**RESEARCH ARTICLE**

# Controlled Release Levetiracetam Loaded Eudragits Microspheres for Oral Drug Delivery: Preparation and Evaluation

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**ABSTRACT**

This work aims to prepare controlled release microspheres loaded with levetiracetam (LEV) for oral use that will have a targeted release site, thus reducing dose frequency and improving patient compliance. Levetiracetam is a 2nd generation anti-epileptic medication with a T/half-life of 7 hours that is administered twice daily, which makes it suitable for formulation that will reduce dosing intake. The microspheres were prepared by solvent evaporation method using Eudragit E100, L100, and S100 polymers as matrix core polymers at different ratios 1:1, 1:2 and 1:3 with levetiracetam. These polymers have different pH sensitivity profiles, which will aid the release of levetiracetam in a controlled manner along the gastrointestinal tract. The prepared microspheres were evaluated for yield percentage, entrapment efficiency (EE%), morphological characteristics and *in-vitro* release profile. The yield percentage and EE% for the formulation at different ratios ranged from 69–99%. The *in-vitro* release analysis showed favorable targeted release of the drug at specific pH ranges matching specific sites in the gastrointestinal tract.

**Keywords:** Drug, Drug released, Eudragits microspheres.

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**Conflict of interest:** None

## INTRODUCTION

Microspheres are multi particulate drug delivery systems with a size range of 1–1000 µm. Interestingly, they have the potential to be incorporated into several pharmaceutical formulations such as tablets, capsules, creams, etc. This demonstrates the convenience of integration to many routes of drug administration.[1,2]

Microspheres can play a good in achieving controlled drug release at the desired site,[1] by improving bioavailability and less required dosing, thus improving patient compliance.[3] Moreover, microspheres improve dosage form reliability through several advantages such as rapid gastric emptying and transit through the intestine, their high surface area which offers the potential for rapid release and favorable absorption profile, and protecting the medicinal formulation from the human body factors (such as gastric juice or enzymes), where all this is especially beneficial for targeted drug delivering.[4,5]

However, they still have many drawbacks such as the expensive cost of production,[1] the manufacturing scale-up can be troublesome,[3] plus the low loading capacity for hydrophilic drugs,[6] low stability of the active medicinal agent,[7] and finally their presence at the absorption site can be short lived.[8]

The LEV is an anti-epileptic drug (AED) that is approved by the United States Food and Drug Administration (FDA) for the treatment of wide variety of seizure disorders, whether as monotherapy or in combination with other anti-epileptics that have a short half-life of around 7 hours.[9,10] Although LEV's exact mechanism of action as an anti-epileptic drug is still unknown, it is suggested that it reversibly binds with the synaptic vesicle protein within the brain cell membranes in a saturable fashion. Consequently, LEV will delay or retard the conduction of neurons accountable in the major seizure activity.[9,10]

Eudragit polymers were synthesized in the 1950s at Germany by Rohm GmbH and Co. KG via the polymerization of acrylic and methacrylic acids or their esters. They are mainly marketed as coating agents for oral dosage forms that can withstand the stomach's acidic environment, while dissolving in alkaline condition, releasing the drug substances in the intestines. Over the following decades, Eudragit polymers were produced in various modified forms where each variant has specific characteristics and applications.[11]

The pH-specific dissolution and swelling features of the wide portfolio of Eudragits polymers made them particularly attractive controlled release pharmaceutical formulation, including microspheres implemented solely or incorporated with other polymers.[12] Joshi *et al.* (2013) formulated controlled release glipizide loaded microspheres to increase its half-life

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with Eudragit RS 100, RL 100 or their blends by utilizing solvent evaporation method.[13] Furthermore, Sahoo *et al.* (2005) had formulated Stavudine loaded microspheres with Eudragit RL 100, RS 100 or their blends by the solvent evaporation method to tackle the short-lived half-life of Stavudine when administered orally.[14] Interestingly, microspheres of levetiracetam for oral route delivery were formulated by Balaiah *et al.* (2012) with ethyl cellulose to control the release of the drug through extending the release time duration and masking the bitter taste of the drug.[15]

This work aims to prepare and evaluate microspheres of levetiracetam by utilizing different types of Eudragits using modified version of the solvent evaporation method. in order to evaluate the potential improved drug delivery for longer durations and reducing dosing frequency.

