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Original Article

THE EFFECT OF CO-PROCESSED EXCIPIENTS DURING FORMULATION AND EVALUATION OF PEDIARIC LEVETIRACETAM ORODISPERSIBLE TABLETS IN RATS

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ABSTRACT

Objective: The main aim of this research was to make cost-effective taste-masking oral pediatric orodispersible tablets (ODTs) of Levetiracetam as an antiepileptic drug (AED) using various co-processed excipients by direct compression method.

Methods: Eight kinds of ready-made co-processed excipients in addition to sucralose and menthol as a sweetener, were utilized. The weight variation, drug content, friability, *in vitro* disintegration, dissolution time, hardness, thickness, and pharmacokinetics of the produced ODTs were determined.

Results: The optimized formula (F5) containing Pharmaburst® 500 showed the shortest disintegration time (11.66 sec) and more than 98% of Levetiracetam within 10 min (Q10). The Pharmacokinetic study of this optimum formula (F5) in rats using an HPLC-UV detector showed 26.904±2.027 ng/ml as the Cmax and 101.935±0.894 h ng/ml as AUC compared to commercial Tiratam® solution 10.421±0.295ng/ml and 23.135±0.43 h ng/ml respectively.

Conclusion: Levetiracetam orally orodispersible tablets were successfully prepared with acceptable hardness, satisfactory taste, and rapid disintegration in the oral cavity avoiding first-pass metabolism to yield the desired rapid effect in facing epilepsy for patients who experience dysphagia like pediatric and geriatric. In addition to the unconsciousness of the epileptic patient followed the seizure attack.

Keywords: Epilepsy, Levetiracetam (LVT), ODT, Pharmaburst® 500, Direct compression

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INTRODUCTION

It was known that epilepsy is a highly predominant chronic neurological disorder that leads to social, behavioral, health, and economic consequences, where the brain exhibits a pathologic and lifelong proclivity for repeated seizures. The International League Against Epilepsy (ILAE) categorized epilepsy as a disease rather than a disorder in 2014 to emphasize the disease's significance and impact [1].

Knowledge of the effectiveness range, clinical pharmacology, and routes of administration of specific AEDs is critical for the most effective epilepsy treatment. Therefore, the complexity of the disease, the agent's tolerability, the efficacy, and the patient's characteristics must all be considered when selecting an AED [2]. Numerous antiepileptic medicines displayed a variety of methods of action, including ion channel regulation, an increase of inhibitory neurotransmission, attenuation of excitatory neurotransmission, and unique mechanisms involved, including Levetiracetam [3].

Levetiracetam (LVT), ((S)-a-ethyl-2-oxo-1-pyrrolidine acetamide) is a novel broad-spectrum antiepileptic drug that is chemically unrelated to other currently available AED, and it is effective against various kinds of seizures because of minimal drug interactions and fewer side impacts. It has an excellent pharmacokinetic profile for pediatric children in terms of safety. The means mechanisms of Levetiracetam involve neuronal binding to synaptic vesicle protein 2A(glycoprotein), By suppressing calcium release from intracellular reserves, we are able to counteract the activity of negative modulators of GABA-A and glycated currents, hence suppressing excessive synchronized activity between neurons [4].

Orodispersible tablets (ODTs) are fast melt, quick melts, porous tablets, effervescent drug absorption system "EFVDAS," and fast disintegrating [5]. As per the European Pharmacopeia, these are solid dosage forms comprising medications that degrade within three minutes in the oral cavity, leaving an easily-swallowable residue [6].

This oral route has a number of advantages over the standard tablet route in terms of providing medication to patients who are unable to swallow, such as pediatrics, geriatrics, mental, stroke, and bedridden patients. Patient compliance, rapid onset of action, enhanced bioavailability, and excellent stability have made these tablets a popular dosage form in today's market. Rather than the excellent mouth feel property that allows the relief of drugs' bitter taste to be suitable for pediatric patients [7]. The palatability, pleasant taste, and lack of unpleasant feelings associated with an oral dispersible tablet formulation depending on the inclusion of fragrance and sweeteners.

