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Research Article

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Preparation and Characterization of Immediate and Extended Release Levetiracetam Coated Pellets using Extrusion-Spheronization Technique

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Abstract

Levetiracetam (LEV), an antiepileptic compound with a bitter taste, is used to treat different types of epilepsy in both adult and pediatric patients. While a wide range of doses is required for various age groups, some patients have difficulties in swallowing large solid dosage forms. Therefore, this study aimed to prepare and evaluate taste-masked LEV coated pellets with immediate and extended release behavior for flexible drug dosing, ease of swallowing, and higher patient compliance. LEV core pellets were prepared using the extrusion-spheronization technique and evaluated in terms of physical properties. In the next step, two coating processes were performed separately on the optimal formulation using different polymers to prepare a taste-masked immediate release formulation and to achieve an extended release product. Further experiments were conducted on the coated pellets, such as dissolution, morphology, and taste-masking evaluations.

Based on the results, optimum LEV-loaded core pellets with suitable physical properties were prepared with the size, aspect ratio, and projection sphericity of 1.18 mm, 1.08, and 0.92, respectively. Coating the pellets with Eudragit E, while having appropriate dissolution in an acidic medium, provided an acceptable taste-masking, confirmed by *in-vitro* and *in-vivo* analysis. Extended release LEV pellets were obtained by coating the core pellets with a proper Eudragit RL/RS combination. Desirable dissolution profiles were achieved using 30 % coating polymer on the surface of the pellets. In addition to the advantages of taste-masked immediate and extended release LEV pellet formulations, it should be pointed out that preparing these multi-particulate systems by coating similar core pellets with various polymers can be cost-effective from the production point of view.

Keywords: Extended release; Extrusion–spheronization; Levetiracetam; Pellets; Taste-masking.

1. Introduction

Levetiracetam (LEV), a second-generation antiepileptic drug with multiple mechanisms and broad-spectrum efficacy, is used to treat different types of epilepsy in adults and children [1]. It is a BCS (biopharmaceutics classification system) class I compound, with high solubility and permeability [2]. This drug is rapidly absorbed orally [3, 4] and has a relatively short elimination half-life of 6-8 hrs [5]. Conventional solid

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medications of LEV, available in 250 to 1000 mg strength, are associated with difficult swallowing in elderly patients with dysphagia, as well as children, due to the large tablet size. On the other hand, liquid preparations, which are easier to swallow, could face limitations such as packaging, high cost, and inaccurate dosing [6]. LEV has a bitter taste that reduces long-term patient compliance, especially in children.

Pellets, consisting of fine powders bonded by the binding solution, are spherical particles commonly with a diameter of 0.5 to 1.5 mm [7]. These are multi-particulate delivery systems with several advantages such as good flow, less friability, lower probability of dose dumping [8, 9], reduced gastric transit time following oral administration, and less gastrointestinal tract irritation [10]. Due to the flexible dose fractionation, one of the problems related to dosing in pediatrics can be easily solved using these systems [11]. At the same time, ease of swallowing compared to other solid dosage forms is an important feature, leading to better patient compliance [12, 13]. On the other hand, coating the pellets with suitable polymers, while covering the unpleasant taste, could control the drug release rate. The *in-vivo* behavior of coated pellets is an advantage of this system over monolithic matrices when modified drug release is desired.

Different methods could be applied for pellet preparation, including extrusion-spheronization. This technique has been considered by researchers as well as the pharmaceutical industry for different reasons, such as easy operation, high efficiency, uniformity of the particles (narrow size distribution), high drug loading capability [9], and more appropriate physical properties of the pellets [14, 15]. Considering that most active ingredients do not have appropriate physico-mechanical properties for making pellets, using different additives in their formulations is often necessary. These additives play an important role in improving the production process. However, minimizing the use of additives is essential for higher drug loading.

The present study aimed to formulate high drug-loaded LEV pellets and to investigate the effect of different additives on their physical properties. Then, the optimal pellet formulation with suitable physical characteristics in terms of appearance and *in vitro* drug dissolution was coated with Eudragit (Eud) E, the acid soluble polymer, for taste-masking purpose or a combination of Eud RL, and Eud RS, cationic ammonium methacrylate copolymers, to prepare a taste-masked extended release (ER) formulation. Considering that LEV is used as two dosage forms of immediate release (IR) and ER, the possibility of preparing both formulations only by different coatings applied on similar core pellet particles could be considered as one of the advantages of this study.

2. Materials and Methods

2.1. Materials

LEV was obtained from Hetero Pharmaceuticals Ltd, Hyderabad, India. The microcrystalline cellulose (MCC, Avicel PH-101), starch, lactose, polyvinyl pyrrolidine (PVP), sodium starch glycolate (NaSG), sodium lauryl sulphate (SLS), propylene glycol, talc, and isopropyl alcohol were all purchased from Merck (Germany). The coating polymers, including Eudragit E100 (Eud E), Eudragit RL (Eud RL), and Eudragit RS (Eud RS), were obtained from Evonika (Germany).