## MATERIALS AND METHODS

### Materials

Levetiracetam was a gift from pioneer company for pharmaceutical industries–Iraq, the Eudragit polymers were purchased from Shanghai Ruizheng Chemical Technology Co. LTD–China, Acetone HPLC was purchased from CHEM. LAB–Belgium, ethanol absolute 99% was purchased from Chem-Lab–India, Span 60 was purchased from Sinopharm Chemical Reagent Co. LTD–China, hydrochloric acid, methanol 99%, monobasic potassium phosphate $KH_2PO_4$, n-hexane 95%, paraffin liquid light and sodium hydroxide were all purchased from Thomas Baker-India. At the same time, all other chemicals and glassware were purchased from local suppliers in Baghdad city.

### Pre-formulation Studies of Levetiracetam

*Melting Point Determination*

The procedure was performed in accordance to the capillary method stated in the United States Pharmacopeia (USP).[16]

*Construction of Calibration Curve for Levetiracetam*

A stock solution of levetiracetam was prepared by weighing and dissolving 100 mg of the drug in 100 mL of ethanol absolute 99%, where this solution will have a concentration of 1000 µg/mL. Subsequently, serial dilutions of specific samples taken from this stock solution by dilution with the same solvent in 10 mL volumetric flask to achieve the following concentrations: 5, 10, 15, 20, 25, 30, 35, and 40 µg/mL.

Then, 1-mL samples taken from each solution and its respective maximum absorbance is measured by the UV-visible spectrophotometer at their designated $\lambda_{max}$. Afterward, a graph is extrapolated for absorbance against concentration to generate the calibration curve for levetiracetam in ethanol absolute 99%. Accordingly, the same procedure is repeated for the stock solutions of LEV in 0.1N HCl, 6.8 and 7.4 pH phosphate buffers, respectively.

*Preparation of Levetiracetam Loaded Microspheres*

The preparation method follows a modified version of the solvent evaporation method that involves several steps where the internal phase consists of dissolving 300 mg of levetiracetam in 5 mL methanol in a 50 mL beaker and using glass rode to dissolve the drug powder to make the drug solution. In contrast, different weights of Eudragits are being dissolved at different volumes of acetone in a 50 mL beaker which will be placed in an ultrasonicated bath with no heat source for around 20–50 minutes to assist the dissolving process in making the polymer solution. Eventually, the drug solution is added to polymer solution with continuous mixing by glass rode to make the internal phase which will have different volumes and content as stated in Table 1.

The external phase consists of 90 mL light liquid paraffin with 30 mL n-hexane and 0.05% span 60 all placed in 250 mL beaker and stirred by paddle-shaped blade attached to an electrical stirrer rotating at 500 rpm for 30 second to ensure proper mixing of the contents. The internal phase is added drop by drop to the external phase, already being stirred by an electrical stirrer at 500 rpm speed for 2 hours. Afterward, the stirring is stopped, the formulation will be left overnight undisturbed for settling purpose. Then, it will be washed with copious amounts of n-hexane and filtering the mix through qualitative filter paper. Eventually, the formulation is left overnight on the filter paper to dry and then a spatula will collect it.

