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

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Abstract

In 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 preformulation 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%, Drug content 85.7% Comparison was made between the best formulations E3 & 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 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 hours 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 GI transmit profile could be the focus of next few decades and might results 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 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.

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Keywords: Formulation, Evaluation, Levetiracetam, Microspheres, Scanning electron Microscope.

INTRODUCTION

The constraints associated with conventional dosage forms and classical oral drug delivery systems is leading the pharmaceutical community towards a new era of drug delivery systems i.e., Novel Drug Delivery Systems (NDDS). The concept of targeted drug delivery, indeed, as a subset of NDDS is being investigated substantially

nowadays. However, the concept of targeting is not new to the drug delivery domain. It dates back to 1906, when sir Paul Ehrlich, postulated the concept of 'magic bullet' and laid down the foundation of a new paradigm in the field of drug delivery [1]. Thenceforth, the concept has been evolving continuously, with newer and innovative approaches adding on to the existing knowledge.

Targeting refers to the selective accumulation of cargo in organs, tissues, cells or intracellular structures by systemic or local drug delivery [2]. The preferential accumulation of the drugs at the targeted site spares the rest of the healthy tissues of the body and increases the therapeutic index of the drug, thus improving the overall treatment outcome [3]. Targeting a drug delivery system, either passively or by specific means requires the use of carriers such as nanoparticles, liposomes, micellar systems, microspheres etc [4].

The growing number of studies in the recent years, illustrating the potential use of microspheres as drug delivery carriers for targeted delivery has attracted the attention of researchers across the globe. Microspheres are free-flowing particles ranging between 1 μm and 1000 μm and are capable of delivering the therapeutics with a satisfactory sustained release/controlled release profile [5]. They are matrix particles in which the actives are homogeneously distributed in the polymeric network. They are capable of encapsulating small molecules, proteins/peptides and nucleic acids [6]. The high translational efficiency and clinical success rate compared to nanoparticles give them an upper-hand over nanoparticulate drug delivery systems [7]. They provide several advantages over conventional dosage forms like enhanced solubility of poorly soluble drugs, protection of drugs from enzymatic and photolytic degradation, decreased dosing frequency, improved bioavailability, providing controlled release profile, reduction in dose and drug toxicities, etc [8]. They can be manufactured by various techniques including solvent evaporation [9, 10], spray drying [11, 12], phase separation [13] and polymerization [14].

The currently marketed microsphere formulations are available as long-acting injectable depots which provide controlled release of the encapsulated drug over a specific period of time. Most of these formulations contain hormonal analogues as the encapsulated drugs [15]. Apart from hormones, several other drugs acting on central nervous system and some opioid antagonists are also available as microsphere formulations for several applications [16]. Unfortunately, microspheres for targeted delivery of the drugs are not available in the market till date. However, a lot of research is currently in progress where these carriers are being explored for their applications in Targeted Drug Delivery System (TDDS). Indeed, several ongoing clinical trials on microspheres encapsulating anticancer drugs like doxorubicin (DOX) and irinotecan for colon cancer, rectal cancer and hepatocellular carcinoma are the proofs which showcase the potential of microspheres to be used in targeting drugs to desired locations [17, 18].

Levetiracetam is an antiepileptic drug which acts by attach to specific sites (SV2A) on surface of nerve cells and supress the abnormal activity of the nerve cells in the brain and prevent the spread of signals that causes seizures.

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.

Hence an attempt was made in the present study to deliver the drug in the form of microspheres. Smaller amount of drug is sufficient to elicit the pharmacological response for longer period of time. Moreover, first pass metabolism can be minimized and the utilization of the drug delivery. This would be advantageous over conventional solid dosage forms.

To achieve this goal various prototypic trails were taken and evaluated with respect to the various quality parameters such as bulk density, tapped density, carr's index, angle of repose, swelling index, particle size determination, scanning electron microscopy and *In-vitro* drug release studies were done.

MATERIALS AND METHODS

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

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)

Weighed 27.218 grams of potassium dihydrogen phosphate and dissolved in 1000 ml of water.

Sodium Hydroxide Solution (0.2M)

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

Determination of λmax

A solution of Levetiracetam containing the concentration 10 µg/ml was prepared in pH 7.4 phosphate buffer and UV spectrum was taken using double beam spectrophotometer. The solution was scanned in the range of 200–400 nm. Wavelength maximum absorption of Levetiracetam was found to be 221 nm.

Standard Graph of Levetiracetam in Phosphate Buffer pH 7.4

100 mg of Levetiracetam was dissolved in 100 ml of phosphate buffer pH 7.4 which contains the concentration 1000 µg/ml. From this 10 ml was transferred and made to 100 ml with phosphate buffer pH 7.4 which contains the concentration of 100 µg/ml. from this 10 ml was transferred and made to 100 ml with phosphate buffer pH 7.4 which contains the concentration of 10 µg/ml.

From this 1 ml to 10 ml were pipetted out and made up to 10 ml with phosphate buffer pH 7.4 to get solution of concentration ranging from 1 µg/ml-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 Table 1 and Table 2.