2.2. Preparation of pellets

LEV pellets were prepared using an extrusion-spheronization method based on the following steps. Specific amounts of LEV, MCC, lactose, starch, and NaSG were well mixed following passing through a sieve with a mesh size of 40, and the powder mixture was prepared. The amount of active ingredient in the powder mixture was kept constant at 70 % to achieve particles with high drug loading. SLS (as an anionic surfactant) and PVP (as a binder) were dissolved in deionized water and used as the granulation (wetting) liquid to prepare the paste.

Granulation liquid was added to the powder mixture until a suitable wet mass was formed. The mixing time of the wet mass was kept constant for all formulations. The prepared wet mass was inserted into the axial-type extruder (Dorsa Tech, Iran) equipped with a 1.2 mm die. The extrudates were spheronized using a spheronizer with a speed of 600 rpm for 15 min, which was kept constant for all formulations. The composition of different pellet formulations is presented in **Table 1**. The obtained pellets were dried and analyzed in terms of physical properties.

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Table 1. Composition of the prepared pellet formulations

Formulation	MCC[a] (%)	Lactose (%)	Starch (%)	NaSG[b] (%)	PVP[c] (%)	Granulation liquid[d] (%)		
						0.1% SLS[e] solution	0.5% SLS solution	1% SLS solution
F1	_	_	27	1	1	12	_	16
F2	_	_	21	1	1	_	12	16
F3	_	_	25	1	1	8	_	20
F4	_	_	23	1	1	_	8	20
F5	_	_	25	1	1	4	_	24
F6	_	_	25	1	1	_	4	24
F7	_	_	25	1	1	_	_	28
F8	_	_	27	1	1	_	_	28
F9	_	_	29	1	1	_	_	28
F10	25	_	_	1	1	_	_	28
F11	25	_	_	2	1	_	_	27
F12	25	_	_	1.5	1	_	_	27.5
F13	_	25	_	1.5	1	_	_	27.5
F14	_	25	_	1	1	_	_	28

[a] MCC: Microcrystalline cellulose, [b] NaSG: Sodium starch glycolate, [c] PVP: Polyvinyl pyrrolidine, [d] Aqueous solution added as a percentage of the total dry weight of each formulation, [e] SLS: Sodium lauryl sulphate.

2.3. Preparation of coating formulations

A) Eud E: The polymer was dissolved in isopropyl alcohol as the organic solvent by stirring until a 10 % solution was prepared. Talc (4 %) as an anti-tacking agent, and propylene glycol (1 %) as a plasticizer [16], were also added to the above mixture. The prepared formulation was applied to the core pellets for taste-masking.

B) Eud RL/RS: To prepare the ER pellet formulations, LEV core pellets were subjected for coating using 25 % w/v organic solution of Eud RL, and RS with the ratios of 1:1, 2:3, and 3:2, respectively (F1:1, F2:3, and F3:2). Polymers were dissolved in isopropyl alcohol using a magnetic stirrer. Then, other components, including talc and propylene glycol, were added to the above solution and mixed thoroughly.

2.4. Coating process

LEV core pellets (10 g) were subjected to coating using a conventional laboratory-scale coating pan with a diameter of 17 cm and a rotation speed of 10 rpm. The coating solution was sprayed at the rate of 0.2 mL/min on the rotating pellets using a spray gun. Inlet air at a temperature of 50-60 ^{o}C was used to evaporate the solvent. The coating process was continued until a uniform coating layer formed on the surface of the particles, and the required coating level was obtained (5 % for the Eud E-coated IR pellets, and 20 % and 30 % for the Eud RL/RS-coated ER pellets).

2.5. Characterization of pellets

2.5.1. Shape and particle size

An image analysis system was used to evaluate the particle size and shape of the pellets. The images of the pellets were taken by a microscope (Optika, B810, Italy) equipped with a camera. The pellets were placed on a black background, and an overhead light source was used to reduce the effect of shadows on image processing. The information of the prepared images (under 40-fold magnification) was processed using ImageJ software. Image analysis was performed on 50 pellets of each formulation sample. The aspect ratio (AR), a most common shape factor and indicator of particle elongation, was then calculated by dividing the maximum by minimum Feret diameters for each pellet. In addition, the projection sphericity of the particles was calculated by the following equation [17]:

Eq. 1 Projection sphericity (PS)= $4A/\pi d^2$

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where d is the maximum diameter and A is the area of the two-dimensional particle outline. The maximum Feret diameter of the pellets was reported as the particle size. A perfect spherical pellet has AR and PS values equal to 1. As the pellet sphericity decreases, the AR becomes larger, and the PS becomes smaller than unity. The sphericity of the core pellet particles is an essential factor in creating a uniform coating layer.

2.5.2. Friability test

A sample of pellets equal to 3 g was placed inside the abrasion wheel of the friability tester, combined with 50 glass beads with a diameter of 4 mm, equivalent to 3 g. The chamber was rotated on a horizontal axis for 4 min at a speed of 25 rpm, and the pellets were affected by the impact of falling, colliding with each other, and with glass beads. Then, the pellets were placed on a sieve with a mesh size of 45 for 4 min on a shaker to remove their fine particles, and the samples above the sieve were weighed accurately [18].