*Yield Percentage Calculation of the Formulations*

The formulations will be weighed and compared with the theoretical weight for the contents of the formulation where the yield percentage will be calculated accordingly by using this equation:

**Table 1:** The contents of the internal phase.

| *Formulation No.* | *Drug solution* | *Polymer solution* | *Total volume (mL)* | *Drug:polymer ratio* |
|---|---|---|---|---|
| 1 | Drug 300 mg in 5 mL Methanol | Eudragit E100 300 mg in 10 mL Acetone | 15 | 1:1 |
| 2 | Drug 300 mg in 5 mL Methanol | Eudragit E100 600 mg in 15 mL Acetone | 20 | 1:2 |
| 3 | Drug 300 mg in 5 mL Methanol | Eudragit E100 900 mg in 20 mL Acetone | 25 | 1:3 |
| 4 | Drug 300 mg in 5 mL Methanol | Eudragit L100 300 mg in 10 mL Acetone | 15 | 1:1 |
| 5 | Drug 300 mg in 5 mL Methanol | Eudragit L100 600 mg in 15 mL Acetone | 20 | 1:2 |
| 6 | Drug 300 mg in 5 mL Methanol | Eudragit L100 900 mg in 20 mL Acetone | 25 | 1:3 |
| 7 | Drug 300 mg in 5 mL Methanol | Eudragit S100 300 mg in 10 mL Acetone | 15 | 1:1 |
| 8 | Drug 300 mg in 5 mL Methanol | Eudragit S100 600 mg in 15 mL Acetone | 20 | 1:2 |
| 9 | Drug 300 mg in 5 mL Methanol | Eudragit S100 900 mg in 20 mL Acetone | 25 | 1:3 |

Yield% = x 100%

*Calculation of Entrapment Efficiency%*

The required sample will be taken from each formulation and dissolved in 100 mL ethanol absolute 99% by placing the sample in the ultrasonicator bath with no heat application until it is completely dissolved. Then, 1-mL sample is analyzed in a UV-visible spectrophotometer to calculate the actual drug content in the formulation. Eventually, this weight will be compared with the theoretical drug content in each formulation to calculate the drug loading using this equation:

Entrapment Efficiency% = x 100%

*Morphological Characterization of the Microspheres*

The morphological properties of the prepared microspheres were studied by scanning electron microscopy model (Zeiss). The samples were placed on slides to be inserted into the device, then appropriate images were captured accordingly.

*In-vitro Dissolution Profile*

The *in-vitro* release profile for the prepared formulations were performed by using the USP dissolution apparatus II. Where samples of the F1, F2, and F3 formulations were studied in 500 mL of 0.1N HCl dissolution media which was prepared by dilution of concentrated HCl. While, samples of formulations F4, F5, and F6 were studied in 500 mL of pH 6.8 phosphate buffer, and lastly, samples of formulations F7, F8, and F9 were studied in 500 mL of pH 7.4 phosphate buffer. All samples were placed in the dissolution jar stirred by paddle rotating at 100 rpm and heated at 37°C. Then, 5 mL samples are withdrawn at designated intervals as stated in Table 2 which is replaced by another 5 mL fresh dissolution media.

## RESULTS AND DISCUSSION

### Melting Point Determination

The recorded melting point for LEV sample tested by the capillary method was 115.5°C which is consistent with the lower limit for standard range of LEV melting point (115–119°C).[17]

### Construction of Calibration Curve for Levetiracetam

The calibration curve of LEV in various solvents is shown in Figure 1, where UV absorbance is assigned to the Y-axis and the concentration of LEV (µg/mL) is assigned to the X-axis. The curve has a straight line resulting from intercrossing each sample's specific concentration with their designated UV absorbance. This line has a regression coefficient ($R^2$) obtained from the curve. This curve obeys Beer's-Lambert law as a single molecular element, *i.e.,* LEV, gives rise to each absorbance point dotted on the line.[18]

### Yield Percentage Calculation of the Formulations

The yield percentage was deduced accordingly as stated in Table 3, which ranged from 79.25% for F-1 to 92.57% for F-8. Since all formulations had been fabricated under the same circumstances including the volume of the external phase and the speed of stirring during fabrication. Therefore, loss of some formulation that may occurred during washing, filtration and collection of the formulation accounted for the difference between the theoretical and actual weight for each formulation.

