*Research Article*

Available Online at: www.ijpir.com

**International Journal of Pharmacy and Industrial Research**

ISSN Print 2231 – 3648
Online 2231 – 3656

# Preparation, Characterization and Evaluation of Pregabalin Microspheres

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## ABSTRACT

In the present work, Microspheres of Pregabalin using PLGA, Ethyl cellulose and HPMC K4M as polymers were formulated to deliver pregabalin via oral route. The results of this investigation indicate that solvent evaporation method can be successfully employed to fabricate pregabalin microspheres. In this work an effort was made to formulate microsphere of pregabalin by using different polymers. Prepared formulations are evaluated for bulk density, tapped density, precent mucoadhesion, Percent compressibility, hausners ration, percentage yield, size and interaction study by Differential scanning calorimeter and *in vitro* drug release. Formulation which passed all the evaluation parameters was considered as best formulation of Pregabalin. The present study conclusively that pregabalin microsphere could be prepared successfully and formulation E5 was shows satisfactory result.

**Keywords:** Pregabalin, PLGA, Ethyl cellulose and HPMC K4M and Microspheres.

## INTRODUCTION

Oral route drug administration is by far the most preferable route for taking medications. However, their short circulating half life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. Rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamics profile is to release the drug in a controlled manner and site specific manner. Microspheres are small spherical particles, with diameters 1 µm to 1000 µm. They are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Microsphere play an important role to

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improve bioavailability of conventional drugs and minimizing side effects [1-5]. Pregabalin is structurally similar to gamma-aminobutyric acid (GABA) - an inhibitory neurotransmitter. It may be used to manage neuropathic pain, postherpetic neuralgia, and fibromyalgia among other conditions [6]. The aim of this study is to prepare pregabalin microspheres containing different polymers by solvent evaporation method to achieve a controlled drug release profile and to study the effect of different formulation variables such as drug:polymer ratio on particle size, encapsulation efficiency, and its *in vitro* release behavior[7, 8].

## METHODOLOGY

The microspheres were characterized by their micromeritic properties such as Particle size, Bulk density, Tapped density, Compressibility index, Hausners ratio and Angle of repose.

### Solvent evaporation method

Pregabalin microspheres were prepared using PLGA, Ethyl cellulose and HPMC K4M and distilled water as continuous phase by solvent evaporation technique. Initially dichloromethane (DCM) and methanol was mixed uniformly at room temperature, then PLGA, Ethyl cellulose and HPMC K4M in various proportions was dissolved in the above solution. To this mixture, a drug solution corresponding was added and mixed thoroughly and injected drop wise in to the continuous phase consisting of 100mL of 0.2% (w/v) SLS (sodium lauryl sulphate) at 250 rpm. The microspheres obtained was washed for 2-3 times with distilled water and dried at room temperature. Different concentrations and ratios of polymers used in the formulation of microspheres are mentioned in Table 1 [9].

## CHARACTERIZATION AND EVALUATION OF MICROSPHERES

**Table: 1 Formulation of Pregabalin Microspheres**

| INGREDIENTS (MG) | FORMULATIONS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **E1** | **E2** | **E3** | **E4** | **E5** | **E6** | **E7** | **E8** | **E9** |
| Pregabalin | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| PLGA | 5 | 10 | 15 | - | - | - | - | - | - |
| Ethyl cellulose | - | - | - | 5 | 10 | 15 | - | - | - |
| HPMC K4M | - | - | - | - | - | - | 5 | 10 | 15 |
| Dichloro methane (mL) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Methanol (mL) | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Sodium lauryl sulphate (mg) | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |

### Micrometric properties

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing PLGA as a polymer had a size range of 312.14µm to 3.32.41 µm. microspheres containing Ethyl cellulose as polymer exhibited a size range between 310.15 µm to 341.65 µm. Microspheres containing HPMC K4M as copolymer had a size range of 309.54 µm to 325.14 µm. The results are mentioned in Table 2.