So, the choice of excipients is crucial for developing a tablet formulation and the quality control of dosage forms. Due to flowability, compressibility, and stability properties, a minimal number of excipients is used for direct compression. Co-processed excipients for utilization in directly compressed Orodispersible tablet formulae as Prosolv easy tab sp, Prosolv easy tab Nutra, Prosolv 50 SMCC, F-melt, Prosolv ODT, Pharmaburst 500, Prosolv HD90, Spress B820, and Lactochem Regular 2096 that we used in our study [8].

Thus, this study aims to prepare Levetiracetam Orodispersible tablets to obtain a more convenient and effective dosage form for epileptic patients and achieve objectives like rapid onset of action, good mouth feels, and enhanced patient compliance.

MATERIALS AND METHODS

Levetiracetam was a gift from El Andalous Medical Company, Cairo, Egypt. Pharmaburst 500 was received from Eva Pharma, Cairo, Egypt. Prosolv ODT, Prosolv®Easytab Nutra, Prosolv® SMCC, HD90, and Prosolv®Easytab SP were gifts from JRS Pharma GmbH and Co. KG, Rosenberg, Germany. F-melt type C was obtained from Fuji Chemical Industry Ltd., Toyama-Pref, Japan. All other chemicals and solvents used were of the highest analytical grade. Distilled water was used all over the study.

Preparation of levetiracetam orodispersible tablets

Orodispersible tablets were made by the direct compression approach utilizing a single punch tablet machine under continuous pressure using a concave-faced 9 mm punch and die set (Royal Artist, Mumbai, India). Eight kinds of ready-made co-processed excipients (Prosolv easy tab sp, Prosolv easy tab Nutra, Prosolv 50 SMCC, F-melt, Prosolv ODT, Pharmaburst 500, Prosolv HD90, Spress B820) were added at 100 mg from each one to the 150 mg Levetiracetam (LVT), 10 mg sucralose and 5 mg menthol were added to all formulas to mask the bitter taste of the drug. The formulas contained a ratio of (1.5: 1: 0.1: 0.05) w/w representing drug, excipient, sucralose, and menthol, respectively, to produce a tablet with a total weight of 265 mg. The powder blend for each tablet was manually loaded into the die and crushed into tablets.

Table 1: Composition of different ODTs made by direct compression using different co-processed excipients

Formula code	Ratio of drug: Co-excipient: sucralose: menthol	
F1	1.5: 1: 0.1: 0.05	LVT: Prosolv easy tab sp: sucralose: menthol
F2	1.5: 1: 0.1: 0.05	LVT: Prosolv easy tab nutra: sucralose: menthol
F3	1.5: 1: 0.1: 0.05	LVT: Prosolv 50 SMCC: sucralose: menthol
F4	1.5: 1: 0.1: 0.05	LVT: Fmelt: sucralose: menthol
F5	1.5: 1: 0.1: 0.05	LVT: Pharmaburst 500: sucralose: menthol
F6	1.5: 1: 0.1: 0.05	LVT: Prosolv ODT: sucralose: menthol
F7	1.5: 1: 0.1: 0.05	LVT: Prosolv HD90: sucralose: menthol
F8	1.5: 1: 0.1: 0.05	LVT: Spress B820: sucralose: menthol

***In vitro* assessment of the prepared levetiracetam orodispersible tablets**

The prepared tablets were validated as per pharmacopeia concerning weight variation, friability, drug content, wetting time, thickness, hardness, *in vitro* disintegration time, and *in vitro* dissolution studies. The best formulation will be chosen for *in vivo* pharmacokinetics studies. All results were conducted in triplicate and expressed as (n = 3±SD).

Weight variation

Weight variation was conducted as per British Pharmacopeia (BP 2013). For each tablet formula, the weights of twenty randomly selected tablets were measured individually, then calculate the mean and standard deviation (SD) of weight.

Hardness and thickness variation

Five tablets of each formula were taken randomly, and their hardness and thickness were measured utilizing (Pharmatron AG Sotax Multi Test 50, Switzerland), then calculated their mean and SD values were. The results of thickness were expressed in millimeters (mm) and hardness kilopound (KP) [9].

Friability test

The friability of tablets was determined using Friabilator (LABOAO CS-1, China). Ten tablets of each formula were weighed (W1) and placed in the drum of a Friability tester. The friabilator was rotated for 4 min at 25 rpm. The tablets were reweighed (W2) after removing the dust. Then the percent friability was measured according to the following equation:

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

The weight reduction showed a friability value that was considered acceptable when the percent friability varied from 0.1 to 0.9% [10].