### Calculation of Entrapment Efficiency (EE%)

The estimated EE% for all formulations are listed in Table 4, which shows a proportional increase when the ratio of the polymer was increased in the formulations fabricated with Eudragit E100 and L100. Since both polymers exhibited good

**Table 2:** Sampling intervals of dissolution profile

| *Formulation* | *Sampling intervals* |
|---|---|
| 1, 2, and 3 | 5, 10, 15, 30, 45, 60, 90, 120 minutes |
| 4, 5, and 6 | 0.25, 0.5, 1, 2, 3, 4, 5, 6 hours |
| 7, 8, and 9 | 0.25, 0.5, 1, 2, 3, 4, 5, 6 hours |

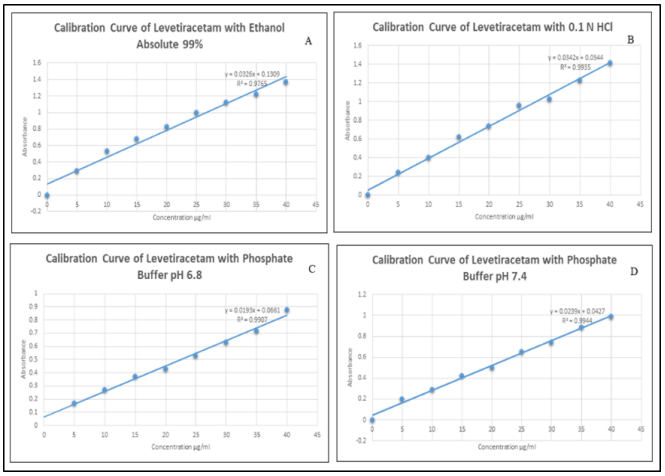


**Figure 1:** Calibration Curve of LEV in (A) Ethanol Absolute 99%, (B) 0.1N HCl, (C) Phosphate Buffer pH 6.8, (D) Phosphate Buffer pH 7.4

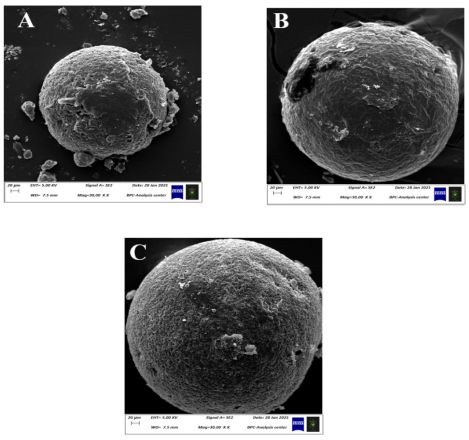


**Figure 2:** SEM Study of the Prepared Microspheres Formulations, (A) Eudragit E100 Formulations, (B) Eudragit L100 Formulations, and (C) Eudragit S100 Formulations.

**Table 3:** Theoretical, actual weight and yield percentage% of all formulations

| *Formulation* | *Theoretical weight (mg)* | *Actual weight (mg)* | *Yield percentage (%)* |
|---|---|---|---|
| F-1 | 667.5 | 529 | 79.25 |
| F-2 | 970 | 850 | 87.62 |
| F-3 | 1272.5 | 1100 | 86.44 |
| F-4 | 667.5 | 582 | 87.19 |
| F-5 | 970 | 859 | 88.55 |
| F-6 | 1272.5 | 1153 | 90.6 |
| F-7 | 667.5 | 547 | 81.19 |
| F-8 | 970 | 898 | 92.57 |
| F-9 | 1272.5 | 1128 | 88.64 |

**Table 4:** Drug: polymer ratio and its estimated EE% for all formulations

| *Formulation* | *Drug:polymer ratio* | *Estimated EE%* |
|---|---|---|
| F-1 | LEV 1:1 Eudragit E100 | 76.89 |
| F-2 | LEV 1:2 Eudragit E100 | 90 |
| F-3 | LEV 1:3 Eudragit E100 | 95 |
| F-4 | LEV 1:1 Eudragit L100 | 69.32 |
| F-5 | LEV 1:2 Eudragit L100 | 81 |
| F-6 | LEV 1:3 Eudragit L100 | 99 |
| F-7 | LEV 1:1 Eudragit S100 | 73.66 |
| F-8 | LEV 1:2 Eudragit S100 | 83.13 |
| F-9 | LEV 1:3 Eudragit S100 | 77.5 |

solubility profile in acetone during fabrication. So higher content of the polymers was available for engulfing the drug molecules before solvent evaporation during fabrication process.