The friability (F) percentage was calculated using the following equation based on the change in the weight of the pellets after the experiment (W_2) compared to the initial weight (W_1).

Eq. 2 $$F\% = ((W_1-W_2) \div W_1) \times 100$$

2.5.3. Disintegration time (DT)

To measure the disintegration time, six samples, each weighing 250 mg of the pellet formulations, were placed in disintegration tester tubes (Erweka, ZT6-1-D, Germany) along with a disc to apply stress to the pellets during testing. The bottom of the tubes was covered with mesh 40. The tubes moved uniformly up and down in 0.1 N hydrochloric acid at 37 ±0.2 °C. The passage of all particles from the mesh was recorded as the endpoint [19, 20].

2.5.4. Flow properties

To determine the flowability of the prepared pellets, the following three methods were used:

A) Flow time

A flowmeter was used to determine the flow time of the pellets (Erweka GmbH, Germany). The pellets were placed in the flowmeter, and the time required for the sample to flow through the funnel was measured [21].

B) Density and Carr's index

Pellet samples were poured into a measuring cylinder, and the initial volume (V_b) was recorded. Then, the cylinder was tapped 1250 times (until no further change in the volume), and the tapped volume (V_t) was obtained. Bulk (D_b) and tapped densities (D_t) were calculated by dividing the mass of the pellets by V_b and V_t, respectively [22]. The Carr's index was also calculated according to the following equation [23]:

Eq. 3 $$\text{Carr's index } (\%) = ((D_t - D_b) \div D_t) \times 100$$

C) Angle of repose

For this purpose, a cone of pellets was formed on a surface by passing the sample through a small funnel installed at a fixed height. The cone height and the base radius were measured and used to calculate the angle of repose as follows [21]:

Eq. 4 $$\text{Angle of repose} = \tan^{-1} (\text{Cone height} / \text{Base radius})$$

2.5.5. Residual moisture content

The residual moisture content of the optimum dried pellets was determined by a thermogravimetric method using a moisture analyzer (Ohaus, MB45, US). A sample of pellets equivalent to 10 g (M_1) was placed on the sample pan and heated at a constant temperature (80 °C) until no weight change was observed (M_2). The percentage of moisture content of the pellets was calculated by $((M_1–M_2)/M_2)\times100$ [24].

2.5.6. Drug assay

A pellet sample equivalent to 250 mg of LEV was ground in a mortar and transferred to a 100 mL volumetric flask containing water and acetonitrile in a ratio of 80:20 and stirred on a magnetic stirrer for three hours. The mixture was then filtered through a 0.45 µm membrane filter, diluted, and analyzed for the drug content using high-performance liquid chromatography (HPLC, Smartline, Knauer, Germany) by the method described in the USP [22]. Chromatography was performed on an L1 column (4.6 × 250 mm; 5 µm). As a mobile phase, a potassium phosphate monobasic solution (1.4 g/L) containing 0.6 g/L sodium 1-heptanesulfonate, adjusted to pH 2.8 by the addition of phosphoric acid, was mixed with acetonitrile in a ratio of 92:8. The flow rate was set at 2 mL/min. Detection was accomplished using a UV detector at 220 nm. This experiment was carried out in triplicate.

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2.5.7. Dissolution test

A) IR pellets

In vitro dissolution studies for IR pellets were performed using a USP type-II apparatus (Erweka DT6R, Germany) with a stirring rate of 50 rpm, adapted from the USP dissolution test no. 1 for the IR tablet of LEV. Uncoated and Eud E-coated pellets, equivalent to 250 mg of LEV, were dispersed in 900 mL water and 0.1 N hydrochloric acid (pH 1.2) medium at 37 ±0.5 °C for 60 min, respectively. Sampling was carried out at predetermined time intervals and replaced with an equal volume of fresh medium. The collected samples were centrifuged for 20 min at a speed of 14000 rpm, and the drug concentration was determined by the HPLC method (column L1) at the wavelength of 220 nm. The mobile phase was made by mixing monobasic potassium phosphate buffer solution (pH=5.6) and acetonitrile in the ratio of 85:15, with the flow rate set at 1.2 mL/min.

B) ER pellets

In vitro dissolution of ER pellets was carried out using USP type-I apparatus in 900 mL monobasic potassium phosphate buffer solution (pH=6) as dissolution medium (37 ±0.5 °C), adapted from the USP dissolution test no. 4 for ER tablet of LEV. Pellets equivalent to 500 mg of LEV were placed in the baskets, rotating at 100 rpm. Samples were withdrawn and analyzed for drug content using the HPLC method at a wavelength of 210 nm. Other test conditions were similar to the method mentioned for IR pellets.