Uniformity of drug content test

Each Levetiracetam Orodispersible tablet was crushed and dissolved in activated saliva fluid (SSF) pH 6.8 at 37±0.5 °c in a volumetric flask. The solution was filtered; 1 ml of filtrate was taken into 100 ml of the volumetric flask, diluted with SSF (pH 6.8), and measured the absorbance at the predetermined λmax (205 nm) through a preconstructed standard calibration curve using a UV-VIS spectrophotometer. Measurements were performed in triplicate for each formula, and the results were represented as mean±SD [11].

***In vitro* disintegration time (DT) test**

This is a valuable performance test for immediate-release dosage forms, such as our ODT formula. Implementing the USP's guidelines should lead to a time limit of three minutes. According to the European Pharmacopeia, one tablet was dropped into the cylinders of the basket-rack assembly of the disintegration tester (Hanson, Phase One Disintegration Tester, Chatsworth, USA) filled with activated saliva fluid (SSF), pH 6.8 at 37±0.5 °C, and the time needed for whole tablet disintegration was measured. All trials were conducted in triplicate for each formula, and the findings were represented as (n = 3±SD) [12].

Wetting time (WT) test

Two folds of Whatman filter paper were placed in a petri dish holding 6 ml dye solution (methylene blue aqueous solution). Using a set of forceps, a single tablet was carefully put on the surface of the filter paper to properly calculate the time required for the dye solution to reach the upper surface of the tablet, which was characterized as the wetting time. The blue dye was used to detect the appropriate endpoint. This technique triggers physiological conditions on the tongue's wet surface; the primary shortcoming is that the effect of the human tongue's mechanical tension is ignored [13]. The wetting time for each formula was conducted in triplicate (n = 3±SD).

***In vitro* dissolution study**

A USP paddle apparatus (type II) was used to measure the release of producing Orodispersible tablets (Hanson SR8 Plus, USA). This test was conducted using 900 ml of phosphate buffer solution pH 6.8 at a temperature of 37±0.5 °C and a rate of 50 r. p. m. At predetermined time intervals (2, 4, 6, 10, 15, 20, 25, 30, 45, and 60 min), 5 ml of the solution was removed from the dissolution apparatus and replaced with an equivalent volume of fresh dissolution media to maintain the volume constant. After filtering the samples via a 0.45 m membrane filter, they were diluted with SSF (PH 6.8). The absorbance of these solutions was determined using a double-beam UV spectrophotometer at LVT max 205 nm (Shimadzu UV-2700i, Japan). The concentration of the medication was represented as a percentage (percent) of the total amount released [14]. *In vitro* dissolution tests were conducted in triplicate (n = 3±SD).

Research ethical committee (REC)

The research protocols were authorized by the Ethics Committee of the Faculty of Pharmacy, Cairo University, Egypt, and were assigned a serial number by the Animal Care Committee of the National Research Center (Cairo, Egypt) (PI 2898 on 25 January 2021).

***In vivo* pharmacokinetics study of levetiracetam orodispersible tablet**

Nine healthy Male Wistar Rats weighing (250-300 g) were utilized in the bioavailability study. Rats were obtained from the Animal House of the Faculty of Pharmacy Cairo University, Giza, Egypt. All animals were adapted and maintained under steady temperature (25 °C±2 °C), having free access to water and standard rodent pellet food, and performed in submission to the Research Ethics Committee (REC). Animals were categorized randomly into three groups; 3 rats were assigned to each group. Group 1 received a commercial Tiratam®

solution using the insulin syringe. Group 2 received the prepared optimized ODT formula F5 (1.5: 1:0.1: 0.05) (LVT: Pharmaburst 500: Sucrolose: Menthol), and group 3 was a negative control group. The tablet was held under the tongue of rats by tweezers until it dissolved; it was static and returned to the tongue when moved.

One ml of blood was withdrawn from the retro-orbital vein of the rats into heparinized plasma tubes at time intervals (n) of 0, 0.25, 0.5, 0.75, 1, 2, 4, and 8 h. The collected blood samples were immediately centrifuged at 4000 rpm for 10 min to separate plasma and kept at-20 °C until analysis. Levetiracetam analysis in plasma was quantified using High-Performance Liquid Chromatography (HPLC) method (Agilent 1200 series) as reported.