METHOD OF PREPARATION

Preparation of Levetiracetam Microspheres by Solvent Evaporation Method

The preparation of microspheres using organic solvent (ethyl acetate), stirring speed (700 rpm), and organic to aqueous ratio (1:10). Ethyl cellulose was taken in a crucible is dissolved in ethyl acetate to form a homogenous solution. Levetiracetam was added to the homogenous solution and mixed thoroughly. Dispersion was then added as a thin stream to 100 ml of aqueous mucilage of 0.5% sodium CMC contained in a 250 ml beaker while being stirred at 700 rpm to emulsify the added dispersion as

a fine droplet. The solvent removal was achieved by continuous stirring at room temperature for three hours to produce spherical microspheres. The microspheres formed were collected by filtration and washed repeatedly with distilled water. The product was then air dried as seen in Table 3 and Table 4

Preparation of Levetiracetam Microspheres by Ionotropic Gelation Technique

The preparation of microspheres using calcium chloride concentration. Levetiracetam loaded microspheres were prepared by dissolving sodium alginate in distilled water by gently heating it on using magnetic stirrer to get a bubble free solution comprising different concentrations (1% to 4%). Levetiracetam was accurately weighed and dissolved in methanol and added to the polymeric solution to form a clear solution. The dispersions were sonicated for 30 min to remove any air bubbles that may have been formed during the stirring process. The homogenous dispersion was added dropwise via a 20-gauge hypodermic needle fitted with a syringe into 50 mL of 4 % solution of gelling agent $CaCl_2$ being stirred at 200 rpm for 10 min. The droplets from the dispersions instantaneously gelled into discrete Levetiracetam-alginate matrices upon contact with the solution of gelling agents. The formed alginate microspheres were further stirred in the solution of gelling agents for an additional 1 h. On expiration, solution of gelling agent was decanted and the microspheres were washed with distilled water. The microspheres were filtered and dried at 50°C as seen in Table 3 and Table 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.

Table 2. Composition of Ethyl cellulose containing Levetiracetam

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

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

Data for Calibration Curve of Levetiracetam

Drug Excipient Compatibility Studies

Drug-excipient compatibility is confirmed by FTIR Spectroscopy for which, FTIR spectra of Levetiracetam, ethyl cellulose, sodium alginate alone was compared with FTIR spectrum of physical mixture of Levetiracetam, ethyl cellulose, sodium alginate. The spectrum of Levetiracetam showed a characteristic peaks at 3357 cm^{-1} (N-H Stretching), 2891 cm^{-1} (C-H Stretching), 1425 cm^{-1} (C-H Bending) 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 Table (5–10).

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

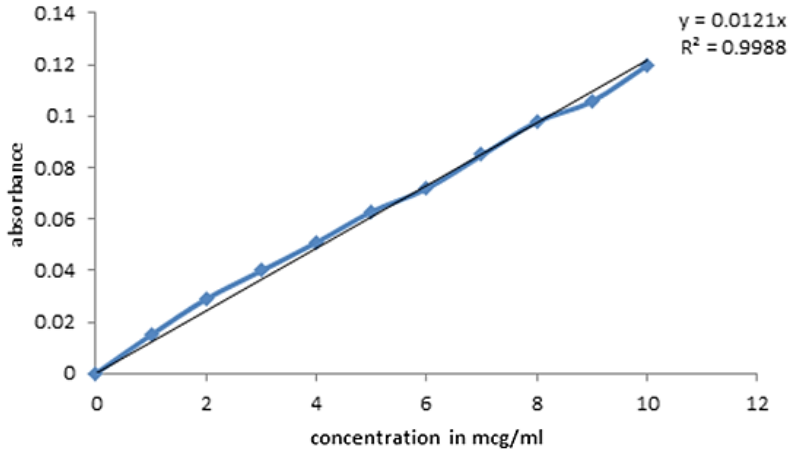


Figure 1. Calibration curve of Levetiracetam.