To evaluate the effect of the composition and percentage of the coating layer on the release behavior of the pellets, the mean dissolution time (MDT) was calculated for the ER formulations by the following equation [17]:

Eq. 5 $$MDT = \frac{\sum_{i=1}^{n} ti\ \Delta Mi}{\sum_{i=1}^{n} \Delta Mi}$$

where ΔMi is the fraction of drug released in time ti (calculated by (ti+(ti−1)/2), n is the number of dissolution sample times, and i is the sample number.

2.5.8. Taste evaluation

A) In vitro analysis

To cover the bitter taste of LEV, the optimal pellets were coated with Eud E as a cationic polymer, which is not dissolved at the pH of the oral cavity (6.8). Therefore, no significant release was expected from the coated pellets in that medium.

A sample equal to 250 mg of uncoated and Eud E-coated pellets was added to a beaker containing 250 mL phosphate buffer solution (pH=6.8) at 37 ±0.5 °C and stirred for 5 min [25, 26]. Then, the mixture was filtered and analyzed for the amount of drug released from both samples by the HPLC method.

B) In vivo analysis

To evaluate the taste of the above coated pellets more accurately, 10 healthy volunteers, including 5 females and 5 males within the age group of 23 to 30 years, were selected, and all of them were informed about the study. Uncoated pellets equivalent to 300 mg LEV were placed on the tongue of each volunteer. After 60 seconds, the mouths were rinsed with 200 mL of distilled water. The same experiment was also performed on coated pellets at 30-min intervals. Finally, the bitterness level of the pellets was scored by the volunteers based on four degrees: 0 (no bitter taste), 1 (slight bitterness), 2 (medium bitterness), and 3 (strong bitterness) [27]. The Wilcoxon statistical test was used to evaluate the results. This was a single-blind experiment approved by the ethics committee of Shahid Beheshti University of Medical Sciences (approval no. IR.SBMU.PHARMACY.REC.1398.159).

2.5.9. Surface morphology

A scanning electron microscope (SEM; FEI Quanta 200) was used to study the shape and surface morphology of the prepared pellets. A gold coating layer of 10 nm was applied on the surface of coated and uncoated pellets using a sputter coater (COXEM SPT-20) before observation.

3. Results and Discussion

3.1. Core pellet preparation and characterization

First, the effect of various additives on the quality of the pellets was investigated. Due to the fabrication of high drug-load pellets, a reduced portion of the formulations was allocated to the additives. Therefore, their types and concentrations were more significant in achieving the desired formulation.

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As presented in **Table 1**, MCC, lactose, and starch were the main additives used in the formulations. PVP (as a binder) and NaSG (as a disintegrant), were used in the formulations along with the above pelletization aids. SLS was added to the granulation liquid to increase the uniformity of moisture distribution in the wet mass and reduce its adhesion to the extruder. The amount of granulation liquid and rheological properties of the wet mass play an important role in the quality of the pellets. In fact, for successful extrusion-spheronization, there must be a balance between the plasticity and brittleness of the wet mass. Therefore, the amount of granulation liquid in each formulation may vary depending on the type of powder mixture and the properties of the obtained wet mass. Following the preparation and evaluation of the initial pellets (F1-F6), formulations of F7 to F14 were made and studied to investigate the effect of the percentage and the components (surfactant and binder) of the granulation liquid on the pellets' properties. The SLS concentrations in the recent formulations were equal to 0.1, 0.5, and 1% (w / v), and the amount of PVP varied between 1, 1.5, and 2 %. **Table 2** shows the results of the shape and physical evaluation of formulations F1 to F14.

In formulations F1-F6, various concentrations of lactose and starch were used along with MCC as a principal pelletization aid. Lactose-containing formulations were more elongated in shape. As shown in **Table 2**, the presence of lactose in the formulations resulted in the formation of large particles, which decreased in size as the lactose concentration was reduced (F2, F4, and F6). Comparable results have been reported previously [28], which was attributed to the structure of MCC acting as a sponge molecule. The porous molecular structure of MCC highly influences the properties of the extrudates and the pellets. At low lactose concentrations, its molecules may reside in these pores, reducing their effect on the properties of the pellets. However, at higher concentrations, the influence of lactose on particle properties increases, affecting the MCC performance. Using lactose in the formulations also led to the higher friability, followed by pellet fracture, and dust formation, which are undesirable for the film coating process. The presence of starch in the formulations reduced the brittleness of the extrudates in the spheronizer and caused the formation of large particles. It must be noted that increasing the pellet DT in these formulations can have a negative effect on the drug dissolution rate from IR pellets.