Chromatographic conditions for HPLC analysis of LVT

According to the HPLC method was used for the quantification of LVT [15]. The HPLC system (Agilent 1200 series) is equipped with a degasser, binary pump, thermostatic column oven, and a diode-array detector with variable wavelengths. The Agilent Chemstation software package, version A.10.02 used for data analysis and processing on a Phenomenex Luna C18 column (250 × 4.6 mm) containing five µm particle size as stationary phase and detected by UV-VIS detector (Shimadzu UV-2700i, Japan) at 205 nm. The column was kept at room temperature (25±2.0 °C). The samples were eluted using a combination of 50 mm KH2PO4 buffer (6.8045 g/l) and acetonitrile (90: 10, v/v) as mobile phase and delivered at a flow rate of 1 ml/min. And 10 µl injection volume.

The pharmacokinetic parameters analysis

The pharmacokinetic parameters (C_{max} (ng/ml), T_{max} (h), AUC last, AUC INF (ng h/ml), K_e, MRT and terminal elimination rate constant (Lambda_z) were analyzed using the software program PKSolver, for pharmacodynamic and pharmacokinetic data analysis in Microsoft Excel.

Statistical analysis

The findings are expressed as means±SD [16]. The pharmacokinetic parameters, Cmax, AUC last, AUC Inf, were analyzed statistically via ANOVA and non-parametric tests for Tmax. The P-value was calculated at the α level of 5%, using IBM SPSS statistics version 26 (Microsoft software). When $p<0.05$ means there is a statistically significant difference.

RESULTS

***In vitro* evaluation of the prepared levetiracetam orodispersible tablets**

The results were represented as shown in table 2

Table 2: *In vitro* assessment of the prepared levetiracetam orodispersible tablets

formulas code	Weight variation (Mg±SD)	Hardness (KP±SD)	Thickness (Mm±SD)	Friability (%)	Drug content (%)	Wetting time (sec±SD)	Disintegration time (Sec±SD)	Q_{10}±SD
F1	252.05±0.689	13.831±0.302	3.14±0.045	0.776±0.007	102.37±1.646	65.73±4.509	98.60±4.58	74.66±5.847
F2	255.00±1.21	17.99±0.418	3.23±0.035	0.802±0.030	98.051±7.177	100.65±8.404	84.55±2.42	71.91±1.182
F3	254.91±1.87	23.651±1.292	3.36±0.066	0.750±0.043	95.167±23.533	57.10±3.511	320.46±36.66	41.412±3.079
F4	253.42±0.710	17.03±0.605	3.30±0.065	0.998±0.307	94.47±2.262	32.45±4.041	64.90±2.51	78.33±0.288
F5	255.63±0.71	17.92±0.730	3.31±0.0818	0.825±0.062	104.98±3.377	32.86±1.527	14.37±1.527	98.79±0.226
F6	256.65±0.86	17.74±0.659	3.24±0.0416	0.794±0.018	105.146±3.092	35.32±1.154	19.72±1.732	96.64±1.801
F7	255.64±1.47	15.77±0.435	3.26±0.0458	0.973±0.272	109.012±7.680	38.61±2.516	20.53±1.527	97.40±1.735
F8	230.09±5.45	6.35±0.0336	-----	-----	-----	-----	-----	-----

*Each value presents the mean of triplicate (n=3), mean±SD, Q10: The amount of Levetiracetam dissolved after 10 min.

Weight variation

The weights of twenty LVT ODT ranged from (230.09±5.45 to 256.65±0.868 mg). According to BP, the weights of all formulas were within the acceptable range, except F8 was out of range. Although Spress® B820 is supposed to render starch directly compressible, F8 showed unacceptable weight variation (230.09±5.45) [17].

Hardness and thickness variation

Hardness

By applying constant compression force that was adjusted to the lowest level to form a suitable tablet with enough strength and porosity at the similar time to make sure quick wettability and fast disintegration.

All tablets in all formulae had sufficient hardness values that ranged between 6.35 kp–23.651 kp. F3(1.5:1:.01:0.05, LVT: Prosolv 50 SMCC: sucralose: menthol respectively) showed the maximum hardness of 23.651 kp where Prosolv 50 MSCC contains microcrystalline cellulose (MCC) as the primary component in its structure; MCC has a smaller particle diameter and is almost complete fibrous, increasing its hardness value. On the other hand, F8 (1.5:1:.01:0.05, LVT: Spress B820: sucralose: menthol respectively) showed the lowest hardness (6.35 kp); this is maybe due to the presence of Spress® B820 in the formulation so this formula cannot persist further examination.