**Table 2: Micromeritic property of floating microspheres of Pregabalin**

| Formulation code | Mean partical size | Bulk density ((gm./cm$^3$)) | Tapped density (gm./cm$^3$) | Hausner's ratio | Carr's index | Angle of repose |
|---|---|---|---|---|---|---|
| **E1** | 312.14± 3.21 | 0.434 ± 0.12 | 0.476 ± 0.03 | 1.095± 0.01 | 8.62± 0.13 | 23.2 ± 0.2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **E2** | 325.95± 4.23 | 0.277 ± 0.02 | 0.312 ± 0.02 | 1.133± 0.03 | 11.11± 2.33 | 25.2 ± 0.1 |
| **E3** | 332.41± 5.42 | 0.588 ± 0.13 | 0.666 ± 0.04 | 1.333± 0.02 | 11.76± 3.19 | 27.1 ± 0.1 |
| **E4** | 310.15± 5.25 | 0.521 ± 0.13 | 0.631 ± 0.03 | 1.121± 0.03 | 17.39± 2.15 | 24.4 ± 0.4 |
| **E5** | 320.96± 6.27 | 0.625 ± 0.12 | 0.833 ± 0.01 | 1.333± 0.02 | 25.00± 1.15 | 28.3 ± 0.4 |
| **E6** | 341.65± 6.29 | 0.476 ± 0.03 | 0.526 ± 0.02 | 1.105± 0.01 | 9.523± 1.46 | 25.1 ± 0.1 |
| **E7** | 325.14± 3.42 | 0.416 ± 0.02 | 0.476 ± 0.03 | 1.142± 0.04 | 12.50± 0.93 | 26.7 ± 0.4 |
| **E8** | 310.69± 5.62 | 0.384 ± 0.04 | 0.434 ± 0.03 | 1.130± 0.03 | 11.53± 1.53 | 26.0 ± 0.3 |
| **E9** | 309.54± 3.28 | 0.555 ± 0.11 | 0.714 ± 0.01 | 1.285± 0.03 | 22.22± 4.63 | 26.6 ± 0.2 |

## DRUG ENTRAPMENT EFFICIENCY

Percentage Drug entrapment efficiency of Pregabalin ranged from 95.24 to 99.76 % for microspheres containing PLGA, Ethyl cellulose and HPMC K4M polymer, the drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency [10]. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 3 and % swelling in Figure 1 to 3.

**Table 3: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres**

| Formulation code | % yield | Drug Content (mg) | % Drug entrapment efficiency |
|---|---|---|---|
| E1 | 90.56± 3.21 | 97.14± 2.21 | 73.14± 3.68 |
| E2 | 93.91± 4.47 | 98.65± 3.48 | 86.91± 4.29 |
| E3 | 95.21± 2.24 | 99.76± 3.75 | 90.72± 2.63 |
| E4 | 92.47± 3.84 | 98.14± 4.87 | 96.58± 3.83 |
| E5 | 96.14± 3.93 | 96.52± 2.54 | 98.45± 4.34 |
| E6 | 97.35± 1.64 | 99.34± 1.68 | 91.87± 3.58 |
| E7 | 95.41± 3.38 | 95.24± 3.83 | 89.72± 3.23 |
| E8 | 93.11± 4.37 | 97.53± 4.65 | 91.51± 2.45 |
| E9 | 90.48± 3.48 | 99.21± 2.65 | 95.82± 3.62 |

**Table 4: Swelling studies**

| FORMULATION CODE | INITIAL (Wt) | FINAL (Wt) | PERCENTAGE SWELLING |
|---|---|---|---|
| E1 | 10 | 12.45± 0.32 | 62.4± 4.65 |
| E2 | 10 | 11.62± 0.63 | 70.2± 3.83 |
| E3 | 10 | 13.58± 0.73 | 78.4± 4.38 |
| E4 | 10 | 12.45± 0.47 | 75.5± 2.63 |
| E5 | 10 | 13.95± 0.36 | 79.2± 3.48 |
| E6 | 10 | 14.86± 0.37 | 83.7± 6.38 |
| E7 | 10 | 10.59± 0.48 | 60.8± 2.94 |
| E8 | 10 | 11.75± 0.37 | 65.3± 4.48 |
| E9 | 10 | 12.96± 0.28 | 76.7± 4.93 |