Table 2. Results of the shape analysis and physical properties of the pellets (mean±SD)

Formulation	Mean particle size (mm)	AR[a]	PS[b]	Friability (%)	DT[c] (sec)
F1	2.16±0.44	1.54±0.08	0.68±0.07	1.23	416.33±6.09
F2	2.25±0.53	1.48±0.09	0.73±0.07	1.31	78.33±2.81
F3	1.92±0.46	1.69±0.08	0.63±0.06	0.88	296.10±4.19
F4	1.91±0.49	1.33±0.06	0.77±0.04	0.94	62.83±1.94
F5	1.42±0.36	1.14±0.03	0.89±0.04	0.71	46.83±2.48
F6	1.70±0.42	1.16±0.03	0.88±0.03	0.87	35.83±1.47
F7	1.28±0.18	1.14±0.02	0.89±0.02	0.46	25.50±1.52
F8	1.25±0.17	1.12±0.03	0.90±0.02	0.37	26.33±1.75
F9	1.34±0.21	1.08±0.04	0.91±0.02	0.44	26.27±0.97
F10	1.18±0.12	1.07±0.02	0.92±0.02	1.15	16.00±1.79
F11	1.41±0.27	1.13±0.02	0.89±0.02	0.63	31.17±1.47
F12	1.26±0.16	1.09±0.02	0.91±0.02	0.72	16.50±1.52
F13	1.18±0.15	1.08±0.02	0.92±0.01	0.56	23.33±1.51
F14	1.16±0.12	1.07±0.02	0.93±0.02	0.89	19.17±1.84

[a] AR: Aspect ratio; [b] PS: Projection sphericity; [c] DT: Disintegration time

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The results show that with increasing the percentage of MCC, the shape factor and sphericity of the pellets improved significantly (p=0.011). In addition, the average particle size decreased from 2 mm to about 1.2 mm with more uniformity. Increasing the amount of MCC in the pellet formulations was associated with a significant reduction in friability and faster pellet disintegration (p = 0.036). Finally, the friability and appearance of the pellets, such as particle size and AR, were improved by the presence of 28 % MCC in the formulation F7. MCC has good physical properties such as moisture retention, cohesiveness, plasticity, and the appropriate rheological properties of its wet mass [29], which are essential factors in improving pellets sphericity, particle size distribution, and mechanical properties (low erosion) [30].

According to **Table 2**, by increasing the liquid content of F8 and F9, although the AR and PS values were slightly improved compared to F7, the mean particle size increased. The significant effect of the solvent content on particle size and sphericity of the pellets has been reported previously [31, 32]. Increasing the size along with improving the shape of pellet particles due to the use of higher amounts of granulating liquid could be attributed to the higher plasticity of the wet mass, leading to the agglomeration of fine particles as well as the ease of forming spherical particles during the spheronization process. Based on the results, the liquid percentage of 25% (as used for F7) was selected as the optimal due to the appropriate size and acceptable sphericity.

The amount of SLS in the formulation F10 was increased to improve the shape and uniformity of the particles, which led to the higher friability. This could be attributed to the reduced surface tension caused by higher SLS concentration, and therefore, less adhesion force between the wet particles. In the wet mass, surface tension and capillary forces are the main factors for particles agglomeration [33]. Excessive reduction of these forces could weaken the bonds between the particles and, in turn, enhance the friability.

In the next step, different concentrations of PVP were added to the formulations to improve the adhesion and cohesion of the solid particles and, therefore, reduce the pellets friability. Increasing the amount of PVP from 1% to 2 % (F11), despite decreasing the friability, adversely affected the other properties of the particles, including an enhancement of mean particle size and an almost doubling of the DT value. The use of 1.5 % PVP (F12), while improving the strength of the particles, had no significant effect on the PS and DT of the pellets compared to F10. Meanwhile, reducing the SLS concentration from 1 % to 0.5 % led to the formation of particles with better properties. These particles had more uniformity in shape, acceptable friability, and DT value. Therefore, F13 was selected as the optimal core pellet due to its better and more desirable properties compared to the other formulations.

In the next step, further studies were performed on F13. According to the results obtained from the flowmeter, the flow rate of these core pellets was 10.83 g/s, which indicated the desirable flowability [21]. This was confirmed by the angle of repose, which was equal to 21.66 ±1.52 degrees. There was no major difference between the bulk and tapped densities of the pellets (D_b= 0.684 g/cm^3, D_t = 0.696 g/cm^3). Carr's index is a flow indicator, and values equal to or less than 10 indicate high flowability. The Carr's index for the prepared particles was calculated to be 1.72 ±0.08 %, which showed the excellent flowability of the pellets [7].

The residual moisture content of the pellets was 0.62 ±0.05 %, indicating their proper drying. Based on the results, the drug assay was equal to 93.99 ±0.58 %, which was within the United States Pharmacopoeia limit (90-110 %).

The dissolution profiles of F13, performed in both aqueous and 0.1 N HCL media, are depicted in **Figure 1A**. As the results show, the profiles were almost superimposed, which was expected due to the pH-independent solubility of LEV [34]. The drug was dissolved entirely within the first 15 min, following the pellets rapid disintegration. This was in accordance with the USP dissolution criteria for the LEV immediate release tablet (at least 70 % in the first 15 min) [22].
Since the core pellets had desirable characteristics, in the next step, they were subjected to the coating process using various polymers for different purposes, which are discussed below.

3.2. Immediate release (IR) pellets

The prepared core pellets had fast and acceptable dissolution, which was required for the IR formulation of LEV. However, due to the unpleasant taste of the drug, they needed to be coated with a suitable polymer. The

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application of Eud E as the coating layer on the surface of the pellet particles was for this purpose.