Thickness variation

The average thickness ranges from (3.14±0.045 to 3.36±0.066 mm). The reproducibility of the outcomes accepted the uniformity of thickness for all formulas. There is no significant difference in thickness values between different formulas.

Friability

The friability test evaluates the tablets' mechanical resistance, ensuring the physical integrity of the drug product after distribution [18]. The loss of more than 1% of the weight of the tested tablets was not acceptable according to the British Pharmacopeia (BP 2013); all tablets did not break or demonstrate any capping, chipping, or cracking throughout the test. They had accepted friability percent (less than 0.998 %).

Wetting time

Wetting time has a significant impact on tablet disintegration time. The tablet's wettability can considerably reduce disintegration time [11]. F4 and F5 showed a comparable wetting time of (32.45 and 32.86s) respectively; this is related to the presence of crospovidone and mannitol. Crospovidone is a super disintegrant with a rapid capillary activity and pronounced hydration with a slight tendency to gel [19]. F1, F2, F3, F6, and F7all contained microcrystalline cellulose (MCC) in their composition; the porosity of MCC tablets decreases, and consequently, wetting time increases [20].

Drug content

For made tablets, the average drug content for each formula varied from (94-.47±2.262%, F4) to (109.012±7.680%, F7) of the labeled claim (table 2), So all formulas complied with the pharmacopeia limits [21].

Disintegration time (DT)

The DT result of all formulas is shown in (table 2). F5 showed the best DT (14.37±1.527 s). The absence of sorbitol and the presence of

MCC, which decreased the water uptake by the formula (F6), contributed to the increase of DT compared to (F5). The presence of (2-9%) relatively water-insoluble dibasic calcium phosphate in F4 contributed to the high DT comparatively to F5, F6, and F7. F2 and F1 showed high DT of (84.55±2.42 s) and (98.60±4.58 s), respectively. All formulas were in the acceptable range of disintegration time (within 180 sec) except for F3, that showed an undesirable DT of (320 s).

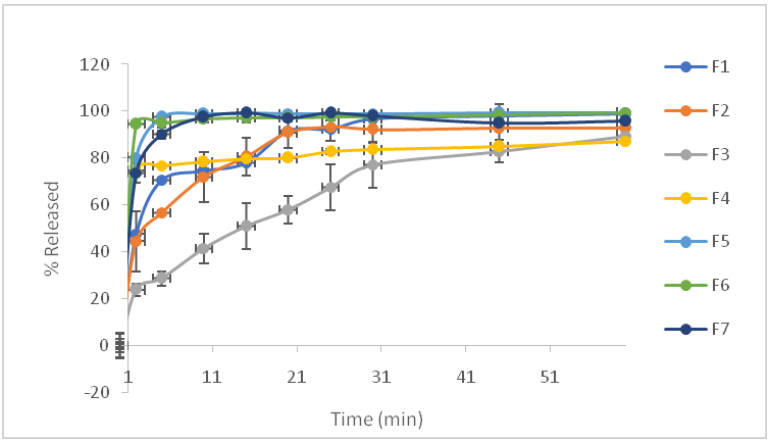

Fig. 1: *In vitro* dissolution profile of prepared levetiracetam ODTs, Data are represented as mean±standard deviation (n=3)

In vitro dissolution of Levetiracetam and Q10

The most crucial criterion for medication absorption is dissolution. The objective of the dissolution test is to ensure the almost complete release of the drug into the medium within an acceptable time; in the case of ODTs, this time is about 10 min to be a reasonable time to calculate the release. Thus, the amount of LVT dissolved after ten minutes (Q10) was utilized to contrast the various ODT formulations. The data in table 2, fig. (1) showed that all formulas gave a dissolution rate>71% after the dissolution throughout the first 10 min, except F3 gave 41.41%. So, ranking of Q10 for prepared ODTs was F5>F7>F6>F4>F1>F2>F3. F5 (LVT: Pharmaburst 500: sucralose: menthol) indicated the quickest dissolution rate at 10 min (98.79±0.226), Whereas only F3 (LVT: Prosolv 50 SMCC: sucralose: menthol) showed the lowest at the same time (41.41±3.079).