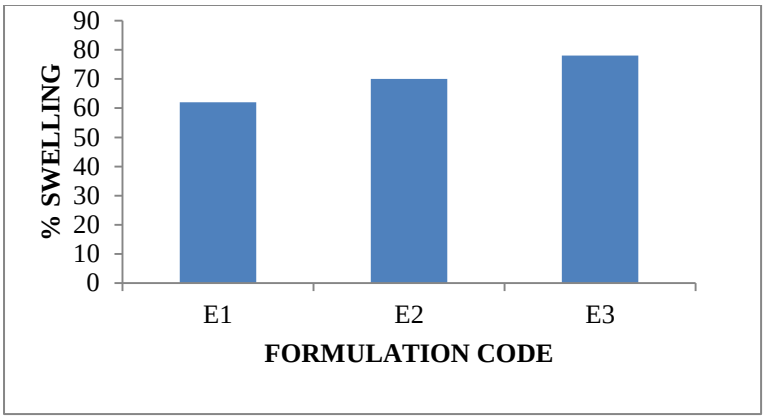


**Figure 1: Percentage swelling of microspheres containing PLGA**

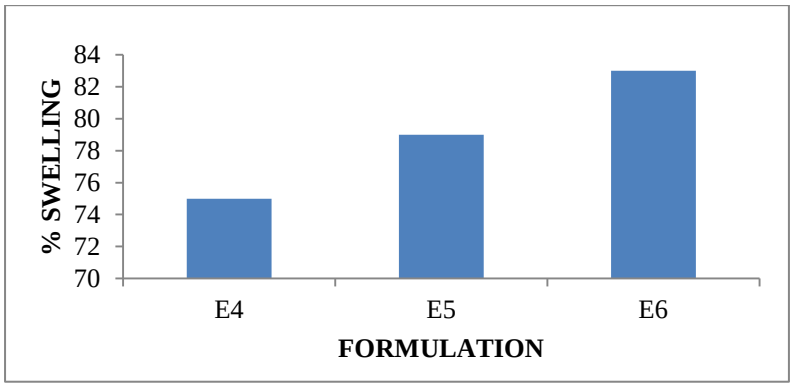


**Figure 2: Percentage swelling of microspheres containing Ethyl cellulose**

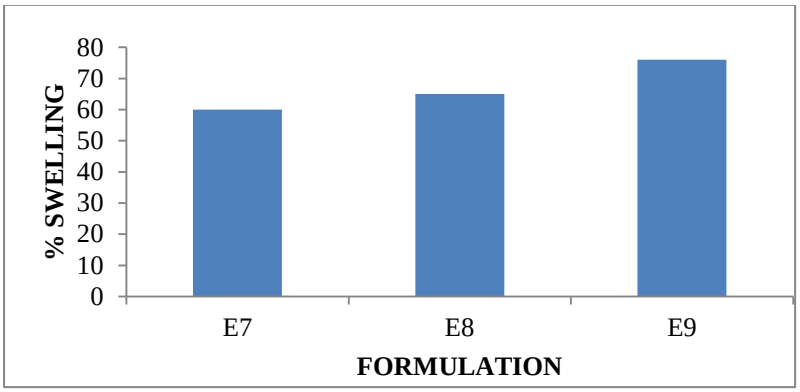


**Figure 3: Percentage swelling of microspheres containing HPMC K4M**

## *IN VITRO* MUCOADHESION TEST

As the polymer to drug ratio increased, microspheres containing PLGA exhibited % mucoadhesion ranging from 69 to 91%, microspheres containing ethyl cellulose exhibited % mucoadhesion ranging from 76 to 91% and microspheres containing HPMC exhibited % mucoadhesion ranging from 58 to 79%. The results of in-vitro mucoadhesion test are compiled in Table 5 and Figures 4 to 6.

**Table 5: *In Vitro* Mucoadhesion Test of all Formulations**

| FORMULATION CODE | No. OF MICROSPHERES | | PERCENTAGE MUCOADHESION |
|---|---|---|---|
| | INITIAL | FINAL | |
| E1 | 20 | 15.48 | 61.4± 4.84 |
| E2 | 20 | 11.85 | 58.5± 2.73 |
| E3 | 20 | 15.14 | 70.5± 3.38 |
| E4 | 20 | 17.96 | 93.8± 2.84 |
| E5 | 20 | 20.71 | 95.3± 3.94 |
| E6 | 20 | 16.17 | 39.7± 1.65 |
| E7 | 20 | 16.80 | 93.5± 2.64 |
| E8 | 20 | 11.58 | 86.6± 4.09 |
| E9 | 20 | 17.21 | 78.0± 4.67 |