Based on the results, the drug assay of coated pellets was 93.34 ±1.07 %, which was in the acceptable range. The release profiles of LEV from Eud E-coated pellets in 0.1 N HCl (pH 1.2) and water are shown in **Figure 1B**. Due to the solubility of Eud E in an acidic medium, the coating layer dissolved within a short time after the beginning of the experiment. Then, 80 % of the drug dissolved in the medium in the first 10 min, which was in accordance with the USP criteria for the IR tablet form of LEV mentioned above. On the other hand, the drug dissolution from coated pellets was delayed in water compared to the acidic medium, and a lower amount of the drug was released, especially at the beginning of the study. This was expected because of the insolubility of Eud E in water. Only 11 % of LEV was dissolved during the first 10 min, which might be by the diffusion mechanism.

Comparing the dissolution profiles of the uncoated and Eud E-coated pellets in HCl (**Figure 1A-B**) reveals that the dissolution of LEV from coated particles was significantly ($p<0.001$) lower than that of the uncoated pellets (11 % and 93 % in 10 min, respectively). This feature is essential to reduce the perception of unpleasant taste by preventing the contact between the dissolved drug and the taste receptors [35].

3.3. Extended release (ER) pellets

At this step, ER pellets of LEV were prepared using Eud RL and RS in combination as coating polymers. The drug release behavior from the coated particles depends on different factors, such as the amount of the coating layer on the surface of the particles (coating thickness) and the polymer type applied in the coating formulation. Considering the characteristics of the two above polymers, including different water permeability [17], it seems that using their suitable combination could result in an appropriate LEV release profile. Also, since Eud RL and RS are pH-independent water-insoluble polymers [36], it was expected that the coating layer, while controlling the drug release rate, would also cover the unpleasant taste of the pellets.

Nasiri et al. reported that the use of up to 15 % Eud RL/RS (2:1) as a coating layer failed to control the initial burst drug release from the pellets [36]. The high ratio of Eud RL to Eud RS and the reduced coating layer thickness could be considered the most probable reasons for this occurrence. Therefore, in the present study, different polymer ratios and coating levels were used to enhance the possibility of controlling the drug release rate and achieving the ER system. Therefore, three different ratios of Eud RL/RS (1:1, 2:3, and 3:2) with two levels (20 % and 30 % based on the weight of pellets) were used for coating the pellet particles.

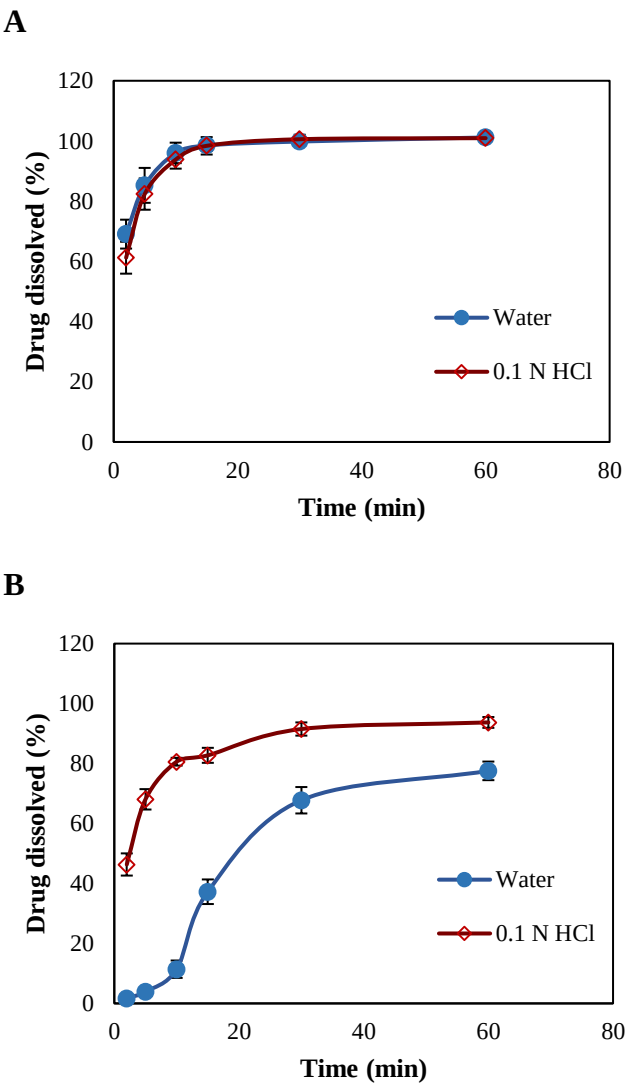

Figure 1. LEV dissolution profiles in water and 0.1 N HCl, A) uncoated F13 pellets, B) Eud E-coated F13 pellets (n=3)

The release profiles of LEV from Eud RL/RS-coated pellets with different ratios are depicted in **Figure 2**.