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

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

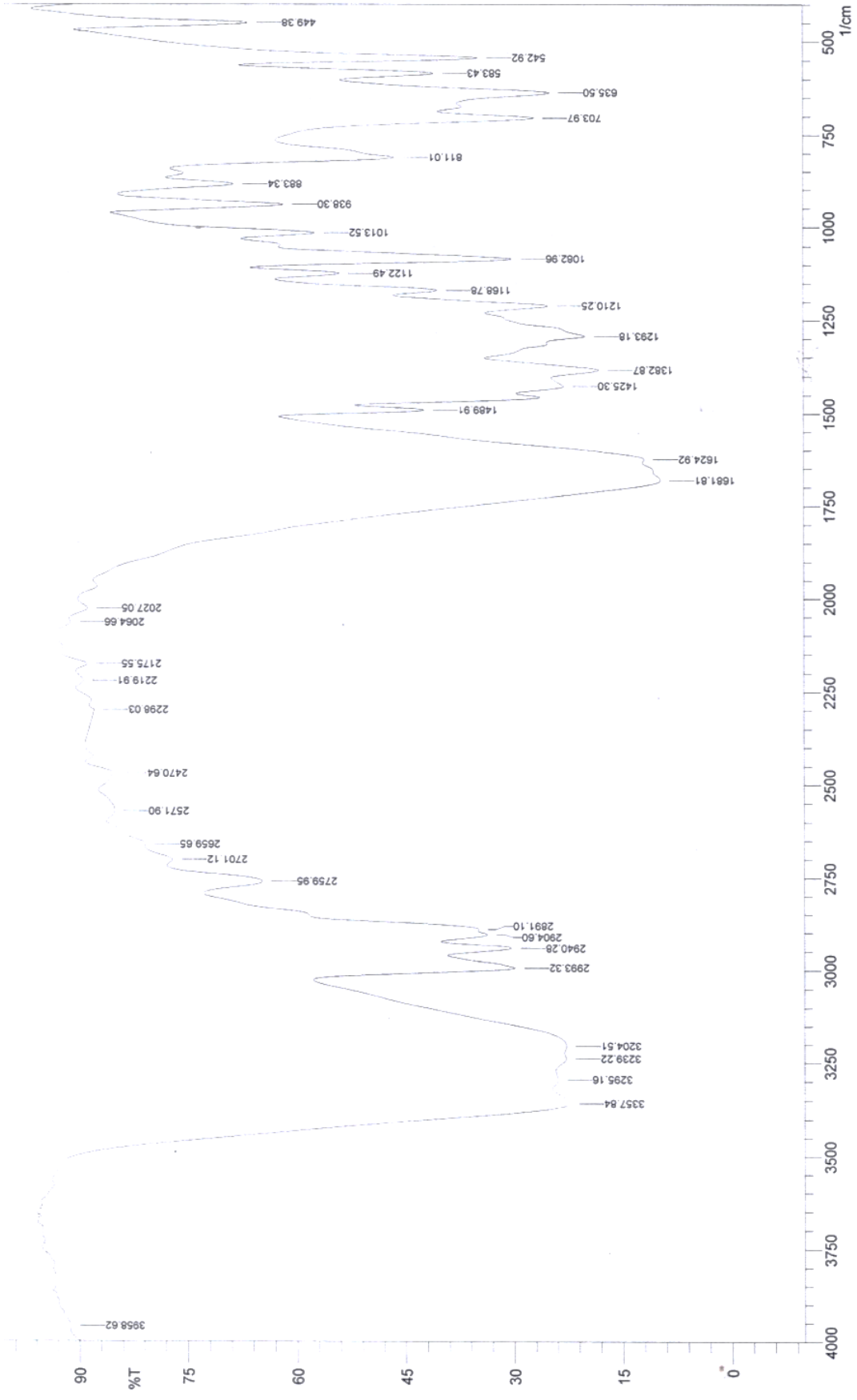


Figure 2. FTIR curve of levetiracetam.

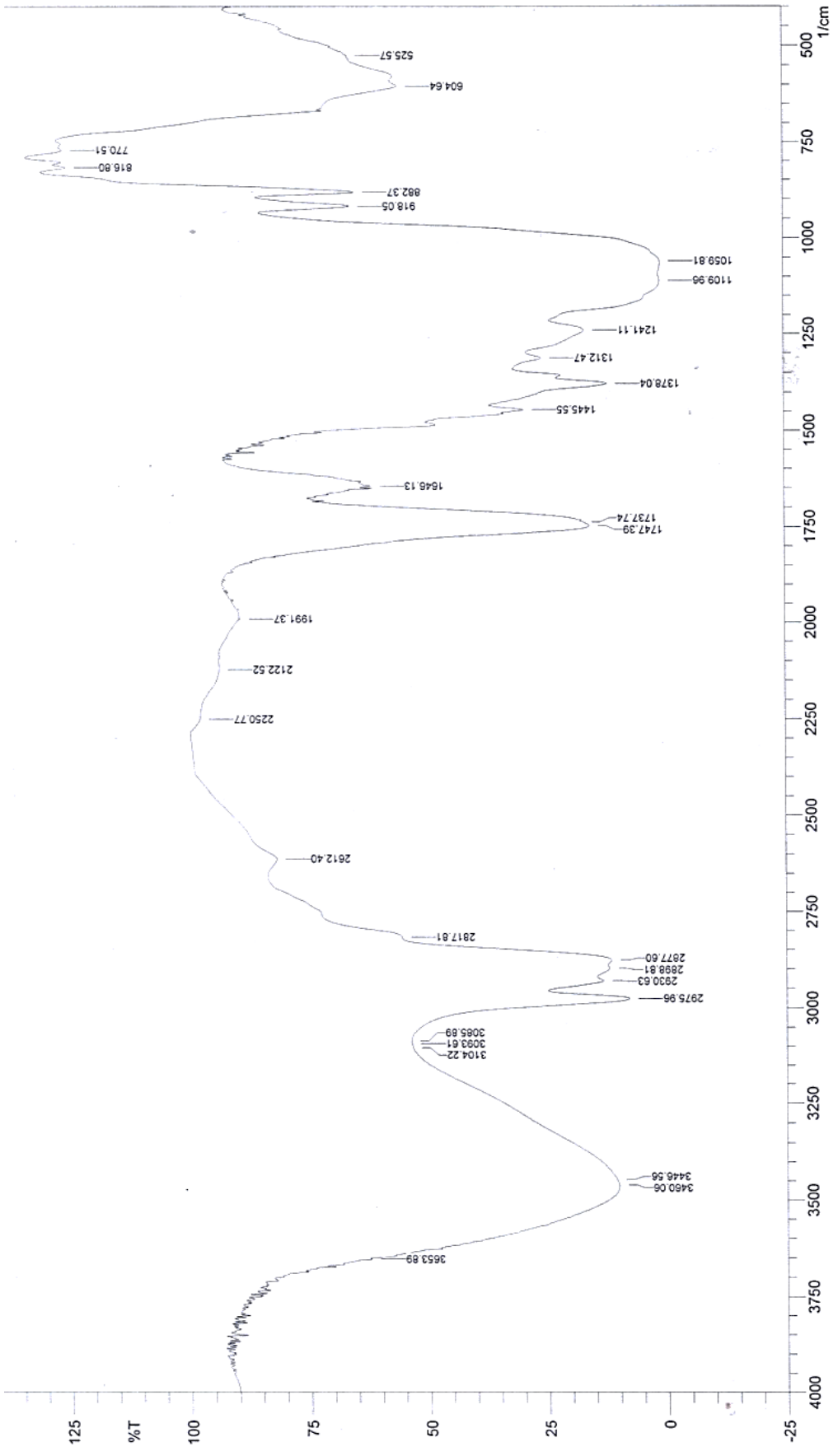


Figure 3. FTIR curve of ethyl cellulose.