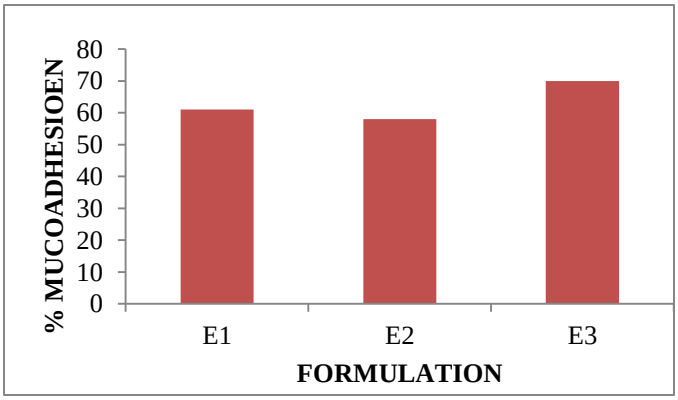


**Figure 4: Percentage mucoadhesion of microspheres containing PLGA**

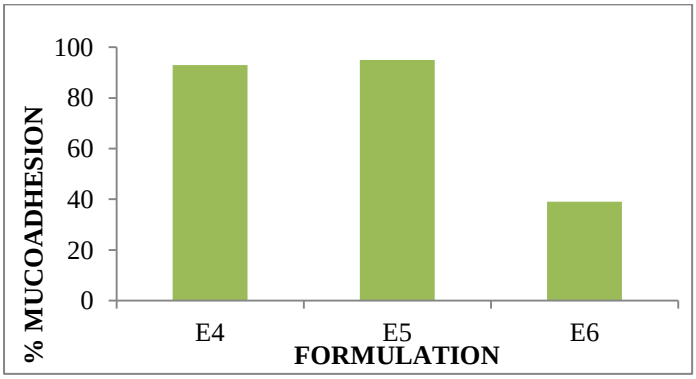


**Figure 5: Percentage mucoadhesion of microspheres containing Ethyl cellulose**

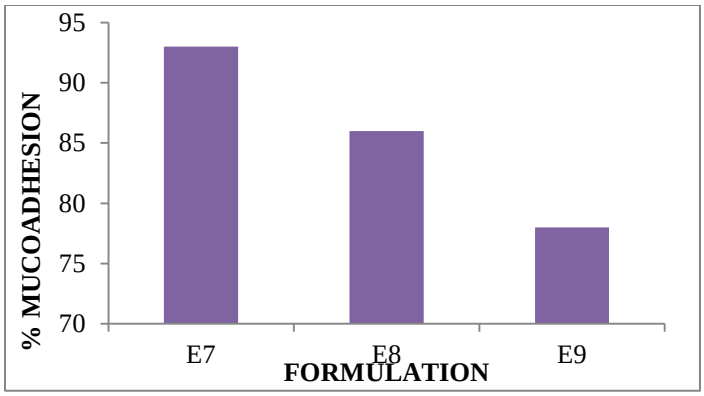


**Figure 6: Percentage mucoadhesion of microspheres containing HPMC K4M**

## *IN-VITRO* DRUG RELEASE STUDIES

**Table 6: *In-vitro* drug release data of Pregabalin microspheres**

| TIME (H) | Cumulative percentage of drug release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **E1** | **E2** | **E3** | **E4** | **E5** | **E6** | **E7** | **E8** | **E9** |
| **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **1** | 21.89 | 16.87 | 16.18 | 17.82 | 13.91 | 15.67 | 18.90 | 20.15 | 26.39 |
| **2** | 28.96 | 25.50 | 27.92 | 24.31 | 18.68 | 21.75 | 23.36 | 27.96 | 35.52 |
| **3** | 35.75 | 31.89 | 36.27 | 34.93 | 24.90 | 26.90 | 30.21 | 26.82 | 42.80 |
| **4** | 48.18 | 45.23 | 49.96 | 47.72 | 36.53 | 33.83 | 38.89 | 37.56 | 59.93 |
| **5** | 55.09 | 52.19 | 58.19 | 53.15 | 47.95 | 40.76 | 47.23 | 41.29 | 65.28 |
| **6** | 62.10 | 60.97 | 65.76 | 64.91 | 52.18 | 47.92 | 50.15 | 48.75 | 70.23 |
| **7** | 78.67 | 68.57 | 72.51 | 68.75 | 63.87 | 53.76 | 56.82 | 56.51 | 78.06 |
| **8** | 85.79 | 74.21 | 78.93 | 73.81 | 68.56 | 62.81 | 64.97 | 60.18 | 82.16 |
| **9** | 90.14 | 78.92 | 82.74 | 82.94 | 78.97 | 70.47 | 68.56 | 74.32 | 87.47 |
| **10** | 97.58 | 87.28 | 87.94 | 97.14 | 84.28 | 78.38 | 72.10 | 78.69 | 98.14 |
| **11** | | 98.12 | 90.75 | | 91.84 | 84.10 | 79.64 | 86.82 | |
| **12** | | | 97.35 | | 99.88 | 91.17 | 84.78 | 90.53 | |