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Based on the results, the pellets coated with 20 % polymer showed a rapid release, and 51-76 % of the drug dissolved in the medium during the first hour of the experiment, which was more than the USP acceptable limits for the ER tablet of LEV (22-42 %). Meanwhile, increasing the ratio of Eud RS to RL (F2:3 20), despite the slight decrease in drug release rate, was not effective in achieving a suitable release profile. The MDT values obtained for F3:2, F1:1, and F2:3 (Eud RL/RS 20 %, **Figure 2A**) were equal to 31.15, 57.06, and 66.05 min, respectively. As is apparent, with increasing the amount of Eud RS in the polymer mixtures, the drug release rate decreased, and the MDT values increased by more than 2 times. The fastest release was obtained for the formulation with a higher amount of Eud RL (F3:2 20) due to having more ammonium groups and, therefore, higher permeability than Eud RS [17, 37].

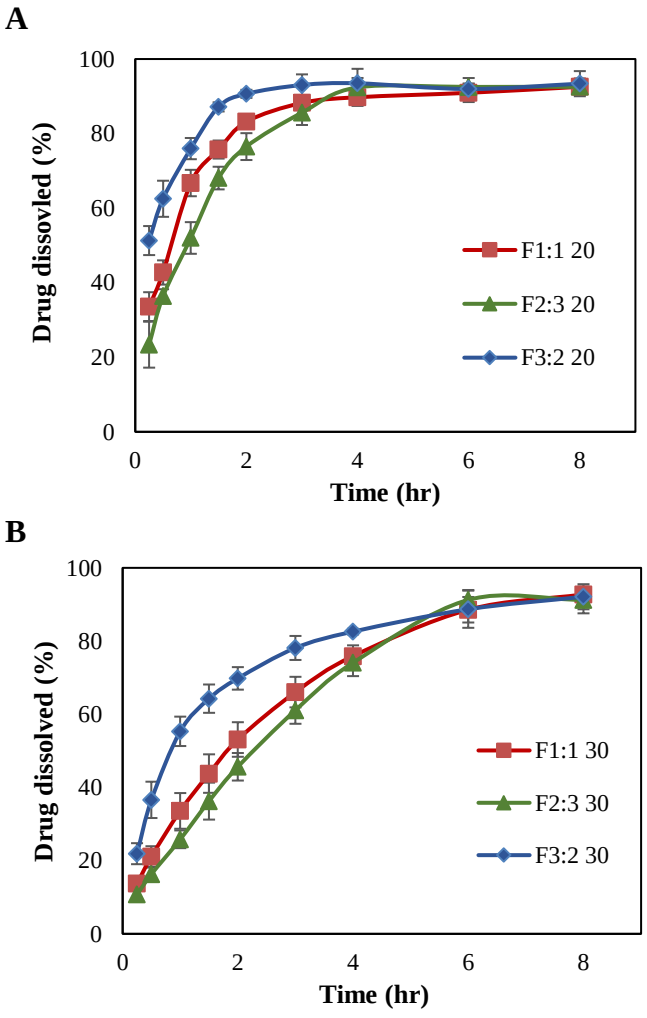

Figure 2. LEV release profiles from Eud RL/RS coated pellets with different ratios, A) 20 % and B) 30 % coating level (n=3)

As shown in **Figure 2B**, by increasing the coating level to 30 %, drug release decreased significantly ($p<0.01$) to 25-56 % in the initial hour. The release rate in the following hours was also slower than that of the pellets with a 20 % coating layer. In other words, 30 % coating performed much better in reducing the release rate and the burst release compared to that of 20 %. Changing the polymer ratios in these formulations caused noticeable differences in the MDT values (87.31, 130.87, and 138.02 min for F3:2, F1:1, and F2:3 (Eud RL/RS 30 %, **Figure 2B**), respectively). The drug release was controlled appropriately in the formulations F1:1 and F2:3 over the 8 hours of the experiment. The cumulative percentages of drug released from the above formulations after 1, 2, 4, and 8 hrs were 25-34 %, 53-45 %, 76-74 %, and more than 90 %, respectively. These values were within the acceptable limits based on the USP monograph for the ER tablet [22]. Therefore, the two above-mentioned formulations were selected as LEV ER pellets. It must be mentioned that the drug assays of those pellets (F1:1 30 and F2:3 30) were equal to 93.08 ±0.51 % and 93.17 ±0.83 %, respectively.

3.4. Taste masking evaluation

A) In vitro analysis

If the pellet particles were coated properly, no significant drug release would be expected at higher pH in the first minutes of the experiment, due to the insolubility of the coating polymers in that medium. The dissolution of LEV from coated and uncoated pellets in phosphate buffer solution (pH = 6.8, similar to the oral cavity) was evaluated and compared over 5 min. Based on the results, the dissolved drug from coated particles (≤2.7 %) was significantly ($p<0.0001$) lower compared to that of the uncoated core pellets (81 %), indicating the efficiency of the coating layers in protecting the drug from being released at oral pH. A release of less than 10 % of the active ingredient from the above-mentioned coated pellets ensured adequate taste masking, which is in accordance with the literature [38].

