STM JOURNALS

International Journal of
Biomedical Innovations
and Engineering

Volume 2, Issue 1, 2024
January–June
DOI (Journal): 10.37591/IJBIE

https://journals.stmjournals.com/ijbie

Research IJBIE

Development and Assessment of Levetiracetam Microspheres Utilizing Synthetic and Natural Polymers: A Biomedical Engineering Perspective

Tatapudi Sowjanya[1,*], Alladi Saritha[2]

Abstract

In the present study, comparative study of Levetiracetam loaded microspheres using Ethyl cellulose as synthetic and Sodium alginate as natural polymers was done. Solvent evaporation and ionic gelation technique has been successfully employed to produce Levetiracetam loaded ethyl cellulose and sodium alginate microspheres with optimal drug encapsulation that sustained the drug release over a period of time. Based on the pre-formulation studies E1 to E4 and S1 to S4 batches were prepared using selected polymers. Prepared microspheres were evaluated for the percentage yield, drug content, drug entrapment efficiency and in-vitro dissolution test. The data obtained from the in-vitro release showed highly correlated with Korsmeyer-Peppas model and Regression was found to be 0.9957 with 1.2 as a n value. The release kinetic study has shown that drug release from microspheres follows the Korsmeyer Peppas as the drug release occurs super case II transport with erosion. For optimised formulation, the drug entrapment efficiency was 91.5%, Percentage yield was 77.3%, and Drug content was 85.7%. Comparison was made between the best formulations E3 and S3 of microspheres prepared by using Ethyl cellulose as synthetic and Sodium alginate as natural polymers respectively. Among these formulations, microspheres prepared by using ethyl cellulose as polymer was found to be best formulation with highest drug content of 85.7%, entrapment efficiency of 91.5%, Percentage yield of 77.3% and in-vitro drug release 88.55% for 16 h and ethyl cellulose polymers was found to be the best formulation for the preparation of novel drug delivery system for Levetiracetam. While control of drug release profile has been a major aim of pharmaceutical research and development of past decade, control of Gl transmit profile could be the focus of next few decades and might result in the availability of products with better therapeutic possibilities and substantial benefits for patients. Dosing frequency and loss of drug also reduced by the use of such type of formulations and the bioavailability of drugs can also be increased. All the above studies reveal that the microsphere can serve as an ideal drug delivery system for Levetiracetam loaded microspheres. Further studies can be done on the stability on Levetiracetam loaded microspheres and the improvement in therapeutic efficacy due to the targeting effort on to the specific receptor sites.

Author for Correspondence
Tatapudi Sowjanya
E-mail: sowjanyaruby2824@gmail.com

[1]Student, Department of Pharmaceutics, Sri Sai Jyothi College of Pharmacy, Hyderabad, Telangana, India
[2]Associate Professor, Department of Pharmaceutics, Sri Sai Jyothi College of Pharmacy, Hyderabad, Telangana, India

Received Date: February 08, 2024
Accepted Date: February 12, 2024
Published Date: March 01, 2024

Citation: Tatapudi Sowjanya, Alladi Saritha. Development and Assessment of Levetiracetam Microspheres Utilizing Synthetic and Natural Polymers: A Biomedical Engineering Perspective. International Journal of Biomedical Innovations and Engineering. 2024; 2(1): 1–18p.

Keywords: Formulation, evaluation, levetiracetam, microspheres, scanning electron microscope

INTRODUCTION

The drawbacks of traditional dosage forms and conventional oral drug delivery methods are pushing the pharmaceutical industry toward an advanced approach called Novel Drug Delivery Systems (NDDS). Targeted drug delivery, a crucial part of NDDS, has been a major focus of research. However, the idea itself isn't new—it dates back to 1906 when Sir Paul Ehrlich introduced the ‘magic

bullet' concept, which set the stage for a groundbreaking shift in drug delivery. Since then, the concept has evolved continuously, with new innovations pushing the boundaries of what's possible in the field. [1].

Targeting involves the precise delivery of therapeutic agents to specific organs, tissues, cells, or intracellular structures through either systemic or localized drug administration. [2]. The selective concentration of drugs at the target site protects healthy tissues from unnecessary exposure, enhances the drug's therapeutic index, and ultimately improves the overall effectiveness of the treatment. [3]. Delivering drugs to a specific target, whether through passive or active mechanisms, necessitates the use of carriers such as nanoparticles, liposomes, micelles, and microspheres. [4].

In recent years, an increasing number of studies have highlighted the potential of microspheres as carriers for targeted drug delivery, drawing significant interest from researchers worldwide. Microspheres are free-flowing particles ranging from 1 to 1000 μm, capable of providing a controlled or sustained release of therapeutics [5]. These matrix-like structures consist of active compounds uniformly dispersed within a polymeric network, allowing them to encapsulate small molecules, proteins, peptides, and nucleic acids. Their higher translational efficiency and clinical success rate give them an advantage over nanoparticulate drug delivery systems [6-9].

Compared to conventional dosage forms, microspheres offer several benefits, including enhanced solubility of poorly soluble drugs, protection from enzymatic and photolytic degradation, reduced dosing frequency, improved bioavailability, controlled drug release, lower dosage requirements, and minimized drug toxicity. Various techniques can be employed for their production, such as solvent evaporation, spray drying, phase separation, and polymerization. [10-14].

Currently available microsphere formulations are primarily designed as long-acting injectable depots, enabling the controlled release of encapsulated drugs over a specific period. Most of these formulations incorporate hormonal analogues as the active ingredients. In addition to hormones, certain drugs targeting the central nervous system and opioid antagonists are also formulated as microspheres for various therapeutic applications [11,12].

However, microspheres specifically designed for targeted drug delivery have yet to reach the market. Nevertheless, extensive research is underway to explore their potential in Targeted Drug Delivery Systems (TDDS) [13-16]. Notably, several ongoing clinical trials involving microspheres encapsulating anticancer drugs such as doxorubicin (DOX) and irinotecan for the treatment of colon cancer, rectal cancer, and hepatocellular carcinoma provide strong evidence of their capability to precisely deliver drugs to intended sites. [17, 18].

Levetiracetam is an antiepileptic drug that works by binding to specific sites (SV2A) on nerve cells, helping to suppress their abnormal activity.

The aim of this work is to formulate and develop oral microspheres containing Levetiracetam to improve bioavailability and reduce the dose frequency by using carriers Sodium Alginate and Ethyl Cellulose. To overcome the problem associated with conventional dosage form, microspheres were formulated using suitable polymers which shows controlled release and reduce the dose frequency.

Therefore, this study aimed to develop a drug delivery system using microspheres. A smaller drug dose is sufficient to produce a prolonged pharmacological effect. Additionally, it helps reduce first-pass metabolism and enhances drug utilization efficiency, offering significant advantages over conventional solid dosage forms.

To accomplish this objective, multiple prototype trials were conducted and assessed based on various quality parameters, including bulk density, tapped density, Carr's index, angle of repose, swelling index, particle size analysis, scanning electron microscopy, and in-vitro drug release studies.

MATERIALS AND METHODS

The materials used in the study: Levetiracetam, Sodium alginate, Ethyl cellulose, Calcium chloride.

EXPERIMENTAL WORK

Methodology

Preparation of phosphate buffer pH 7.4.

Phosphate Buffer pH 7.4

Placed 50 ml of 0.2M potassium di hydrogen phosphate in 200 ml of volumetric flask, added 39.1 ml of 0.2M NaoH and diluted with distilled water up to 1000 ml.