While EE% for formulations fabricated with Eudragit S100 also increased when the polymer ratio increased from 1–2 for F-7 and F-8. Interestingly, except for F-9, the estimated EE% was less than that of F-8 despite the increase of the polymer ratio. This might be attributed to the fact that Eudragit S100 had a higher content of methyl methacrylate (MMA) in their composition than Eudragit L100,[12] which affects its solubility in acetone during fabrication. Therefore, this could lead to some particles of Eudragit S100 may have phased out of the internal phase before engulfing the drug molecules due to their slightly less solubility in acetone.

**Morphological Characterization of the Microspheres**

The morphological profile of the prepared formulations was also studied by SEM as demonstrated in Figure 2. Where all images showed spherical-like particles, a clear confirmation of microspheres fabrication, since both LEV and Eudragit were in solution form within the internal phase solubilized in methanol and acetone, these particles definitely lost their specific morphological features. Furthermore, span 60 which was employed as droplet stabilizer as was implemented by Saffari *et al.* (2008), which had a direct impact on shaping the formed microspheres into spherical-like shapes with the aid of continuous stirring, the evaporation of solvents within the internal phase and the hardening effect exercised by n-hexane.[19]

Interestingly, Figure 2 A showed the presence of LEV drug particles on the prepared microspheres' surface, which may impact their release behavior. All images of Figure 2 showed the presence of pores on the surface of the microspheres which probably formed during fabrication due to rapid evaporation of solvents in the internal phase. These pores may impact the prepared formulations' release profile.[13,14]

***In-vitro* Dissolution Profile**

The release profile for all formulations is demonstrated in Figure 3, where Figure 3(A) shows the dissolution profile for formulations F1-F3 all formulated with Eudragit E100 at 0.1N HCl to simulate stomach environment.[20] During the first 30 minutes, the release curve shows a slight decrease at the rate LEV is being released from the formulation as the ratio of the polymer increases. Since, the polymer concentration governs the rate and extent of drug release from microspheres,[8] yet after 30 minutes to the end of the test after 2 hours of release curves for all 3 formulations converge closer to become more steady state. This can probably be attributed to the highly acidic environment of hydrochloric acid, which causes extensive solubilization of the Eudragit E100 molecules within the formulation, leading to high LEV release accordingly.

While Figure 3B shows the release profile for formulations, F4-F6 fabricated with Eudragit L100 at pH 6.8 phosphate buffer to simulate the intestinal environment.[20] All three formulations had released over 50% of their respective LEV content within the first 15 minutes, which continued in a steady state fashion over the next 6 hours. F4 and F5 almost showed similar release

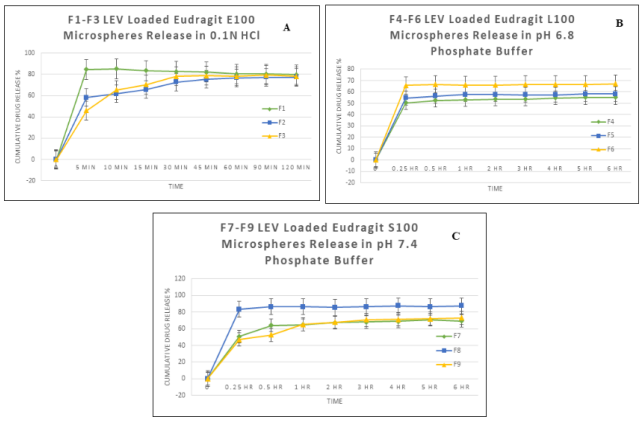


**Figure 3:** *In-vitro* Release Profile of the Prepared Microspheres, (A) F1-F3 LEV Loaded Eudragit E100 Microspheres, (B) F4-F6 LEV Loaded Eudragit L100 Microspheres, and (C) F7-F9 LEV Loaded Eudragit S100 Microspheres.