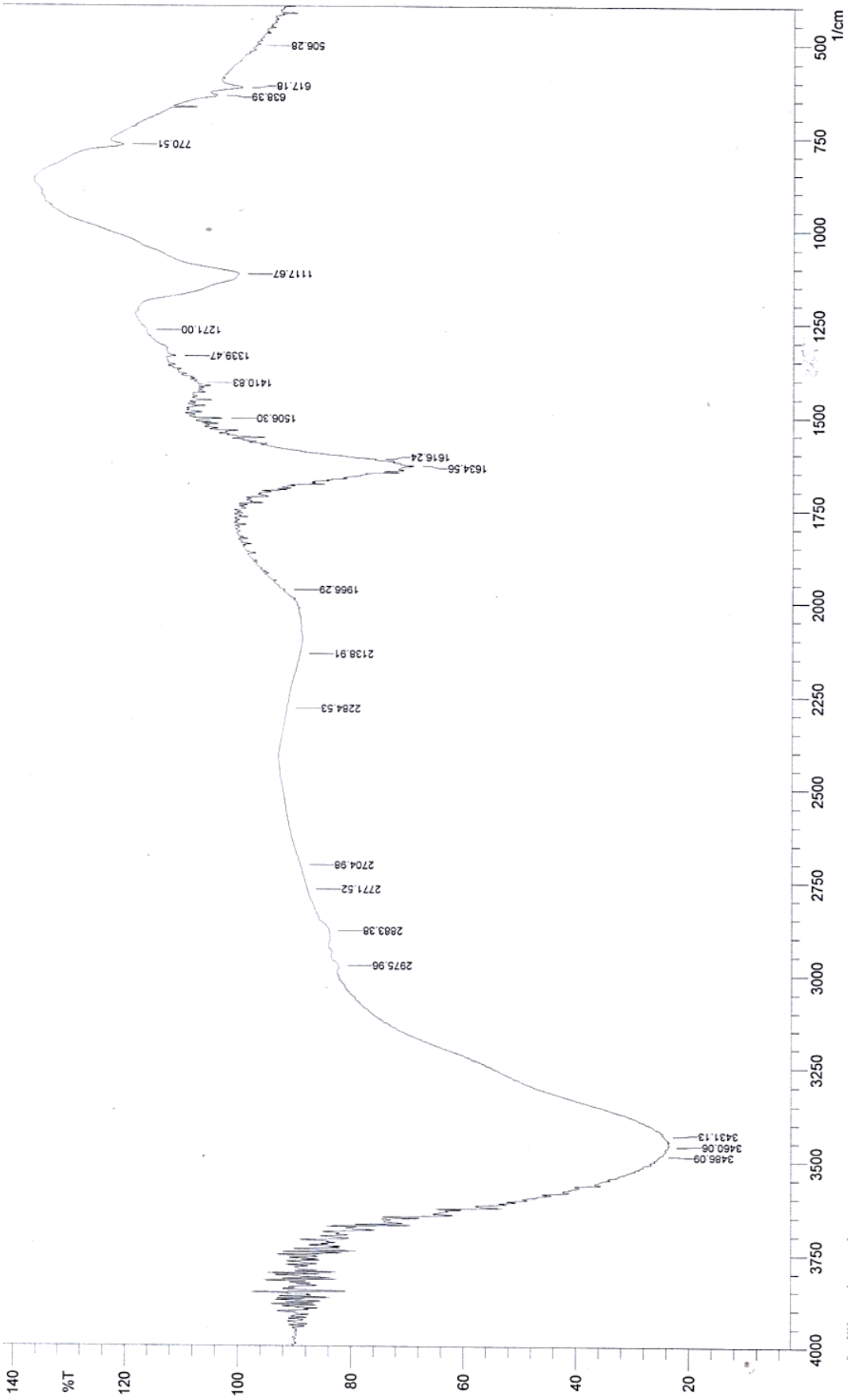


Figure 4. FTIR curve of sodium alginate table.