Potassium Dihydrogen Phosphate (0.2M)

A total of 27.218 grams of potassium dihydrogen phosphate was weighed and dissolved in 1000 ml of water.

Sodium Hydroxide Solution (0.2M)

Weighed 8 gm of sodium hydroxide pellets and dissolved in 1000 ml of water.

Determination of λmax

A Levetiracetam solution with a concentration of 10 µg/ml was prepared using a pH 7.4 phosphate buffer, and its UV spectrum was analyzed with a double-beam spectrophotometer. The solution was scanned within the 200–400 nm range, revealing a maximum absorption wavelength of 221 nm.

Standard Graph of Levetiracetam in Phosphate Buffer pH 7.4

A total of 100 mg of Levetiracetam was dissolved in 100 ml of pH 7.4 phosphate buffer, resulting in a solution with a concentration of 1000 µg/ml. Ten milliliters of this solution was taken and diluted to 100 milliliters using a pH 7.4 phosphate buffer, resulting in a final concentration of 100 µg/ml. Subsequently, 10 ml of this solution was further diluted to 100 ml with pH 7.4 phosphate buffer, yielding a final concentration of 10 µg/ml.

A volume ranging from 1 to 10 ml was pipetted and diluted to 10 ml using phosphate buffer (pH 7.4) to obtain a solution with a concentration between 1–10 µg/ml. The absorbance of these samples was analysed by using UV-Visible spectrophotometer at 221 nm against reference solution phosphate buffer 7.4, as seen in Tables 1 and 2.

Table 1. List of materials used in the formulation.

S.N.	List of chemicals	Manufacturing company/Suppliers
1	Levetiracetam	Micro labs, Bangalore.
2	Sodium alginate	Modern Scientific, Coimbatore
3	Ethyl cellulose	Precision Scientific, Coimbatore
4	Calcium chloride	Nice Chemicals Pvt. Ltd.
5	Ethyl acetate	Precision Scientific, Coimbatore

6	Sodium carboxymethyl cellulose	Nice Chemicals Pvt. Ltd.

Table 2. Composition of Ethyl cellulose containing Levetiracetam.

Formulations	Ratio
E1	1:1
E2	1:2
E3	1:3
E4	1:4

METHOD OF PREPARATION

Preparation of Levetiracetam Microspheres by Solvent Evaporation Method

Microspheres were prepared using an organic solvent (ethyl acetate), a stirring speed of 700 rpm, and an organic-to-aqueous ratio of 1:10. Ethyl cellulose was placed in a crucible and dissolved in ethyl acetate to create a homogeneous solution. Levetiracetam was then added and thoroughly mixed. This dispersion was slowly introduced as a thin stream into 100 ml of an aqueous mucilage containing 0.5% sodium CMC in a 250 ml beaker, while stirring at 700 rpm to facilitate emulsification into fine droplets. Solvent removal was achieved through continuous stirring at room temperature for 3 hours, leading to the formation of spherical microspheres. The resulting microspheres were collected through filtration, washed multiple times with distilled water, and air-dried, as detailed in Tables 3 and 4.

Preparation of Levetiracetam Microspheres by Ionotropic Gelation Technique

Microspheres containing Levetiracetam were prepared using varying concentrations of calcium chloride. Sodium alginate was dissolved in distilled water with gentle heating on a magnetic stirrer to obtain a bubble-free solution with concentrations ranging from 1% to 4%. Levetiracetam was accurately weighed, dissolved in methanol, and added to the polymeric solution to create a clear mixture. The dispersions were sonicated for 30 minutes to eliminate any air bubbles formed during stirring.

The homogeneous dispersion was then introduced dropwise using a 20-gauge hypodermic needle attached to a syringe into 50 ml of a 4% calcium chloride ($CaCl_2$) solution, which was stirred at 200 rpm for 10 minutes. Upon contact with the gelling solution, the droplets immediately solidified into distinct Levetiracetam-alginate microspheres. The formed microspheres were further stirred in the gelling agent solution for an additional hour. After completion, the gelling solution was decanted, and the microspheres were washed with distilled water, filtered, and dried at 50°C. The results are presented in Tables 3 and 4.

RESULTS AND DISCUSSION

Calibration Curve of Levetiracetam

Different concentrations of Levetiracetam from 1 to 10 μg/ml were prepared and the absorbance was taken at 221 nm against pH 7.4 phosphate buffer and graph was plotted between concentration and absorbance as shown in Figure 1.

Drug Excipient Compatibility Studies

The compatibility of the drug with excipients was assessed using FTIR spectroscopy. FTIR spectra of individual components, including Levetiracetam, ethyl cellulose, and sodium alginate, were compared with the FTIR spectrum of their physical mixture to confirm compatibility. The spectrum of Levetiracetam showed characteristic peaks at 3357 cm^{-1} (N-H Stretching), 2891 cm^{-1} (C-H Stretching), 1425 cm^{-1} (C-H Bending), and 1082 cm^{-1} (C-N Stretching) indicating purity of the drug. The characteristic peaks of Levetiracetam were prominently absorbed in FTIR spectra of physical mixture

(Levetiracetam + Ethyl Cellulose, Levetiracetam + Sodium Alginate) with slight shift in their positions as seen in Tables 5–10.

The result indicates that there was no chemical incompatibility between drug and polymer as all the characteristic IR peaks related to pure drug also appeared in the IR Spectrum of the formulation, as shown in Figures 2–6.

Table 3. Composition of Sodium alginate containing Levetiracetam.

Formulation	Ratios
S1	1:1
S2	1:2

Table 4. Calibration curve of levetiracetam.

S.N.	Concentration	Absorbance
1	0	0
2	1	0.015
3	2	0.029
4	3	0.4
5	4	0.051
6	5	0.063
7	6	0.072
8	7	0.085
9	8	0.098
10	9	0.106
11	10	0.12

Table 5. Data for levetiracetam FTIR.

S.N.	Peaks	Groups	Stretching/ deformation
1	3357	N-H (amine)	Stretching
2	2891	C-H (alkane)	Stretching
3	1425	C-H (alkane)	Bending

Table 6. Data for ethyl cellulose FTIR.

S.N.	Peaks	Groups	Stretching/ deformation
1	3460	O-H (Alcohol)	Stretching
2	2975	C-H (Alkane)	Stretching
3	1059	C-O-C (Ether)	Stretching
4	1378	C-H (Alkane)	Bending

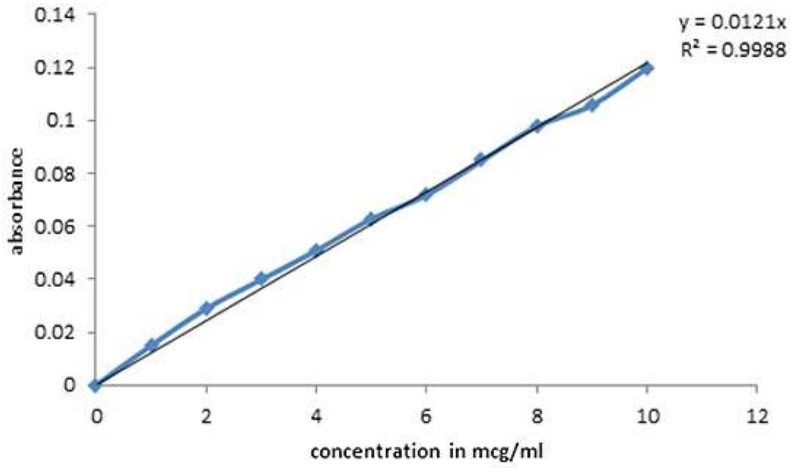


Figure 1. Calibration curve of Levetiracetam.