B) In vivo analysis

The taste-masking efficiency of the developed coated pellets was evaluated *in vivo* with the assistance of ten healthy volunteers. The results obtained from the *in vivo*

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study revealed that LEV uncoated pellets had medium to strong bitterness (3.7 ±0.48), while the coated pellets had no bitter taste to the volunteers. Wilcoxon statistical analysis, performed to compare the results of the above types of pellets, showed significant ($p<0.01$) suppression of the bitter taste for coated pellets, which confirmed the results of the *in vitro* analysis.

3.5. Surface morphology

The morphology of particles can play an important role in their coating. Irregularly shaped particles with poor strength are more difficult to coat. Therefore, the coating layer used for taste-masking or the drug release modification will not be as effective as intended [38].
SEM micrographs of uncoated and coated pellets with two different magnifications are depicted in **Figure 3**. The good shape and sphericity of the core pellet with some pores on its surface could be observed. It seems that the coating process did not have an undesirable effect on the shape of the particles. In other words, the particles were not eroded during the coating processes and kept their structures, which was expected based on the friability study. A smoother texture of the surface of the coated pellets, and also a relatively uniform coverage of the core particles and related surface pores could be observed following coating with both polymer series.

4. Conclusion

Pellets as multi-particulate systems are increasingly used to formulate various medications, which is an influential step for drug delivery, especially in children and elderly patients. LEV pellets were successfully formulated in the present study using the extrusion-spheronization technique. The selection of appropriate formulation variables led to the formation of high drug-loaded pellets with low friability, good disintegration, and desirable appearance. ER and IR dosage forms with suitable characteristics were prepared by coating similar core pellets, which could be very cost-effective due to the absence of a need for separate formulations. Taste-masking of the pellets was well achieved by coating layers, confirmed by *in vitro* and *in vivo* analysis. Dosing flexibility and easy swallowing could be mentioned as other features of LEV immediate and extended release pellet formulations.

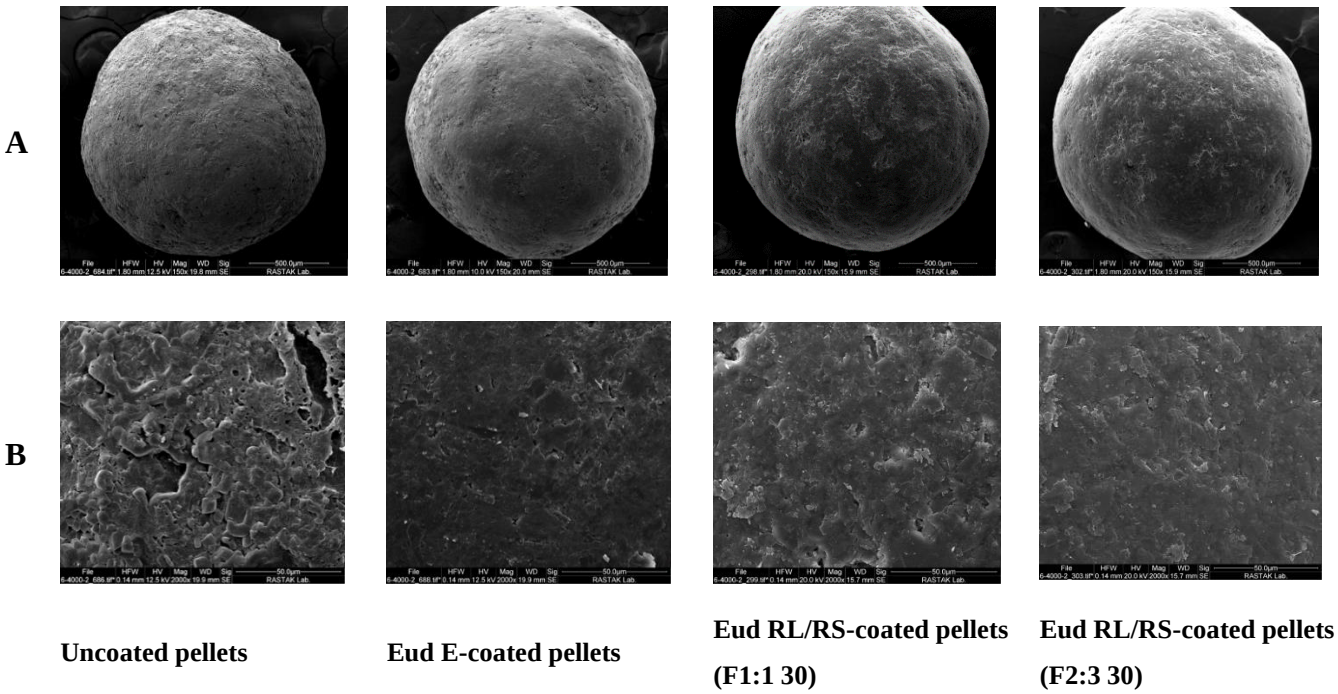

Figure 3. SEM micrographs of the uncoated and coated pellets at two magnifications: A: ×150, and B: ×2000

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Conflict of Interests

The authors declare that they have no conflicts of interest.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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