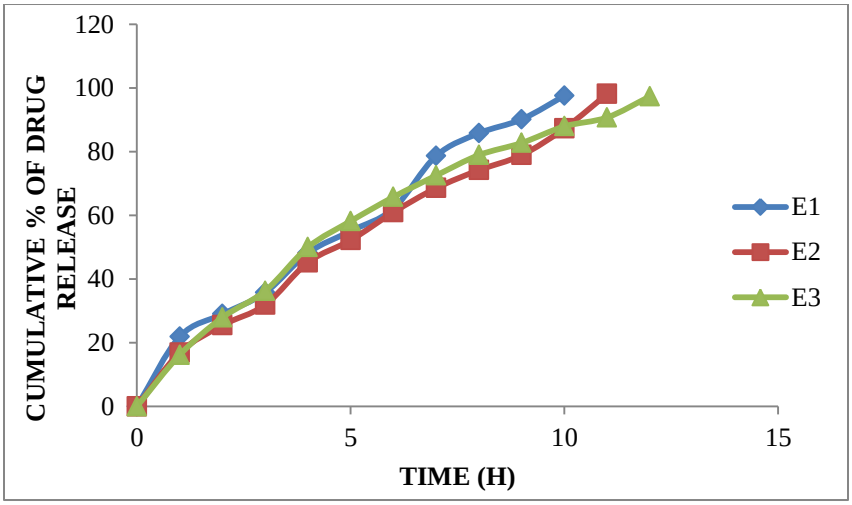


**Figure 7: In-Vitro drug release profile of Pregabalin microspheres containing PLGA**

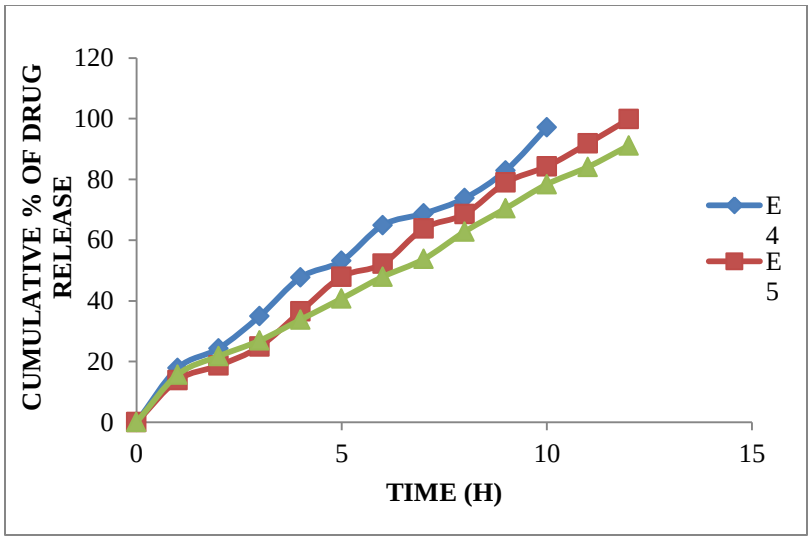


**Figure 8: In-Vitro drug release profile of Pregabalin microspheres containing Ethyl cellulose**

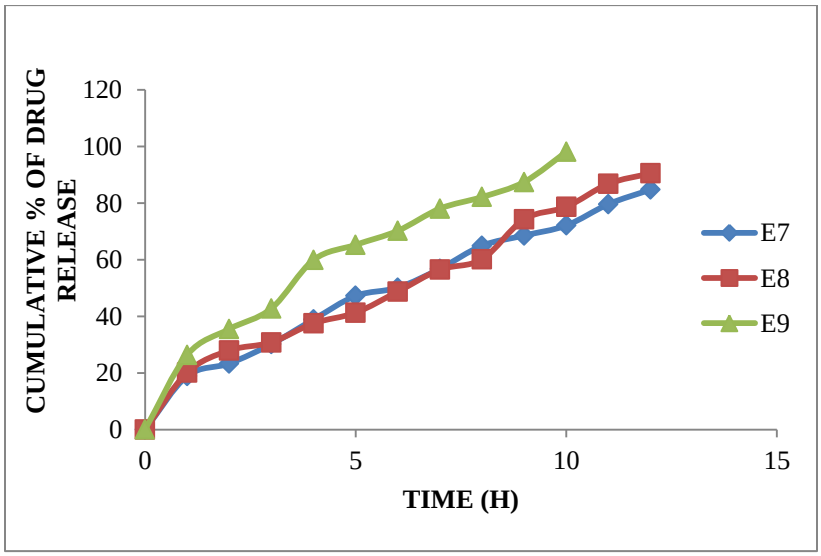


**Figure 9: In-Vitro drug release profile of Pregabalin microspheres containing HPMC K4M**

## *IN-VITRO* DRUG RELEASE KINETICS

**Table 7: Release kinetics studies of the optimized formulation (E5)**

| CUMULATIVE (%) RELEASE Q | TIME ( T ) | ROOT (T) | LOG(%) RELEASE | LOG ( T ) | LOG (%) REMAIN | RELEASE RATE (CUMULATIVE % RELEASE / t) | 1/CUM% RELEASE | PEP PAS log Q/100 | % Drug Remaining | Q0 1/3 | Qt 1/3 | Q0 1/3-Qt1/3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | | | 2.000 | | | | 100 | 4.642 | 4.642 | 0.000 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13.91 | 1 | 1.000 | 1.143 | 0.000 | 1.935 | 13.910 | 0.0719 | -0.857 | 86.09 | 4.642 | 4.416 | 0.226 |
| 18.68 | 2 | 1.414 | 1.271 | 0.301 | 1.910 | 9.340 | 0.0535 | -0.729 | 81.32 | 4.642 | 4.332 | 0.309 |