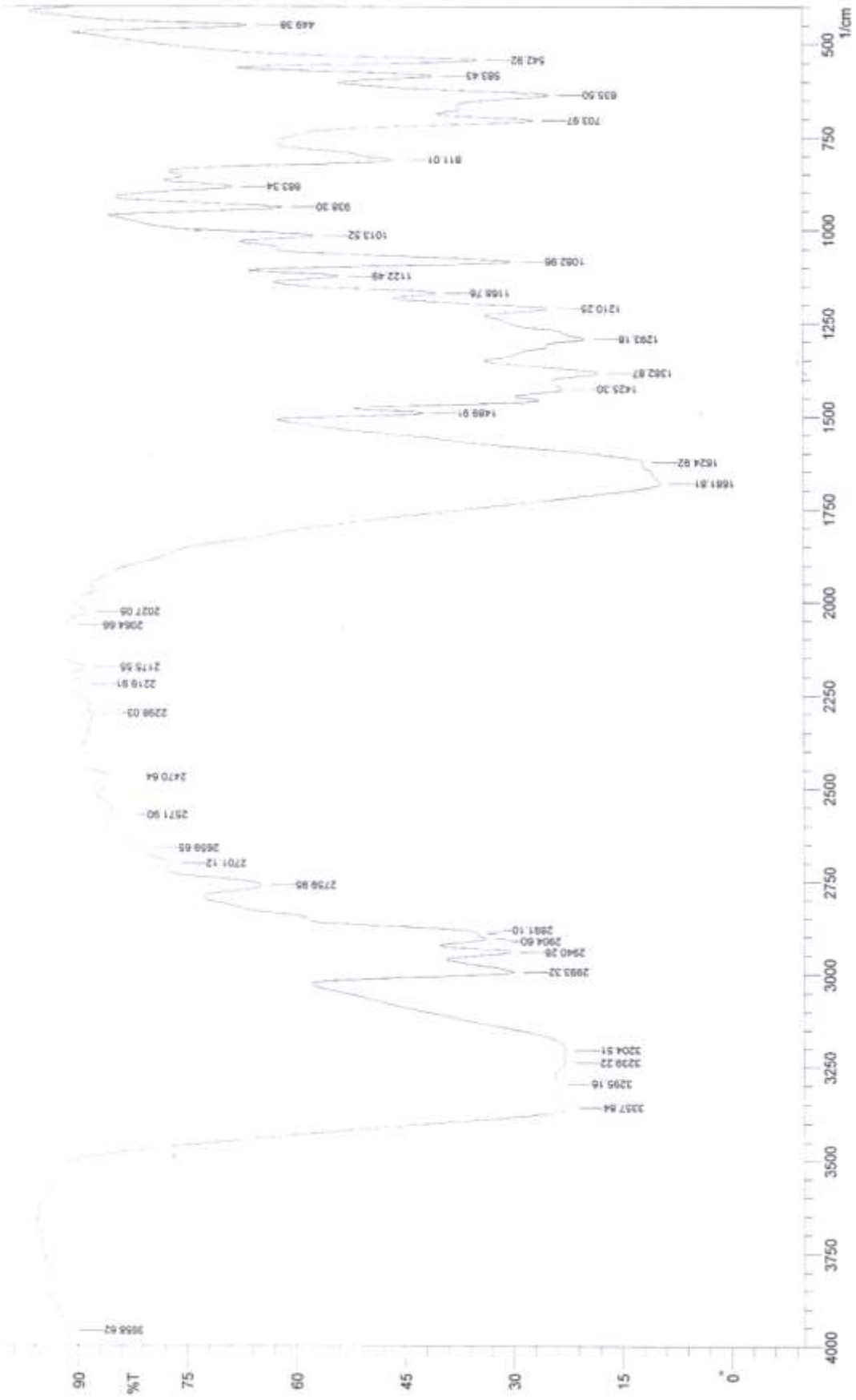


Figure 2. FTIR curve of levetiracetam.

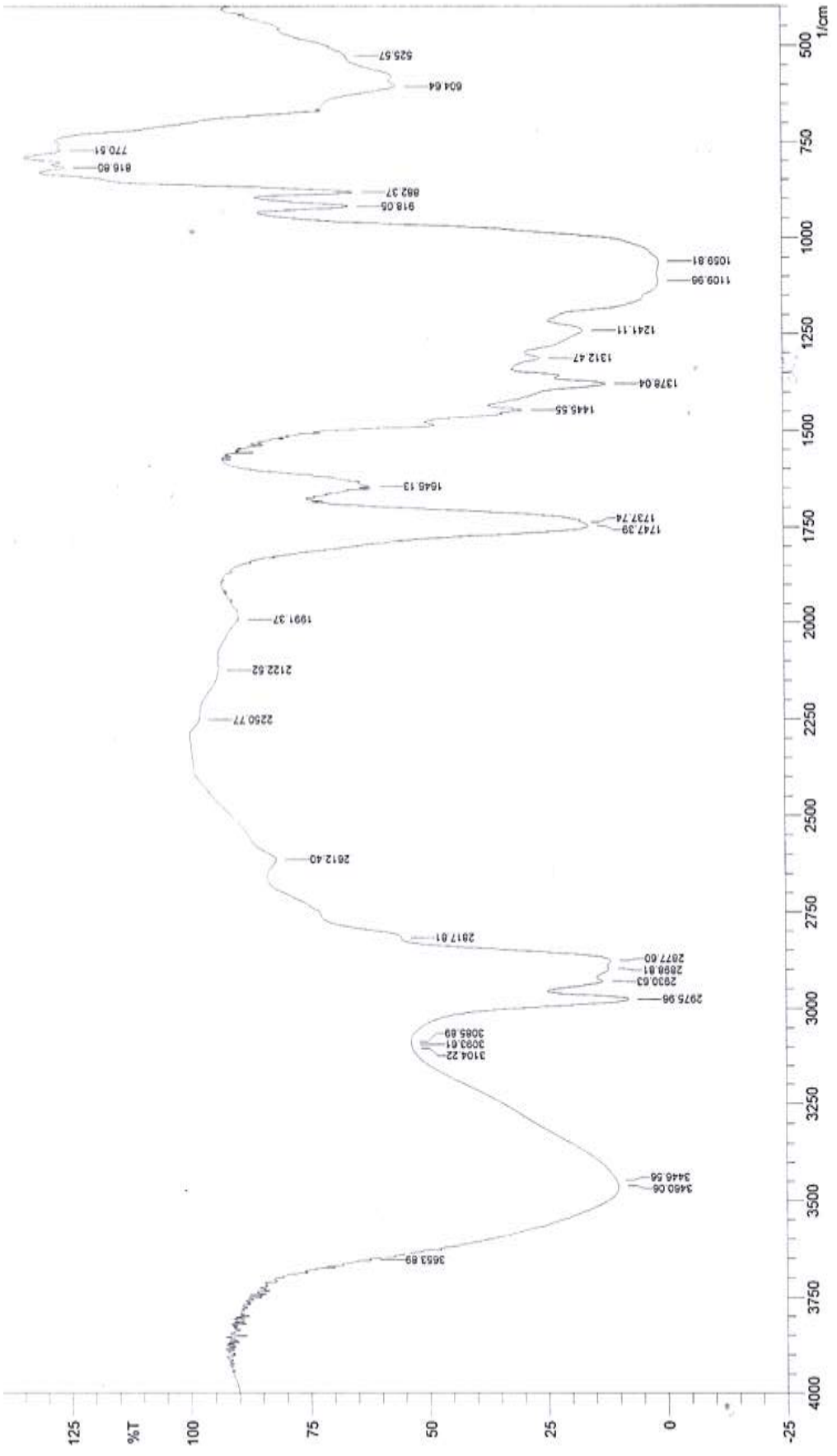


Figure 3. FTIR curve of ethyl cellulose.

