymer** + **Drug** × 100

2) Size Analysis and Determination:

In size distribution analysis, the microspheres of different sizes in a batch were separated by sieving, using standard sieves. The amounts were weighed and retained on different sieves. The mean particle size of the microbeads is calculated by this formula:

$$\text{Mean particle size} = \frac{\Sigma \text{ mean particle size of the fraction} \times \text{weight fraction. Weight fraction}}{\text{Weight fraction}}$$

3) Swelling Index:

The swelling index of microspheres is an indication of the capacity of the microspheres to imbibe the water and swell. For estimating the swelling index, the microspheres were weighed initially and then suspended in 25 ml of phosphate buffer at pH 7.4. The spheres were taken out at different time intervals using a stainless steel grid and blotted carefully without pressing hard to remove the excess surface liquid. The swollen beads are weighed in an electronic microbalance. The studies were performed in triplicate, and average values were taken in data analysis. (10)

The % weight gain by beads was calculated by the following formula:

Swelling Index = (Wt. – W0) / W0 X 100

Where, Wt. = Mass of swollen beads at time t

W_0 = mass of dry beads at t.

4) In Vitro Buoyancy:

Gabapentin-equipped microspheres were assessed for in vitro floating properties on a USP dissolution device 2 (paddle type). Fifty single microspheres were submerged in a vessel of 500 mL SGF from each formulation. The rotation of the paddle at 50 rpm, while maintaining the temperature at 37 ± 0.5°C. The number of microspheres floating was measured up to eight hours at hourly periods. In vitro buoyancy was represented as a percentage, and the following equation was determined. (11)

$$F\% = \frac{\text{Weight of floating microspheres}}{\text{Weight of initial microspheres}} \text{X100}$$

5) Drug Entrapment Efficiency:

The entrapment efficiency of the microspheres was determined by extraction of drug from the microspheres. In a typical procedure, 50 mg of dried microspheres was ground in a pestle and mortar, and the fine microspheres dissolved in a few mL of ethanol and diluted with 50 mL of 0.1 N HCl for 24 h. After 24 h, the solution was moved over a 0.45 µm filter. The gabapentin present in the filtrate was evaluated spectrophotometrically at 210 nm using a UV-visible spectrophotometer (Shimadzu, UV 1800, Japan) using 0.1 N HCl as a blank. (8,9)

$$\text{Drug entrapment efficiency} = \frac{\text{Weight of drug in microspheres}}{\text{Weight of fed drug}} \text{X 100}$$

5) Determination of Drug Loading of Microspheres:

20 mg of hollow-loaded gabapentin microsphere samples were dissolved at room temperature by ultrasonication in 50 mL ethanol to determine the load. The liquid was then purified by a Millipore (0.45 µm) filter. An ultraviolet (UV)-visible sensor (UV 1700-1800) (Shanghai Phoenix Optical Instrument Co., Ltd., Shanghai, China) was used to determine drug concentrations at 210 nm and 284 nm. The drug loading of gabapentin-loaded hollow microspheres was determined by the following equation. (7)

$$\text{Drug loading amount} = \frac{\text{Amount of FD in hollow microspheres}}{\text{Number of hollow microspheres containing}} \cancel{\text{X 100}}$$

7) FTIR Spectral Analysis:

An FTIR study was carried out to check the identity of the drug. The infrared spectrum of gabapentin was determined on a Fourier transform infrared spectrophotometer using the KBr dispersion method. The baseline correction was done using dried potassium bromide. Then the spectrum of the dried mixture of drug and potassium bromide was run, followed by the drug, by using an FTIR spectrophotometer. The absorption maximums in the spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

III. RESULT AND DISCUSSION:

Analytical Methods:

Determination of λ max by using 0.1 N HCl:

The maximum absorption for gabapentin in 0.1N HCl was found to be 210 nm, and it is shown in the figure:

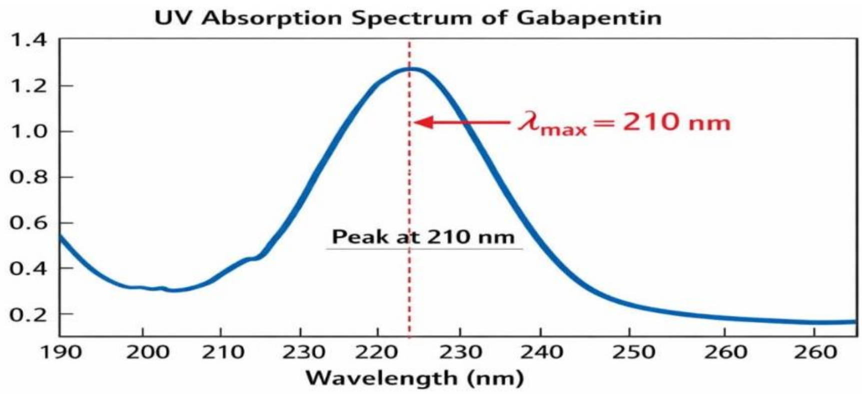

Fig. no. 3: λ max observed for gabapentin in 0.1N HCl.