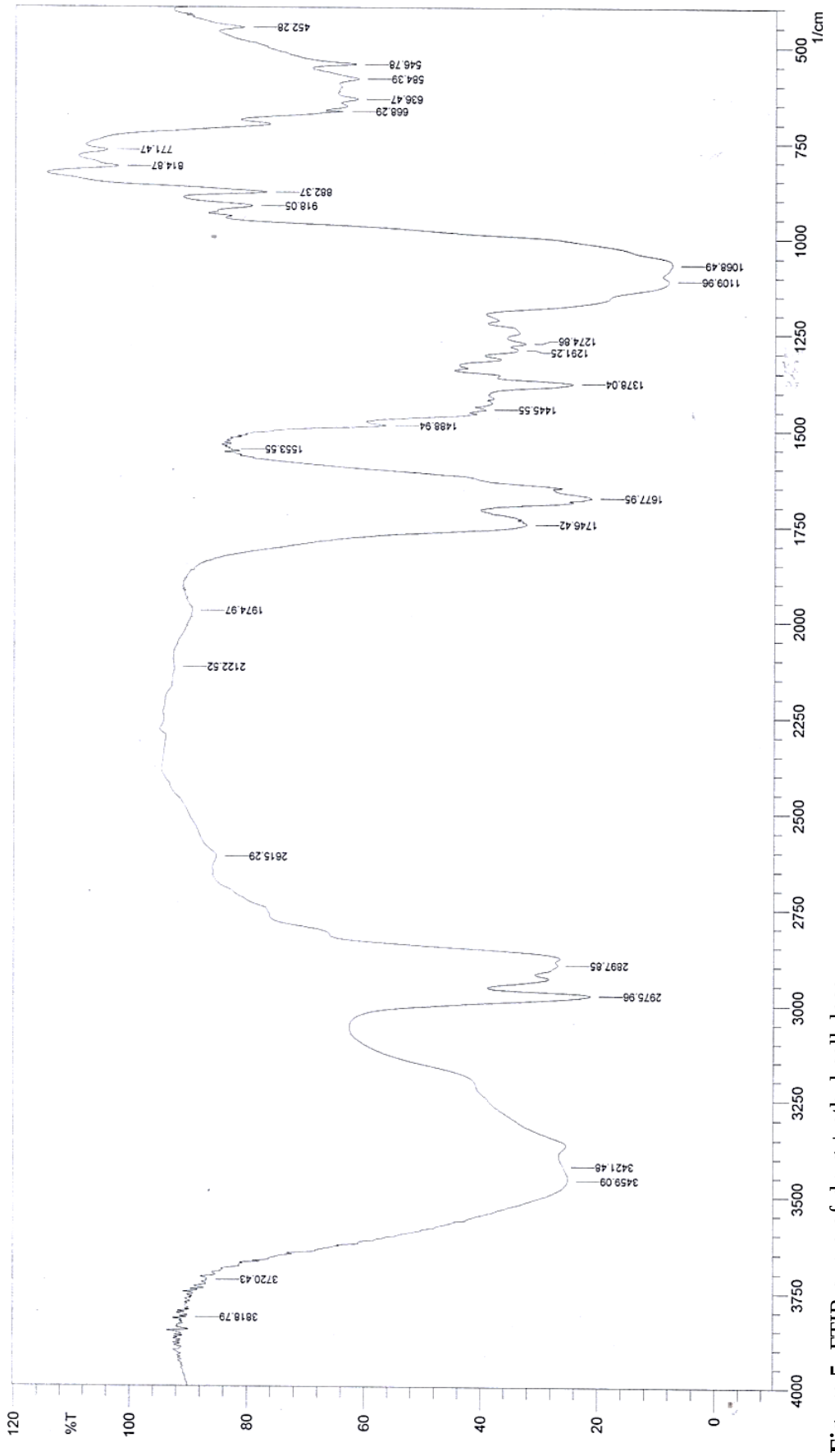


Figure 5. FTIR curve of drug + ethyl cellulose

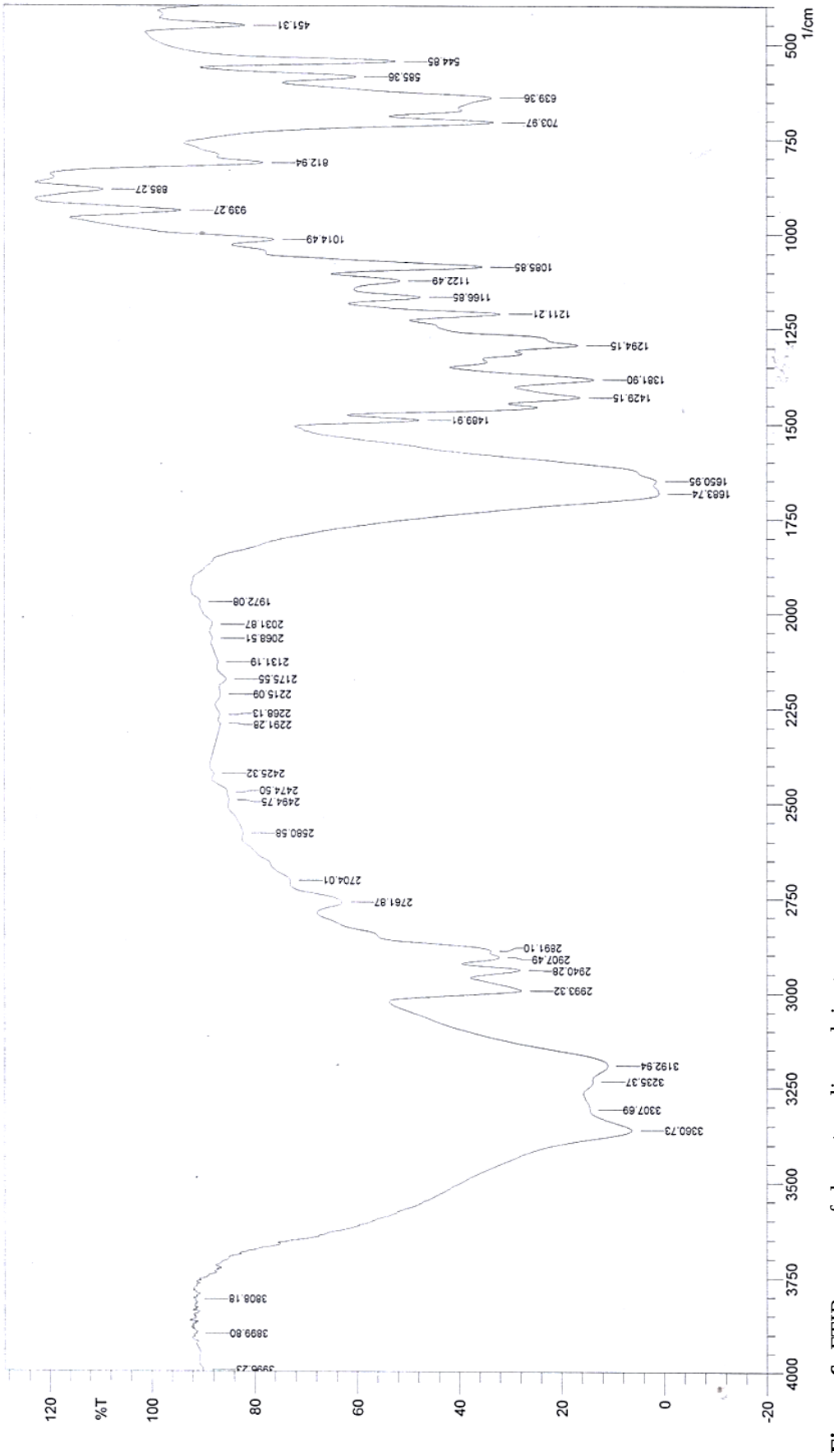


Figure 6. FTIR curve of drug + sodium alginate.

Table 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:

Drug entrapment, Percentage Yield and Drug Content

The prepared microsphere using ethyl cellulose as a synthetic polymer of four formulations E1–E4 were evaluated for percentage yield, drug content, entrapment efficiency. The drug content results for E1, E2, E3 and E4 was found to be 57.2%, 72.4%, 85.7% and 76.1%. Entrapment efficiency of E1, E2, E3 and E4 was found to be 64%, 74.9%, 91.5% and 72%. Percentage yield of E1, E2, E3 and E4 was found to be 67.2%, 61.9%, 77.3% and 65.1%.

The prepared microsphere using sodium alginate as a Natural polymer of four formulations S1 – S4 were evaluated for percentage yield, drug content, entrapment efficiency. The drug content results for S1, S2, S3 and S4 was 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 best formulation of microsphere using ethyl cellulose and sodium alginate polymers, were found to be E3 and S3 respectively. A comparative study was done among the best formulation.