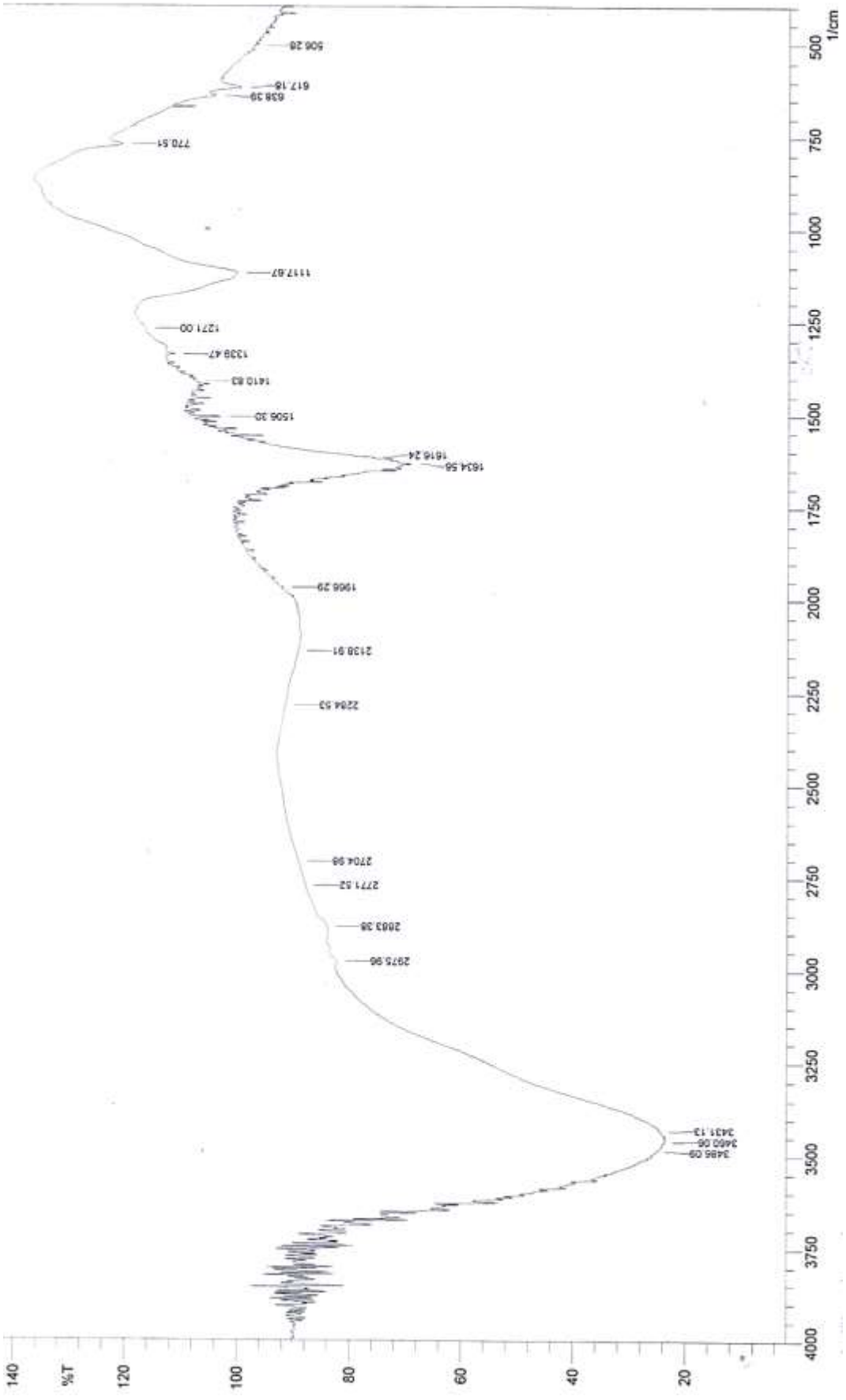


Figure 4. FTIR curve of sodium alginate table.

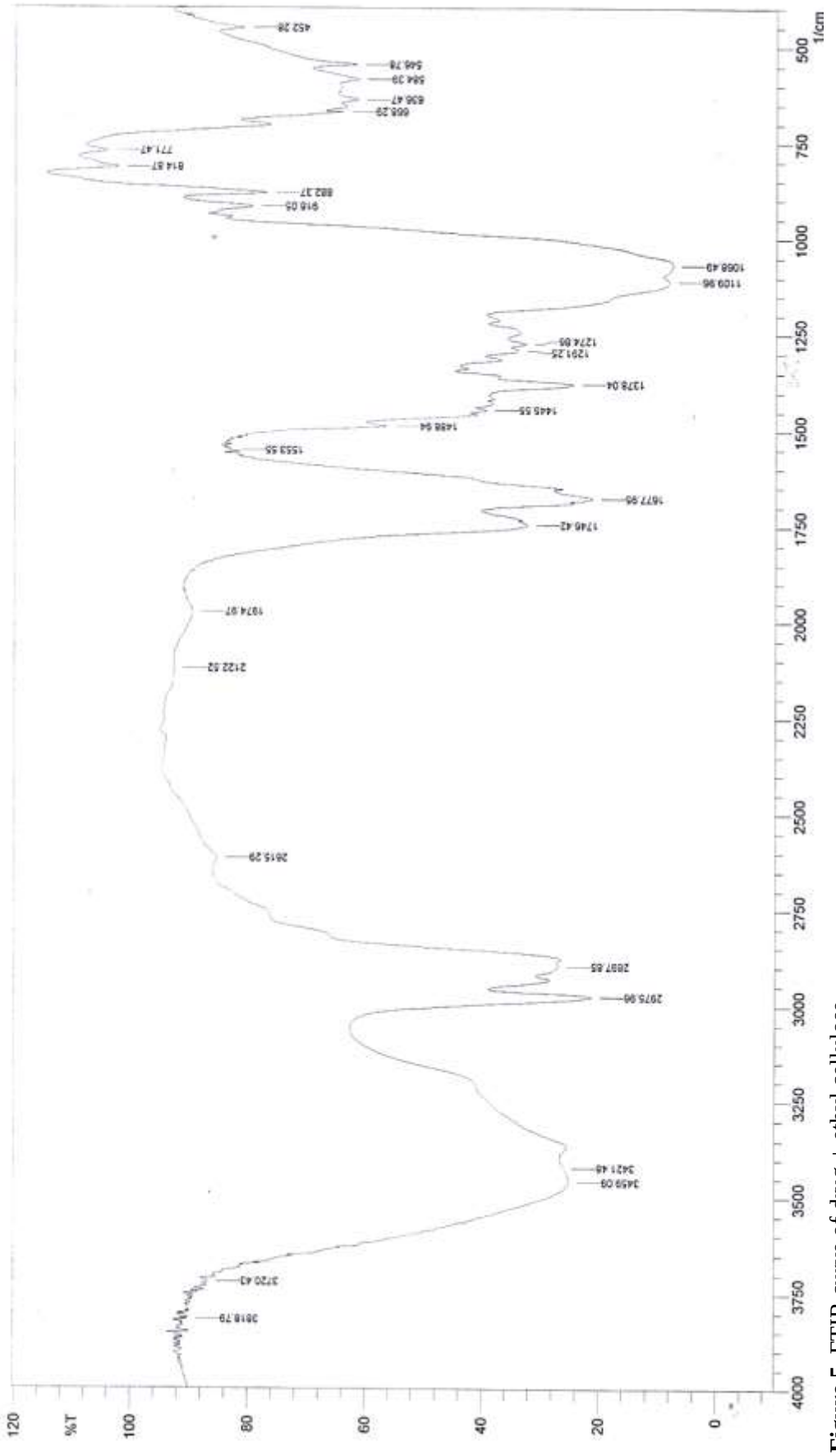


Figure 5. FTIR curve of drug + ethyl cellulose.