| 24.9 | 3 | 1.732 | 1.396 | 0.477 | 1.876 | 8.300 | 0.0402 | -0.604 | 75.1 | 4.642 | 4.219 | 0.423 |
| 36.53 | 4 | 2.000 | 1.563 | 0.602 | 1.803 | 9.133 | 0.0274 | -0.437 | 63.47 | 4.642 | 3.989 | 0.653 |
| 47.95 | 5 | 2.236 | 1.681 | 0.699 | 1.716 | 9.590 | 0.0209 | -0.319 | 52.05 | 4.642 | 3.734 | 0.908 |
| 52.18 | 6 | 2.449 | 1.718 | 0.778 | 1.680 | 8.697 | 0.0192 | -0.282 | 47.82 | 4.642 | 3.630 | 1.012 |
| 63.87 | 7 | 2.646 | 1.805 | 0.845 | 1.558 | 9.124 | 0.0157 | -0.195 | 36.13 | 4.642 | 3.306 | 1.336 |
| 68.56 | 8 | 2.828 | 1.836 | 0.903 | 1.497 | 8.570 | 0.0146 | -0.164 | 31.44 | 4.642 | 3.156 | 1.485 |
| 78.97 | 9 | 3.000 | 1.897 | 0.954 | 1.323 | 8.774 | 0.0127 | -0.103 | 21.03 | 4.642 | 2.760 | 1.881 |
| 84.28 | 10 | 3.162 | 1.926 | 1.000 | 1.196 | 8.428 | 0.0119 | -0.074 | 15.72 | 4.642 | 2.505 | 2.137 |
| 91.84 | 11 | 3.317 | 1.963 | 1.041 | 0.912 | 8.349 | 0.0109 | -0.037 | 8.16 | 4.642 | 2.013 | 2.628 |
| 99.88 | 12 | 3.464 | 1.999 | 1.079 | -0.921 | 8.323 | 0.0100 | -0.001 | 0.12 | 4.642 | 0.493 | 4.148 |