profiles meaning there is no significant impact of increasing polymer ratio on restricting the drug release. Interestingly, F6 had slightly higher LEV released but still non-significant when compared to F4 and F5, this might be related to the presence of pores on the surface of the microspheres as demonstrated in Figure 3B. Since they will slightly increase the penetration of the dissolution medium into the matrix of the microspheres, thus prompting higher solubilization rate of Eudragit L100 molecules within the formulation and causing rapid diffusion of LEV molecules through the pores.[13,14]

Similarly, Figure 3C demonstrated the release profile for F7-F9 formulations that were fabricated with different ratios of Eudragit S100 at pH 7.4 phosphate buffer to mimic the intestinal environment.[20] F7 and F9 which had Eudragit S100 ratio of 1 and 3, respectively, demonstrated an almost matching release profile, releasing around 50% of their LEV content at the first 15 minutes. Thereafter, their release rose slightly when they reached the 1-hour threshold, the release continued in a highly matching steady-state order over the course of the next 5 hours. This showed the non-significant role of increasing the polymer ratio within the formulation on their respective release profiles. While F8 showed relatively higher release than F7 and F9 during the first hour, probably due to the pores on the surface of the microspheres as shown in Figure 3C. As these pores may increase the penetration of the dissolution medium inside the core of the microspheres, and also, they may facilitate the diffusion of LEV throughout the pores.[13,14] However, the release rate for F7-F9 showed no significant difference after passing 1-hour onwards.

The release of LEV from all formulations was controlled mainly by the solubilization of Eudragit polymers in their respective pH range with a small aid of LEV diffusion from microspheres. Since the absorption of LEV through various targeted sites along the gastrointestinal tract.[21] Consequently, this coupled with the appropriate pH range and transit times along the gut,[20,22] interestingly would lead to advantageous controlled oral delivery of LEV from the prepared formulations. As the gastric pH range is 1–2.5 with a transit time of 1.1 hour,[20,22] plus Eudragit E100 is soluble in pH value of less than 5.[11,23] As a result, theoretically, F1-F3 would be able to release its LEV content in the stomach.

While the pH value at the duodenum starts at 6.6 which will rise to 7.5 at the ileum, then it would flunk to 6.4 in the caecum but it will rise again to 7 at the rectum. Additionally, the transit time through small intestine is around 8 hours and the colon is around 17 hours.[20,22] Furthermore, the pH-sensitive range for solubilization of Eudragit L100 and S100 are above 6 and 7, respectively.[11,23] Subsequently, F4-F6 and F7-F9 would achieve theoretical LEV release throughout the small intestine and colon length at various sites. Indeed, this would be convenient to provide targeted controlled oral drug delivery of LEV through specific pH ranges for drug release to bring out steady state drug absorption with minimal fluctuation of the absorbed levels of LEV. Thus, the prepared microsphere formulations would be able to offer a dosage form of LEV that would behave in ideal manner for an anti-epileptic drug.[9]

## CONCLUSION

Levetiracetam-loaded microspheres were successfully prepared using different ratios of Eudragit polymers by utilizing a modified version of solvent evaporation method. All the prepared formulations showed high loading capacity for LEV. Span 60 played a significant role as droplet stabilizer in the fabrication of microspheres. SEM study confirmed the formation of spherical like shaped particles. All formulations in the *in-vitro* release study showed relatively similar release profile in their respective pH-sensitive release media independent of the Eudragit polymer ratio in the formulations.

## FUTURE RECOMMENDATIONS

Conducting a bioavailability study to confirm the potential of fabricating controlled LEV microspheres for oral drug delivery and stability study of the formulations. Finally, designing a suitable dosage form from the prepared formulations.

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