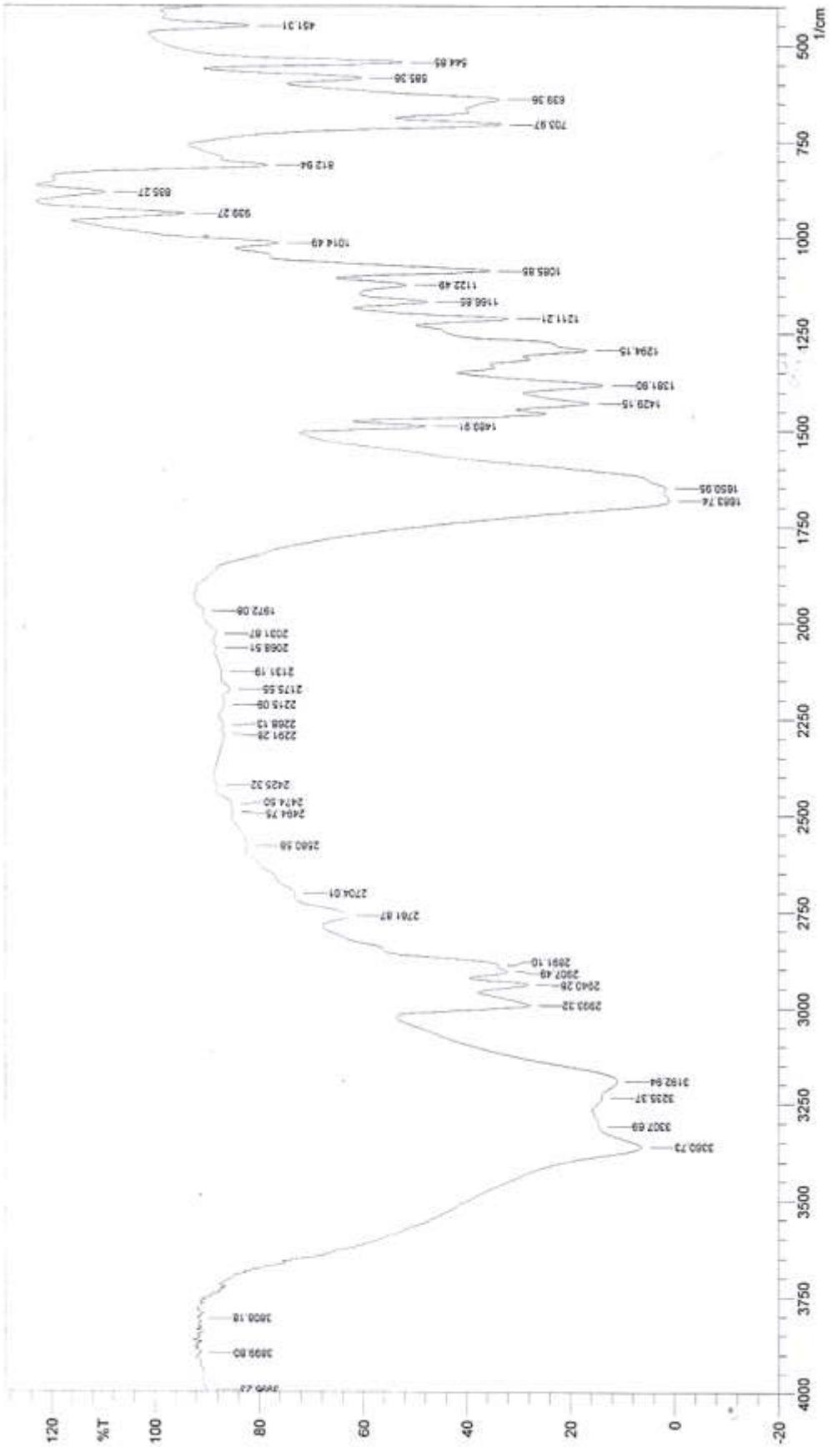


Figure 6. FTIR curve of drug + sodium alginate.

Table 7. Sodium alginate.

S.N.	Peaks	Groups	Stretching/ deformation
1	3431	O-H (Acid)	Stretching
2	1506	C=O (Carbonyl)	Stretching
3	1410	C-H (Alkane)	Stretching
4	1117	C-H (Ether)	Stretching

Table 8. Drug + ethyl cellulose.

S.N.	Peaks	Groups	Stretching/ deformation
1	3459	O-H (Alcohol)	Stretching
2	2975	C-H (Alkane)	Stretching
3	1746	C-O-C (Ether)	Stretching
4	2897	C-H (Alkane)	Bending
5	3421	N-H (Amine)	Stretching
6	1068	C-N (Amine)	Stretching

Table 9. Levetiracetam + sodium alginate.

S.N.	Peaks	Groups	Stretching/ deformation
1	3360	N-H (Amine)	Stretching
2	2891	C-H (Alkane)	Stretching
3	1429	C-H (Alkane)	Bending
4	1085	C-N (Amine)	Stretching
5	1122	C-H (Ether)	Stretching
6	1489	C=O (Carbonyl)	Stretching

Table 10. Micromeritic properties.

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's compressibility (%)	Hausners's ratio	Angle of repose
E_1	0.426	0.477	10.69	1.12	24.59°
E_2	0.422	0.473	10.78	1.12	24.53°
E_3	0.433	0.486	10.91	1.12	24.29°
E_4	0.512	0.598	14.38	1.18	27.54°
S_1	0.519	0.623	16.69	1.20	28.51°
S_2	0.513	0.634	19.21	1.23	29.41°
S_3	0.546	0.650	16.01	1.19	28.52°
S_4	0.539	0.643	16.17	1.19	28.32°

Evaluation of microsphere

The evaluation of microspheres focuses on assessing their performance, properties, and applicability across different fields. This process includes analyzing factors such as size distribution, drug release kinetics, stability, and biocompatibility to ensure their effectiveness and safety in pharmaceutical and other applications.

Drug entrapment, Percentage Yield and Drug Content

Microspheres prepared using ethyl cellulose as a synthetic polymer in four formulations (E1–E4) were analyzed for percentage yield, drug content, and entrapment efficiency. The drug content for formulations E1, E2, E3, and E4 was determined to be 57.2%, 72.4%, 85.7%, and 76.1%,

respectively. The entrapment efficiency for E1, E2, E3, and E4 was recorded as 64%, 74.9%, 91.5%, and 72%, while the percentage yield was found to be 67.2%, 61.9%, 77.3%, and 65.1%, respectively.

Similarly, microspheres prepared using sodium alginate as a natural polymer in four formulations (S1–S4) were also evaluated for percentage yield, drug content, and entrapment efficiency. The drug content results for S1, S2, S3 and S4 were found to be 61.7, 75.5, 81.1 and 83.3%. Entrapment efficiency of S1, S2, S3 and S4 was found to be 60.4, 79.3, 80.2 and 78.5%. Percentage yield of S1, S2, S3 and S4 was found to be 59.9, 64.4, 69.7 and 61.1%.