Preparation of standard curve of Gabapentin 0.1N HCl:

The UV absorption spectrum of gabapentin in 0.1 N HCl showed λ max at 210 nm. The absorbance obtained for various concentrations of gabapentin in 0.1 N HCl is given in the table. The graph of absorbance versus concentration for gabapentin was found to be **linear** in the concentration range of 20–100 µg/ml**.** The drug obeys Beer–Lambert's law in the concentration range of 2–10 µg/ml.

Table No. 2: Data of absorbance vs concentration for Gabapentin

S. No	Concentration (µg/ml)	Absorbance
1	2	0.090
2	4	0.178
3	6	0.266
4	8	0.355
5	10	0.443

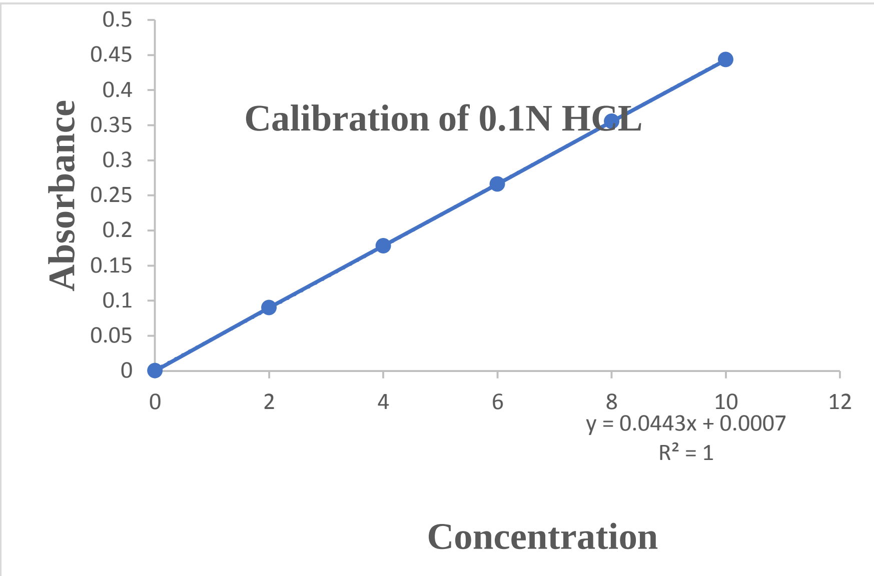

Fig. no: 4 Standard graph of Gabapentin in 0.1N HCl

Percentage Yield:

Formula for Percentage Yield

X 100

Practical yield (mg)

Percentage Yield (%) =

Theoretical yield (mg)

Theoretical yield = Total solid weight = 1200 mg.
Practical yield = Weight of dried microspheres obtained.

Table No: 3 Percentage Yield

S.NO	Formulation	Theoretical yield (mg)	Practical yield (mg)	Percentage Yield %
1	F1	1200	980	81.67 %
2	F2	1200	1020	85.00 %
3	F3	1200	1055	87.92 %
4	F4	1200	1100	91.67%
5	F5	1200	950	79.17 %
6	F6	1200	1080	90.00 %

SIZE ANALYSIS AND DETERMINATION:

The particle size of gabapentin microspheres was determined by the optical microscopy method using a calibrated ocular micrometer.

Procedure:

A small quantity of dried microspheres from each formulation (F1–F6) was dispersed in liquid paraffin.
A drop of dispersion was placed on a clean glass slide and covered with a cover slip.
The microspheres were observed under an optical microscope at suitable magnification.
Around **100 particles** were measured randomly for each formulation.

Table NO: 04 Size Analyses and Determination

S.NO	Formulation	Sodium Alginate (mg)	Ethyl Cellulose (mg)	Mean Particle Size (µm) ± SD
1	F1	600	200	685 ± 18
2	F2	500	300	642 ± 15
3	F3	400	400	598 ± 14
4	F4	300	500	555 ± 12
5	F5	700	100	720 ± 20
6	F6	350	450	580 ± 13

Swelling Index: Method of Determination:

The swelling behaviour of gabapentin microspheres was determined in pH 7.4 phosphate buffer.