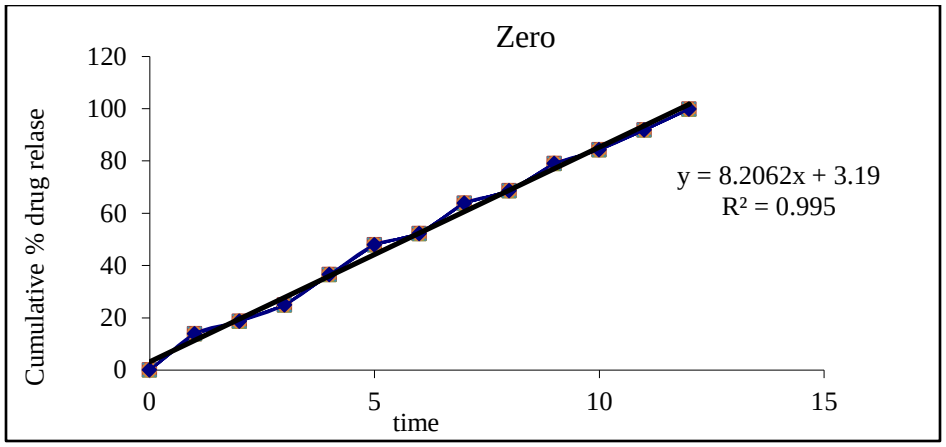


**Figure 10: Graph of zero order release kinetics of optimized formula**

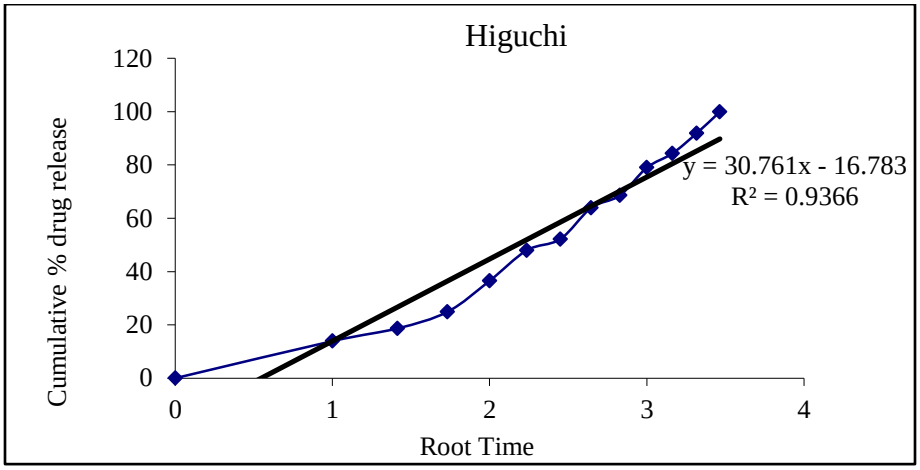


**Figure11: Graph of Higuchi release kinetics of optimized formula**

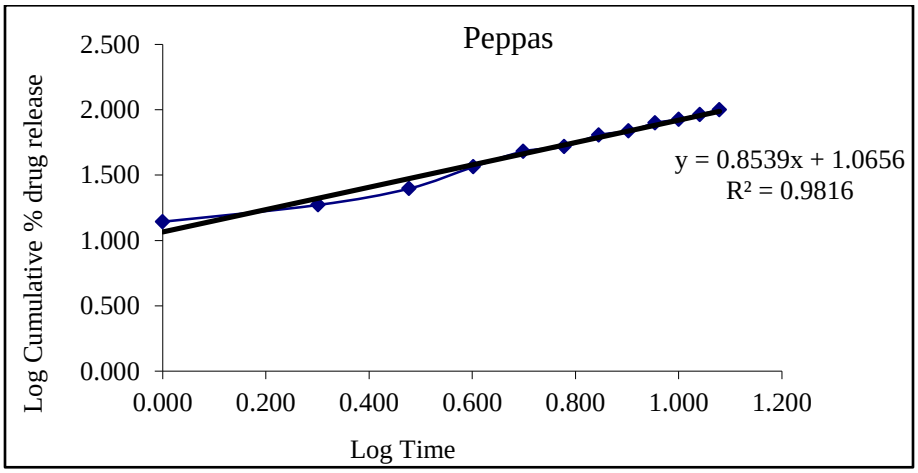


**Figure12: Graph of Peppas drug release kinetics of optimized formula**

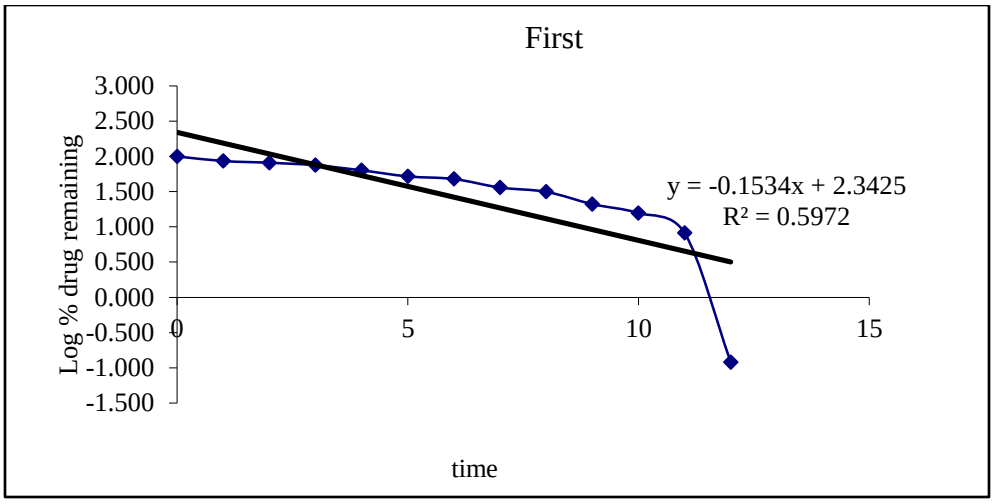


**Figure 13: Graph of first order release kinetics of optimized formula**

## COMPATIBILITY STUDIES

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Drug with the polymers used in the formulation. The FT-IR spectrum of the optimized formulation was compared with the FTIR spectra of the pure drug (Figure 14 & 15).