The optimal microsphere formulations using ethyl cellulose and sodium alginate polymers were determined to be E3 and S3, respectively. A comparative analysis was conducted between these two formulations.

The percentage yields of both the top formulations were compared. The yield of the E3 formulation was 77.3%, while the S3 formulation yielded 69.7%. Among the two, E3 demonstrated the higher yield.

Similarly, the drug contents of both formulations were assessed. The drug content for the E3 formulation was 85.7%, compared to 91.7% for the S3 formulation. Again, E3 showed the higher drug content.

The entrapment efficiency of both the best formulations were compared. The entrapment efficiency of E3 and S3 formulation was found to be 91.5 and 80.2% respectively. Out of two best formulations, E3 formulation yielded highest result as seen in Tables 11–13.

Scanning Electron Microscopy

Shape and surface characteristics of microspheres were examined by scanning electron microscopy analysis, as seen in Figures 7 and 8.

The morphological characterization of the best formulation of natural and synthetic microsphere were examined by SEM with suitable magnification. It revealed that best formulation of natural and synthetic microsphere was more or less spherical with rough surface shown in Figures 9 and 10.

***In-vitro* Dissolution Studies**

In-vitro drug release studies of both the formulation were compared.

Upon comparison, the E3 formulation exhibited sustained release over 16 hours, with a drug release rate of 88.5%, while the S3 formulation also demonstrated sustained release for 16 hours but with a higher drug release rate of 92.9%.

Among the two top formulations, the microsphere prepared using ethyl cellulose as the synthetic polymer was identified as the best, with a drug release of 88.5% over 16 hours.

Table 11. Data for entrapment, percentage yield and drug content of levetiracetam microspheres.

Formulation code	Percentage yield (%)	Drug content (%)	Drug entrapment (%)
E_1	67.2	57.2	64
E_2	61.9	72.4	74.9
E_3	77.3	85.7	91.5
E_4	65.1	76.1	72

S_1	59.9	61.7	60.4
S_2	64.4	75.5	79.3
S_3	69.7	81.1	80.2
S_4	61.1	83.3	78.5

Table 12. Dissolution profile of ethyl cellulose microspheres.

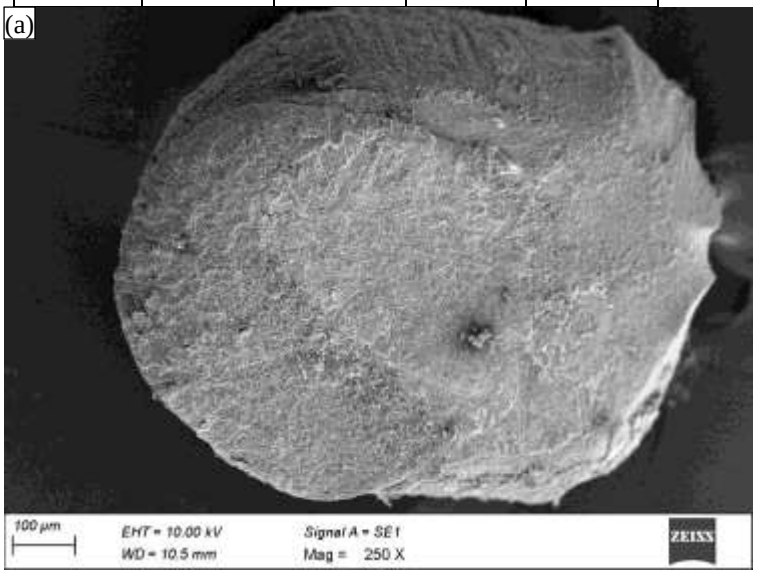
Cumulative % of Drug Release				
Time (h)	***E₁***	***E₂***	***E₃***	***E₄***
0	0	0	0	0
0.5	7.47	5.94	5.95	5.2
1	14.85	11.9	9.69	10.41
2	21.6	18.60	15.62	16.39
3	28.26	26.03	22.31	23.8
4	37.17	32.72	29.75	31.98
5	46.08	44.62	39.42	38.67
6	55.8	46.11	44.62	43.88
7	66.15	51.31	50.58	49.09
8	75.87	55.78	55.04	54.3
9	83.34	59.5	60.25	58.76
10	88.47	66.2	63.97	62.48
11	91.44	72.14	73.63	71.4
12	92.97	78.09	76.61	75.86
13		84.79	82.56	81.07
14		90.79	84.8	83.3
15		92.22	86.27	84.79
16		92.97	88.55	87.77

Table 13. Dissolution profile for sodium alginate microspheres.

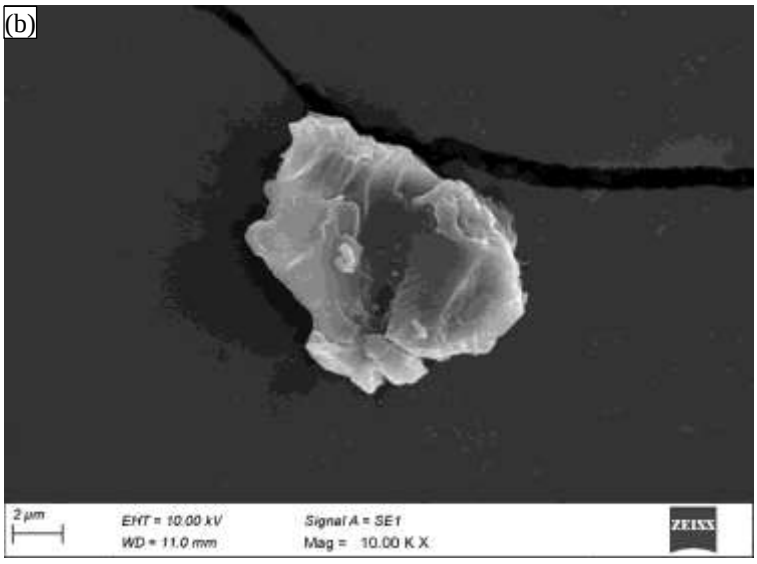
Cumulative % of Drug Release				
Time (h)	***S₁***	***S₂***	***S₃***	***S₄***
0	0	0	0	0
0.5	7.43	5.95	6.69	5.2
1	15.61	12.64	14.13	11.9
2	21.56	19.33	20.83	17.85
3	28.26	23.8	26.78	23.05
4	40.16	29.75	38.67	29
5	45.37	40.9	44.62	38.67
6	55.04	45.37	53.55	44.62
7	63.96	52.07	62.48	51.32
8	75.12	56.52	72.89	55.78
9	81.81	60.25	77.01	59.5
10	87.77	66.94	81.81	72.14
11	90.74	72.9	86.27	78.84
12	92.22	79.58	89.25	84.79

13	92.97	86.27	90.73	89.25
14		90.74	91.49	90.74
15		91.49	92.22	91.49
16		92.22	92.97	92.22

(a)



(b)



(c)