The percentage yield of both the best formulation were compared. The percentage yield of E3 and S3 formulation was found to be 77.3%, 69.7% respectively. Out of two best formulations E3 formulation yielded highest result.

The drug content of both the best formulation were compared. The drug content of E3 and S3 formulation was found to be 85.7%, 91.7% respectively. Out of two best formulations E3 formulation yielded highest result.

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

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 (Hr)	***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 (Hr)	***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

Scanning Electron Microscopy

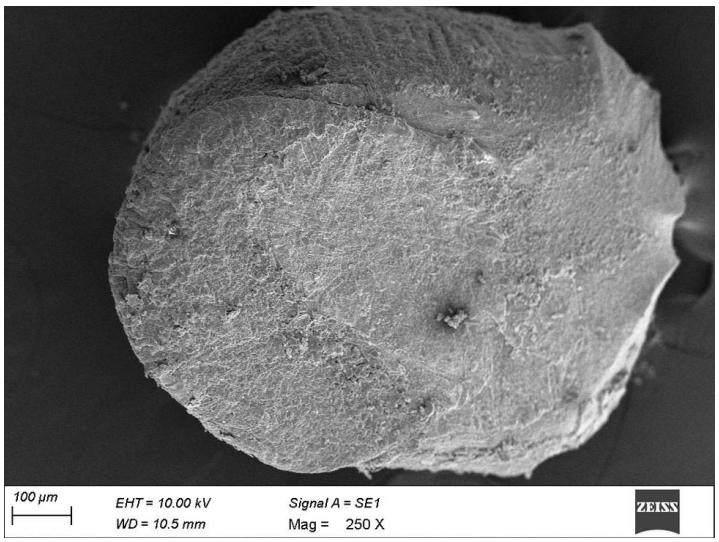
Shape and surface characteristics of microspheres examine by scanning electron microscopy analysis as seen in Figure 7 and Figure 8.

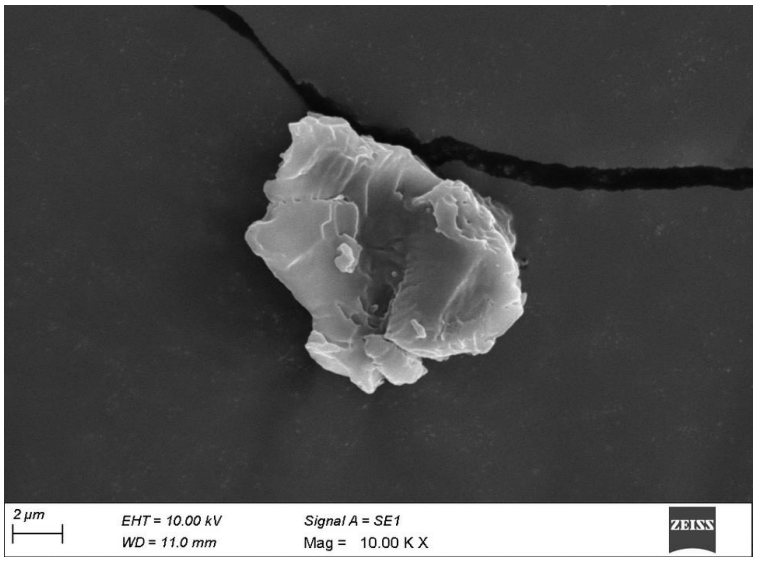
The morphological characterization of the best formulation of natural and synthetic microsphere were examined by SEM with suitable magnification. It revealed that best formulation of natural and synthetic microsphere were more or less spherical with rough surface shown in Figure 9 and Figure 10.