Table No: 05 Swelling Index In Vitro Buoyancy:

S.NO	Formulation	Sodium Alginate(mg)	Ethyl Cellulose (mg)	Swelling Index (%)
1	F1	600	200	118 ± 3
2	F2	500	300	105 ± 2
3	F3	400	400	92 ± 2
4	F4	300	500	78 ± 2
5	F5	700	100	132 ± 4
6	F6	350	450	88 ± 2

After 12 hours, the microspheres that remained floating and those that settled at the bottom were collected separately, dried, and weighed.

Table no.: 06 In Vitro Buoyancy Drug entrapment efficiency:

S. No.	Formulation	Sodium Alginate (mg)	Ethyl Cellulose (mg)	% Buoyancy (12 h)
1	F1	600	200	78.4 ± 1.2
2	F2	500	300	82.6 ± 1.5
3	F3	400	400	88.9 ± 1.3
4	F4	300	500	91.7 ± 1.1
5	F5	700	100	72.3 ± 1.6
6	F6	350	450	93.5 ± 1.0

The solution was filtered and suitably diluted, and the absorbance was measured using a UV–visible spectrophotometer at 210 nm against a reagent blank. The drug content was calculated using the previously prepared calibration curve of gabapentin.

Table no: 07 Drug Entrapment efficiency

S. No	Formulation	Sodium Alginate(mg)	Ethyl Cellulose(mg)	Entrapment Efficiency (%
1	F1	600	200	71.4 ± 1.3
2	F2	500	300	75.8 ± 1.1
3	F3	400	400	82.6 ± 1.4
4	F4	300	500	86.9 ± 1.2
5	F5	700	100	68.2 ± 1.6
6	F6	350	450	89.5 ± 1.0

Determination of Drug-Loading Microspheres:

The drug loading of gabapentin-loaded microspheres ranged from 24.1% to 32.2%**.** Hence, formulation F6 was considered the best formulation in terms of drug loading capacity.

Table no: 08 Determination of Drug-Loading Microspheres

S. NO	Formulation	Weight of microspheres taken (mg)	Amount of Drug Estimated (mg)	Drug Loading (%)
1	F1	100	25.8	25.8 ± 0.46
2	F2	100	27.4	27.4 ± 0.52
3	F3	100	28.6	28.6 ± 0.58
4	F4	100	24.1	24.1 ± 0.43
5	F5	100	26.9	26.9 ± 0.49
6	F6	100	32.2	32.2 ± 0.64

FTIR Spectral Analysis:

IDENTIFICATION OF GABAPENTIN BY FTIR SPECTROSCOPY:

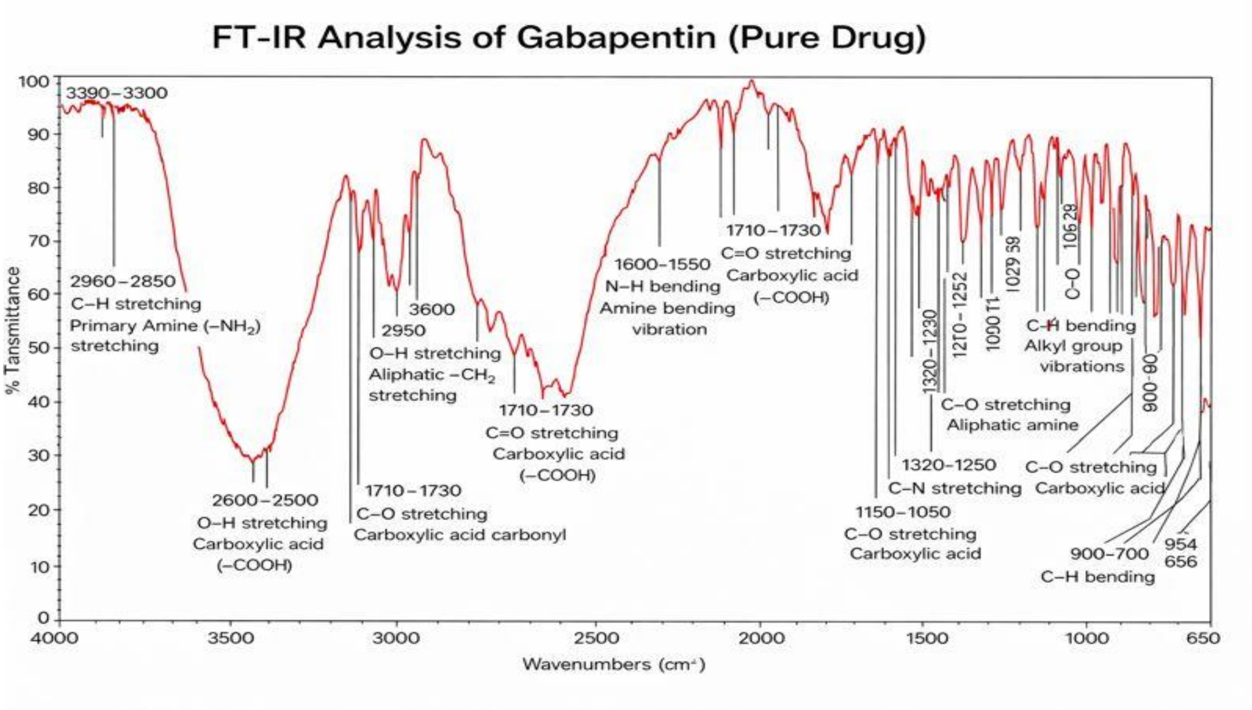

Fig. no. 05: FTIR Spectrum of pure drug Gabapentin

DRUG EXCIPIENT COMPATIBILITY STUDIES:

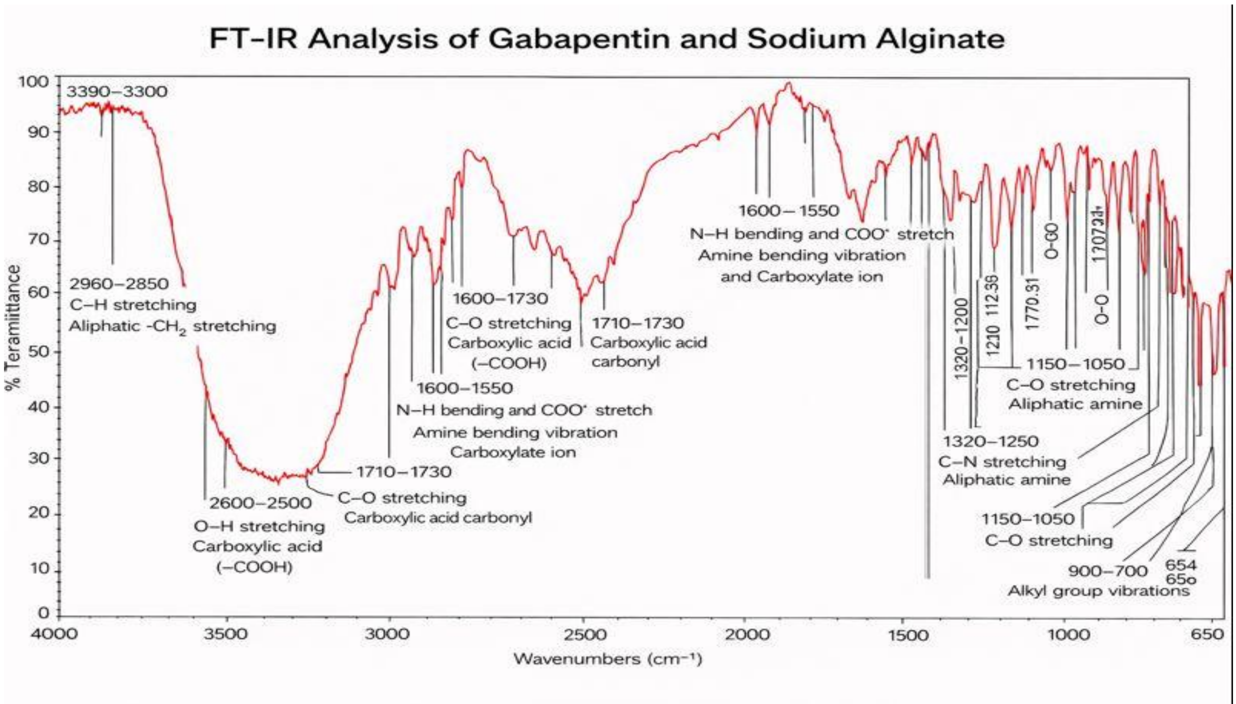

Fig. no. 06: FTIR Spectrum of pure drug Gabapentin and Sodium Alginate

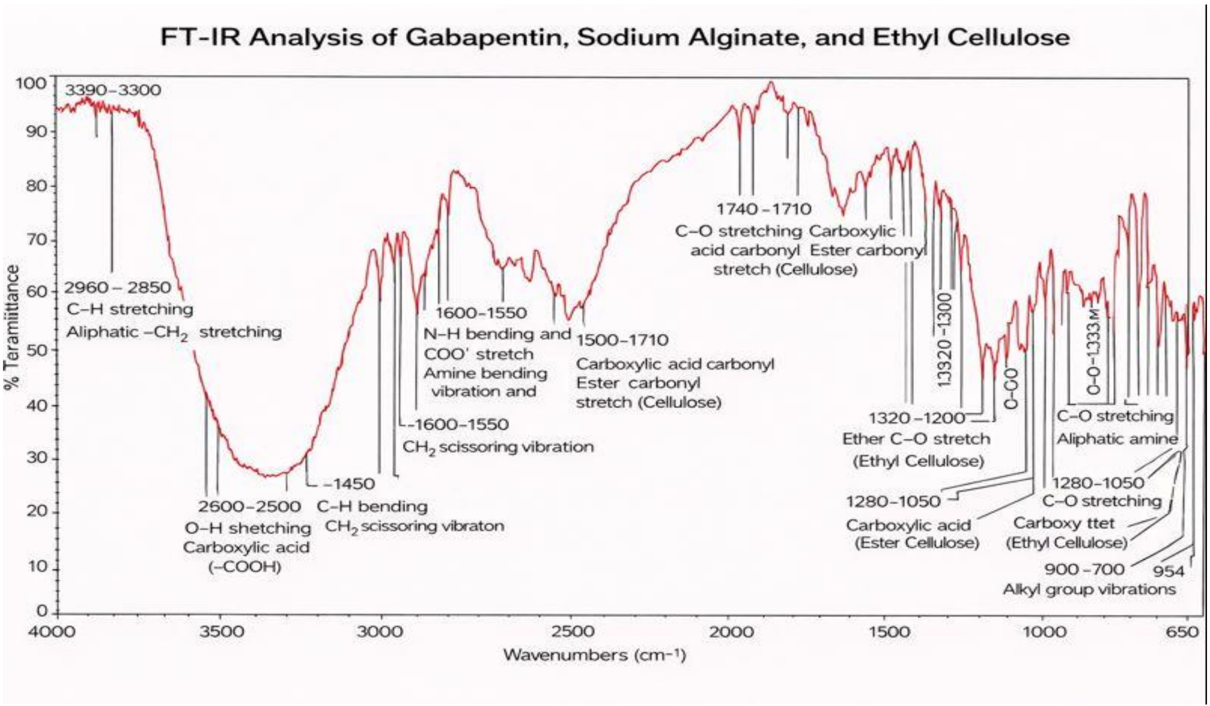

Fig. no. 07: FTIR Spectrum of Gabapentin and sodium Alginate and Ethyl cellulose

Table No.: 09 Major Peaks Observed in the FTIR Spectrum of Gabapentin and a Drug with a Different Polymer Used in the Formulation.

Functional group	**Wave No. (cm^{-1})**	**Drug (Gabapentin)**	**Drug + Sodium Alginate**	**Drug + Ethyl Cellulose**
N–H stretching (Primary amine)	3400–3200	Yes	Yes	Yes
C–H stretching (Aromatic)	3061.88	Yes	Yes	Yes
Asymmetric & symmetric CH_3 stretching	2924.36, 2855.32	Yes	Yes	Yes
Asymmetric & symmetric CH_2 stretching	2896.30, 2827.73	Yes	Yes	Yes
C=O stretching (Carboxylic acid)	1650–1600	Yes	Yes	Yes
N–H bending (Amine)	1540–1520	Yes	Yes	Yes
COO^- symmetric stretching	1410–1450	Yes	Yes	Yes
O–H bending	1380–1360	Yes	Yes	Yes
C–N stretching (Amine)	1254.90	Yes	Yes	Yes
C–O / C–O–C stretching	1100–1050	Yes	Yes	Yes
C–H bending	751.18			

		Yes	Yes	Yes
C_6H_6 (N) substitution	767.08	Yes	Yes	Yes
C_6H_6 (O) substitution	717.66	Yes	Yes	Yes

IV. CONCLUSION:

The present study successfully developed a novel gastro-retentive floating microsphere system of gabapentin using polymeric carriers to enhance gastric residence time and sustain drug release. The prepared microspheres exhibited satisfactory physicochemical characteristics, including good flow properties, high drug entrapment efficiency, and uniform particle size distribution. In vitro buoyancy studies confirmed prolonged floating behavior, validating the gastro-retentive potential of the formulation.

The in vitro release studies demonstrated a controlled and sustained release profile, which is advantageous for improving the oral bioavailability of gabapentin, a drug with a narrow absorption window and short biological half-life.

Overall, the developed floating microsphere system represents a promising gastro-retentive drug delivery approach for gabapentin, with the potential to improve therapeutic efficacy and patient compliance.

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