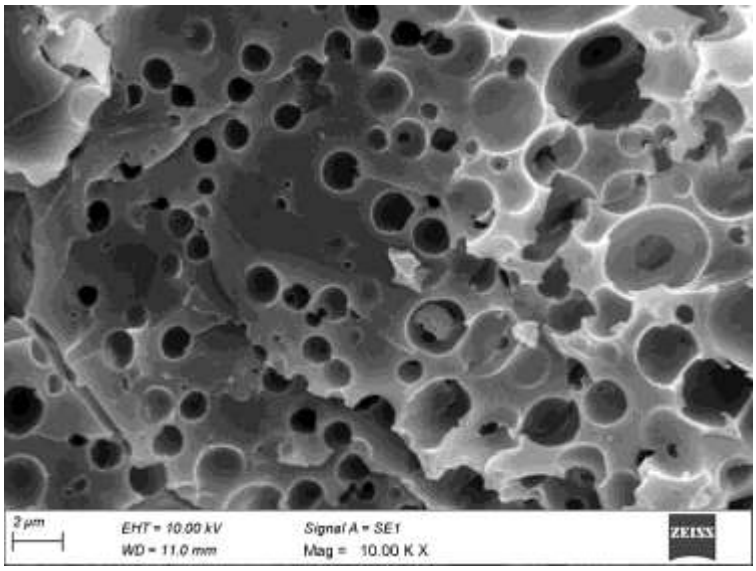
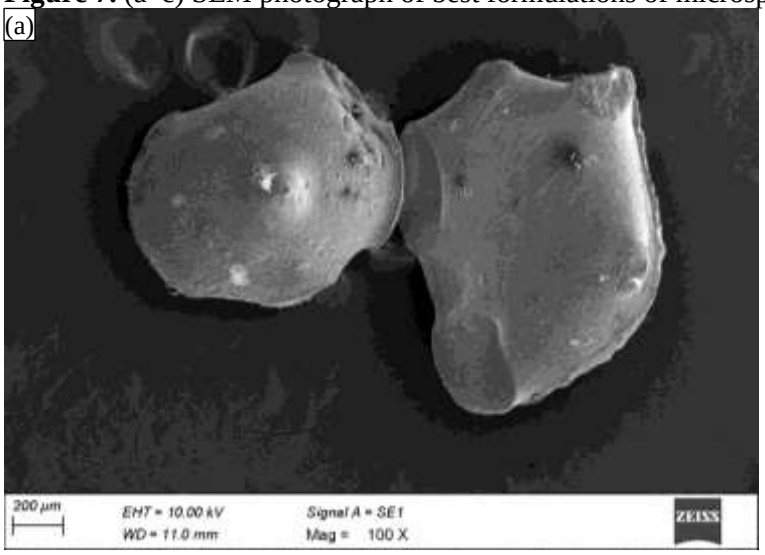
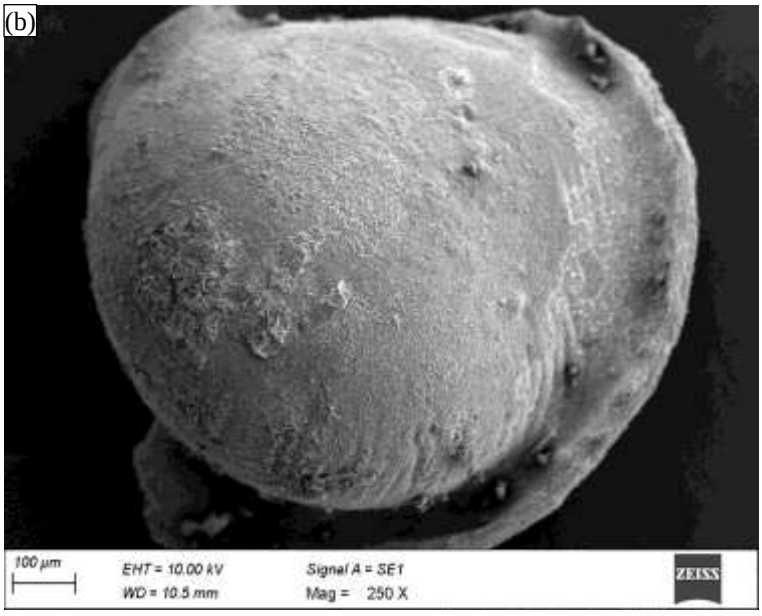


Figure 7. (a–c) SEM photograph of best formulations of microsphere using ethyl cellulose.

(a)



(b)



(c)

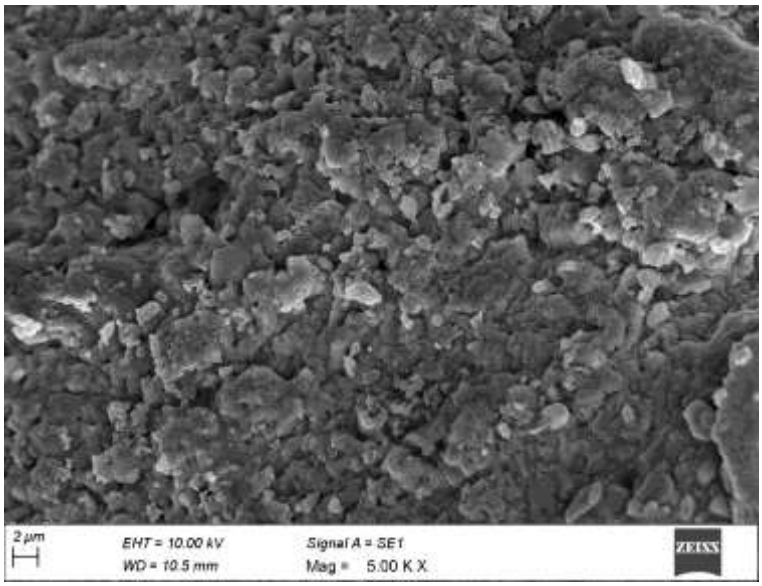


Figure 8. SEM photograph of best formulations of microsphere using sodium alginate.

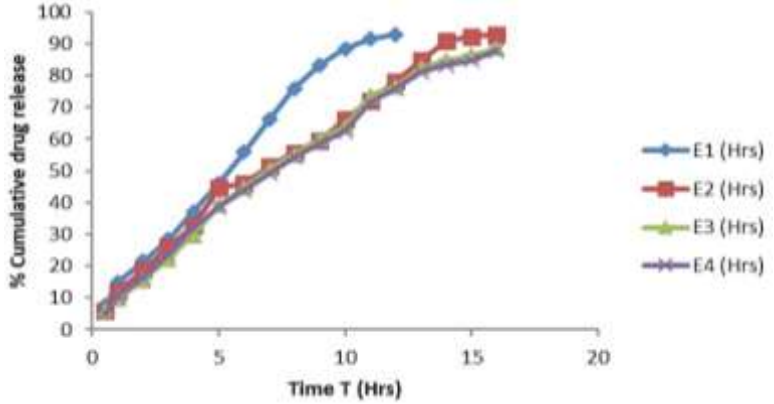


Figure 9. Percentage drug release for formulation E1 to E4.

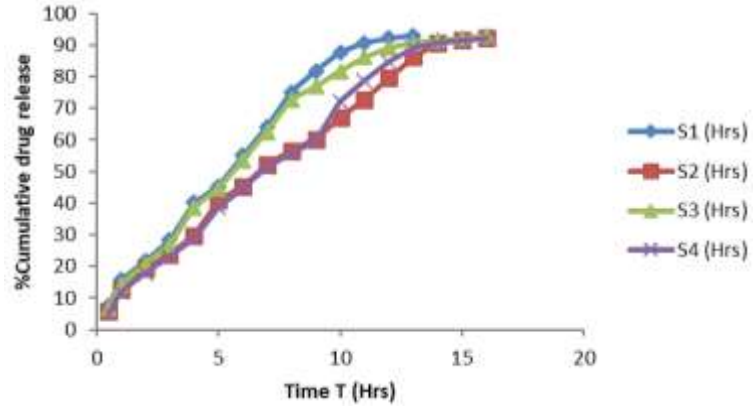


Figure 10. Percentage drug release for formulation S1 to S4.