In-vitro Dissolution Studies

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

On comparison E3 formulation was showing sustained release for 16 hours with drug release rate of 88.5% when compared to S3 formulation which was sustained for 16 hours with 92.9% drug release.





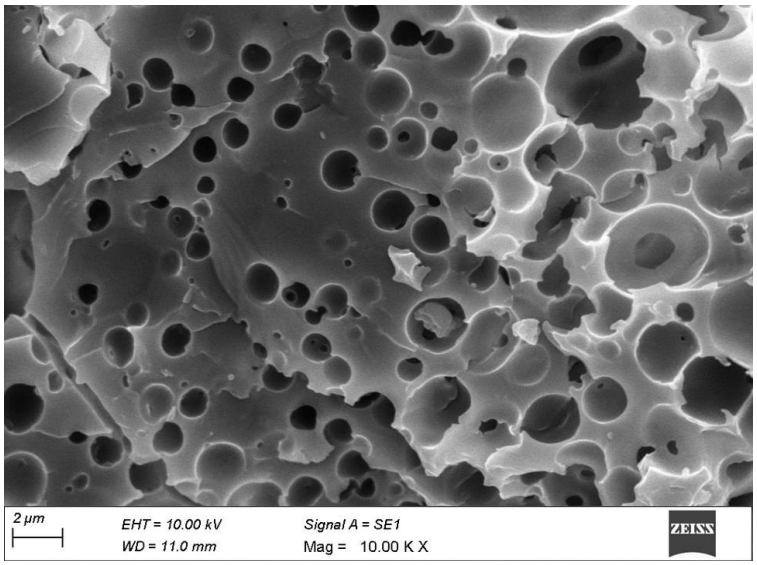
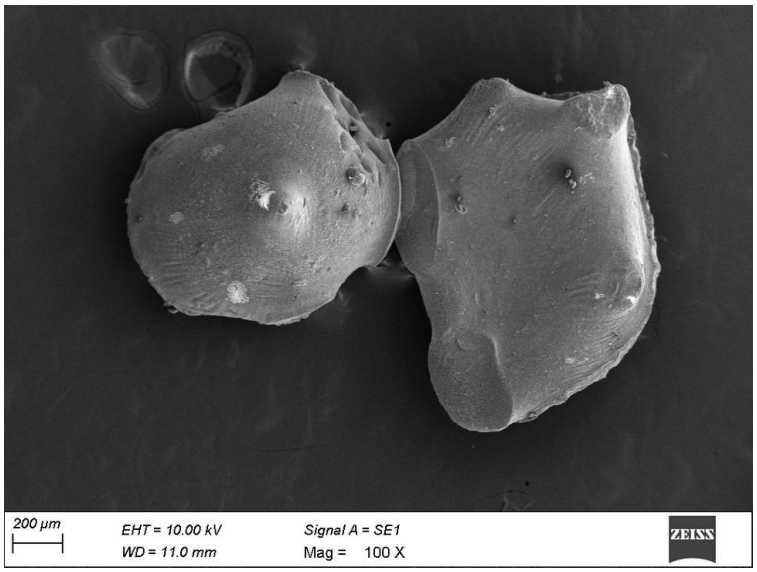


Figure 7. Sem photograph of best formulations of microsphere using ethyl cellulose.