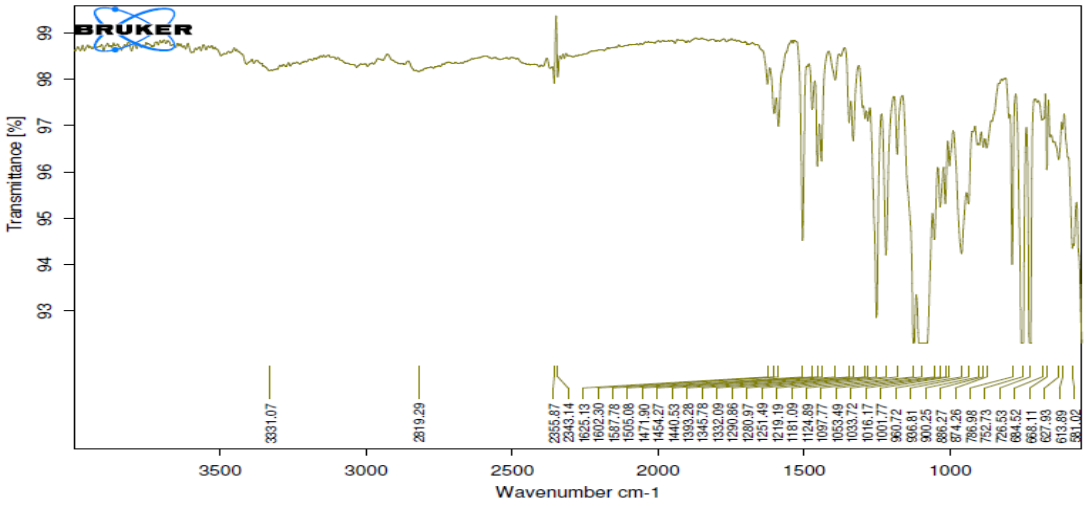


**Figure 14: FT-IR spectra of Pure drug**

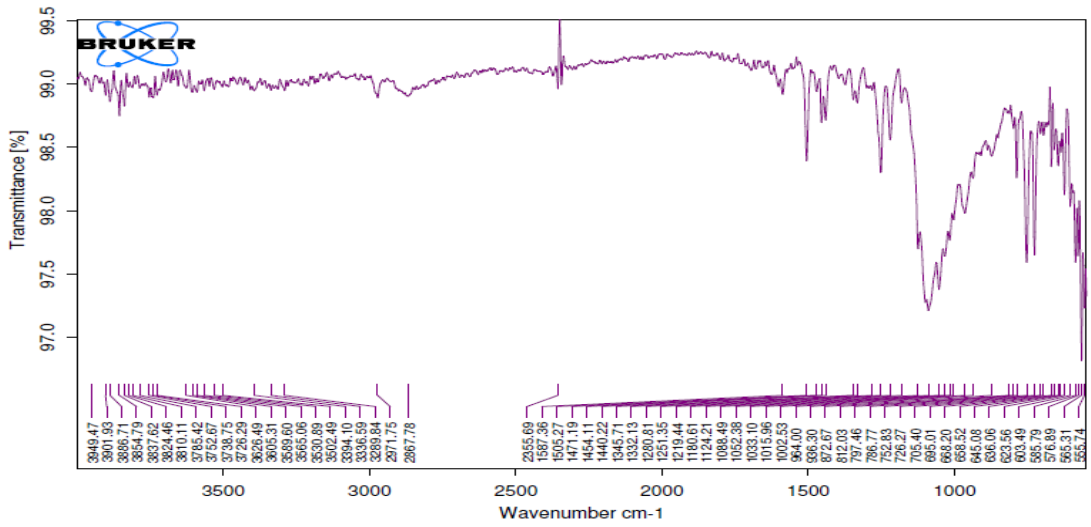


**Figure 15: FT-IR spectra of Optimized formulation**

## SEM

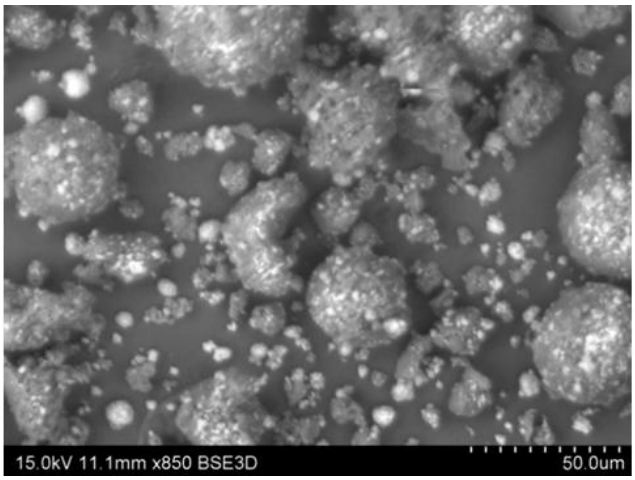


**Figure 16: SEM of Optimized formulation**

## CONCLUSION

Microspheres are prepared with PLGA, Ethyl cellulose and HPMC K4M successfully by the solvent evaporation technique. Microspheres of Pregabalin showed excellent mucoadhesivity,% yield, Drug Content, % Drug entrapment efficiency and prolonged drug release up to 12 hours. Microspheres of different size and drug content could be obtained by varying the formulation variables. Thus the prepared microspheres may prove to be potential candidates for oral delivery devices. Formulation Batch E5 showed best appropriate balance between mucoadhesivity and drug release rate, which can be considered as a best fit for microspheres. The polymer ratio (Ethyl cellulose) of 1:2 were selected as best formulation, The formulated system showed sustained release up to 12 h and the system is potentially useful to overcome poor bioavailability problems associated with Pregabalin. Analysis of drug release mechanism showed that the drug release from the formulations the best fit model was found to be zero order release kinetics. Hence it can be concluded that Pregabalin loaded Ethyl cellulose Microsphere may be useful to achieve sustained drug release profile suitable for oral administration.

**Acknowledgement**

The Author is thankful to project guide Dr.Venu Madhav. And also St Paul's College of Pharmacy, Sura Labs, Dilshukhnagar, Hyderabad for providing necessary facilities for doing of project Work.

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