Table 14. Kinetic data of best formulations.

Formulation Code	Zero order plot (R^2)	First order plot (R^2)	Higuchi plot (R^2)	Peppas plot (R^2)
E3	0.960	0.975	0.987	1.2
S3	0.870	0.984	0.976	1.3

Release Kinetics

The drug release data from in-vitro studies were analyzed using different kinetic models, such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas plots, to determine the release mechanism from the microspheres. Additionally, the rate constants for each model were calculated.

E3 formulation of microspheres using ethyl cellulose as synthetic polymer followed Korsmeyer-Peppas plot with super case II transport mechanism. S3 formulation of microspheres using sodium alginate polymer followed Korsmeyer-Peppas plot with super case II transport mechanism as seen in Table 14.

SUMMARY AND CONCLUSION

Microspheres are considered highly effective for sustained drug delivery. This study highlights the potential of microspheres in slowing down drug release, which can reduce dosing frequency and, as a result, enhance patient compliance.

This study presents a comparative analysis of Levetiracetam-loaded microspheres using ethyl cellulose as a synthetic polymer and sodium alginate as a natural polymer. The solvent evaporation and ionic gelation techniques were successfully utilized to create Levetiracetam-loaded microspheres with optimal drug encapsulation, ensuring sustained drug release over an extended period.

The microspheres were evaluated for their percentage yield, drug content, entrapment efficiency, and in-vitro dissolution performance.

We achieved good yields of microspheres with satisfactory encapsulation efficiency, particularly for the Levetiracetam-loaded microspheres. The drug content and entrapment efficiency were found to be favorable across all formulations. Among them, E3 exhibited the best properties.

The formulations showed efficient drug release in the simulated intestinal medium, making it suitable for absorption. Moreover, the release followed a steady rate in this environment. The in-vitro release data showed a strong correlation with the Korsmeyer-Peppas model, with a regression value of 0.9957 and an n value of 1.2.

The release kinetic study indicated that the drug release from microspheres follows the Korsmeyer-Peppas model, with the release occurring via super case II transport and erosion. Ethyl cellulose was identified as the most suitable polymer for preparing Levetiracetam microspheres, offering high entrapment efficiency, drug content, percentage yield, and sustained release over 16 hours.

The formulations exhibited linear behavior in the kinetic models, with E3 being chosen as the optimized formulation, showing 88.55% drug release after 16 hours. For the optimized formulation, the drug entrapment efficiency was 91.5%, the percentage yield was 77.3%, and the drug content was 85.7%.

A comparison was made between the top formulations, E3 and S3, which were prepared using ethyl cellulose as a synthetic polymer and sodium alginate as a natural polymer, respectively. Among the formulations, microspheres prepared with ethyl cellulose exhibited the best performance, achieving the highest drug content (85.7%), entrapment efficiency (91.5%), percentage yield (77.3%), and in-vitro drug release (88.55%) over 16 hours. Based on these results, ethyl cellulose was identified as the most suitable polymer for developing a novel drug delivery system for Levetiracetam.

While controlling drug release profiles has been a primary focus of pharmaceutical research and development over the past decade, regulating gastrointestinal (GI) transit profiles could become the

focus in the coming decades. This may lead to the development of products with enhanced therapeutic potential and significant benefits for patients.

The use of such formulations reduces dosing frequency and drug loss, while also enhancing the bioavailability of the drug. All the findings suggest that microspheres can be an optimal drug delivery system for Levetiracetam-loaded formulations.

Additional studies can be conducted on the stability of Levetiracetam-loaded microspheres and the enhancement of therapeutic efficacy through targeted delivery to specific receptor sites.

REFERENCES

1. Reddy BV, Krishnaveni K. Formulation and evaluation of efavirenz microspheres. Der Pharm Lett. 2015; 7(6): 1–9.
2. Thanoo BC, Sunny MC, Jayakrishnan A. Cross-linked chitosan microspheres: preparation and evaluation as a matrix for the controlled release of pharmaceuticals. J Pharm Pharmacol. 1992 Apr; 44(4): 283–6.
3. Sahil K, Akanksha M, Premjeet S, Bilandi A, Kapoor B. Microsphere: A review. Int J Res Pharm Chem. 2011; 1(4): 1184–98.
4. Virmani T, Gupta J. Pharmaceutical application of microspheres: an approach for the treatment of various diseases. Int J Pharm Sci Res. 2017; 8(8): 3253–60.
5. Li SP, Kowarski CR, Feld KM, Grim WM. Recent advances in microencapsulation technology and equipment. Drug Dev Ind Pharm. 1988 Jan 1; 14(2–3): 353–76.
6. Kreuter J, Nefzger M, Liehl E, CzokR VR. Microspheres–A Novel Approach in Drug Delivery System. J Pharm sci. 1983; 72: 1146.
7. Margel S, Wiesel E. Acrolein polymerization: monodisperse, homo, and hybrido microspheres, synthesis, mechanism, and reactions. J Polym Sci: Polymer Chemistry Edition. 1984 Jan; 22(1): 145–58.
8. Wakiyama N, Juni K, Nakano M. Preparation and evaluation in vitro of polylactic acid microspheres containing local anesthetics. Chem Pharm Bull. 1981 Nov 25; 29(11): 3363–8.
9. Shanthi NC, Gupta R, Mahato KA, Traditional and Emerging Applications of Microspheres: A Review, International Journal of Pharm. Tech Research. 2010; 2(1):675–81.
10. Toshio Y, Mitsuru H, Shozo M, Hitoshi S. Specific delivery of mitomycin c to the liver, spleen and lung: Nano-and m1crospherical carriers of gelatin. Int J Pharm. 1981 Apr 1; 8(2): 131–41.
11. Patel NR, Patel DA, Bharadia PD, Pandya V, Modi D. Microsphere as a novel drug delivery. Int J Pharm & Life Sci. 2011 Aug 1; 2(8): 992–997.
12. Herfarth H, Obermeier F, Andus T, Rogler G, Nikolaus S, Kuehbacher T, Schreiber S. Improvement of arthritis and arthralgia after treatment with infliximab (Remicade) in a German prospective, open-label, multicenter trial in refractory Crohn's disease. Am J Gastroenterol. 2002 Oct 1; 97(10): 2688–90.
13. Kavita K, Ashvini VR, Ganesh NS. Albumin microspheres. Unique system as drug delivery carriers for non steroidal anti-inflammatory drugs. Int J Pharm Sci Rev Res. 2010; 5(2): 10–17.
14. Virmani T, Gupta J. Pharmaceutical application of microspheres: an approach for the treatment of various diseases. Int J Pharm Sci Res. 2017; 8(8): 3253–60.
15. Gullotti E, Yeo Y. Extracellularly activated nanocarriers: a new paradigm of tumor targeted drug delivery. Mol Pharm. 2009 Aug 3; 6(4): 1041–51.
16. Alagusundaram M, Chetty MS, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S. Microspheres as a novel drug delivery system: A review. Int J Chem Tech Res. 2009 Jul; 1(3): 526–34.
17. Rathore B, Yadav A, Nayak G, Saraogi GK, Singhai AK. A review on microspheres as drug delivery carriers for management of diabetes mellitus. Int J Pharm & Life Sci. 2012 Oct 1; 3(10): 2064–2070.

18. Prasad BS, Gupta VR, Devanna N, Jayasurya K. Microspheres as drug delivery system-a review. J Glob Trends Pharm Sci. 2014; 5(3): 1961–72.