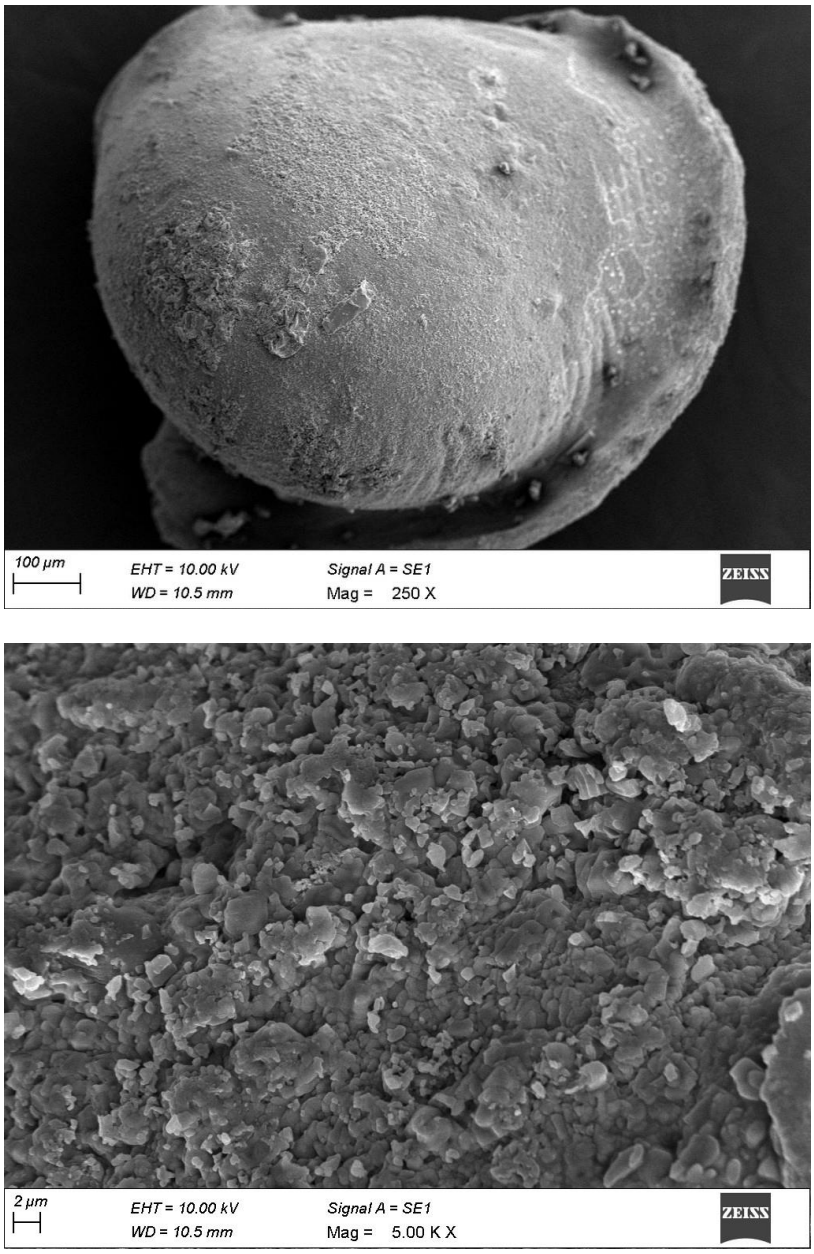


Figure 8. Sem photograph of best formulations of microsphere using sodium alginate.

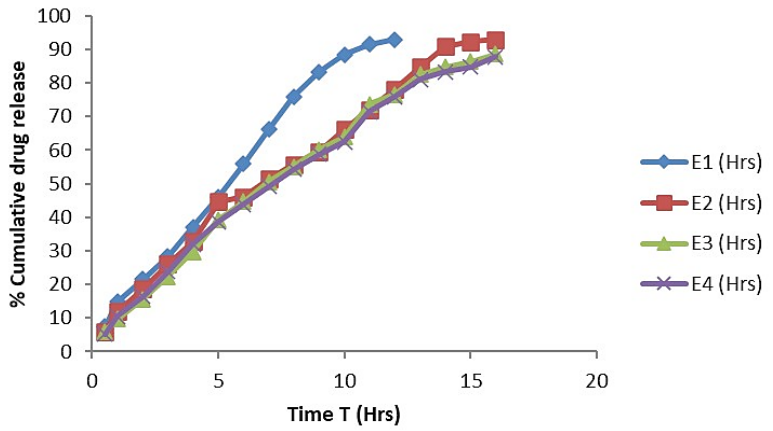


Figure 9. Percentage drug release for formulation E1 to E4.

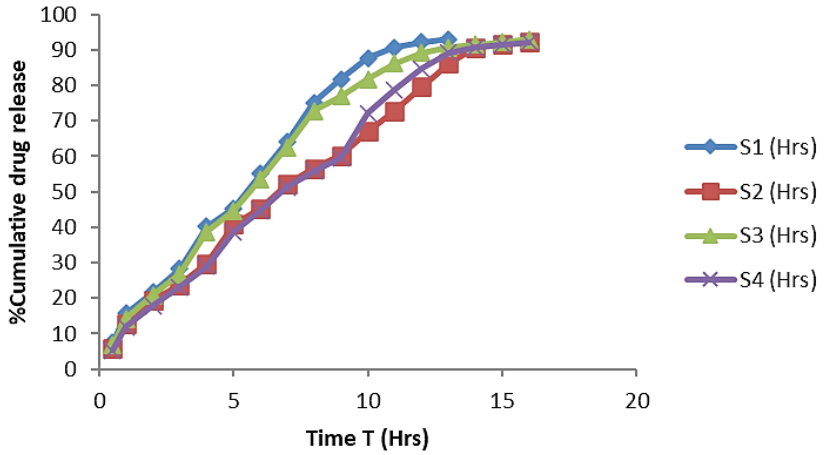


Figure 10. Percentage drug release for formulation S1 toS4.

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

Among the two best formulations microsphere prepared using ethyl cellulose as a synthetic polymer was found to be the best formulation of Levetiracetam microsphere with the drug release of 88.5% for 16 hours.

Release Kinetics

Data obtained from *in-vitro* release studies were fitted to various kinetics equations (zero-order, first-order, Higuchi models and kormeyer-peppas plot) to find out the mechanism of drug release from microspheres. The rate constants were also calculated for the respective models.

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 one of the most promising sustained drug delivery systems. Microspheres are one of the most promising controlled and targeted drug delivery systems. The present study signifies the utility of microspheres in retarding the drug release. This may in turn reduce the frequency of dosing, thereby improving the patient compliance.

In 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 preformulation 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.

We obtained good yields of microspheres with adequate encapsulation efficiency, with the highest for Levetiracetam loaded microspheres. The drug content and entrapment efficiency were good for all formulations. Among all formulations E3 shows better properties.

From the SEM study, it was observed that microspheres were spherical and fairly rough surface.

The formulations have shown good drug release in simulated intestinal medium, which is the desired medium for drug absorption. In addition, the release continues at a constant rate in this medium. All the formulations were evaluated different kinetic models like Zero order, First order, Higuchi matrix and Korsmeyer Peppas equation. 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.

Ethyl Cellulose is found to be a best polymer for preparing the Levetiracetam microspheres with high entrapment efficiency, drug content, percentage yield and sustained release for 16 hours

The formulations were found to be linear in kinetic models and E3 was selected as optimised formulations and shows 88.55% of drug release after 16 hours.

For optimised formulation the drug entrapment efficiency was 91.5%, Percentage yield was 77.3%, Drug content 85.7%

Comparison was made between the best formulations E3 & 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 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 hours 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 results 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 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.

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