In vivo pharmacokinetic study of Levetiracetam ODT

Table 3: *In vivo* pharmacokinetic parameters of optimized levetiracetam ODT formula

PK parameters	Treatment	
	Commercial oral solution	Optimized formula
C_{max} (ng/ml)	10.421±0.295	28.518±2.027
Auc_{last} (h*ng/ml)	23.135±0.43	108.051±0.894
AUC_{INF}_obs (h*ng/ml)	25.224±2.095	195.054±12.625
T_{max} (h)	0.917±0.144	0.5±0
$Aumc_{last}$ (h*h*ng/ml)	50.577±1.521	357.219±2.113
$AUMC_{INF}$_obs (h*h*ng/ml)	74.986±22.312	1878.433±243.516
HL_Lambda_z (h)	2.18±0.714	6.56±1.195
Mrtlast (h)	2.186±0.025	3.513±0.05
Lambda_z (1/h)	0.345±0.124	0.108±0.021

*Statistical values mean±SD, (n=3).

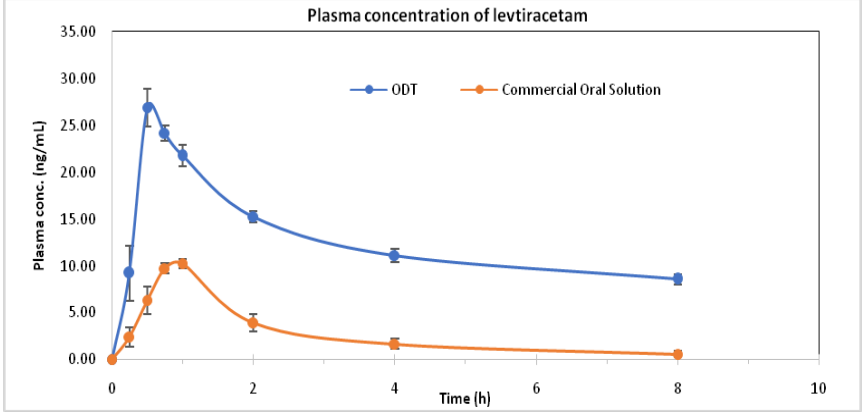

Fig. 2: Plasma concentration of levetiracetam from prepared ODT and commercial oral solution, data are represented as mean±standard deviation (n=3)

A validated HPLC approach was utilized to quantify the concentration of Levetiracetam from the optimized formulation (F5) in rat plasma compared to the equivalent dose (15 mg) Levetiracetam of in the commercial oral solution.

Table 3, fig. 2 shows different plasma pharmacokinetic parameters as The Cmax values were 28.518±2.027ng/ml and 10.42±0.295ng/ml, while AUC last was 108.051±0.894 h*ng/ml and 23.134±0.43 h*ng/ml, Tmax values were 0.5 and 0.917±0.144 h for our prepared ODT and the commercial oral solution respectively. The values of Levetiracetam plasma mean residence time (MRT) are 3.513±0.05 h and in the case of oral solution, 2.186±0.025 h.

DISCUSSION

According to BP, the weights of all formulas were within the acceptable range, except F8 was out of range. Although Spress® B820 is supposed to render starch directly compressible. The maximum hardness of 23.651 kp (F3) where Prosolv 50 MSCC contains microcrystalline cellulose (MCC) as the primary component in its structure; MCC has a smaller particle diameter and is almost complete fibrous, increasing its hardness value. On the other hand, F8 showed the lowest hardness (6.35 kp); this is maybe due to the presence of Spress® B820 in the formulation so this formula cannot persist further examination.

The reproducibility of the outcomes accepted the uniformity of thickness for all formulas. There is no significant difference in thickness values between different formulas, which is similar results to El-Nabarawi MA *et at.* 2018 [11].

F4 and F5 showed a comparable wetting time of (32.45, and 32.86s) respectively; this is related to the presence of crospovidone and mannitol where Crospovidone is a super disintegrant with a rapid capillary activity and pronounced hydration with a slight tendency to gel. Moreover, mannitol increases the hydration capacity due to its axial (OH) on the C-2 atom. While formulae contained microcrystalline cellulose (MCC) in their composition, their porosity decreases, and consequently, wetting time increases.

Unlike this study, Results reported by Tahan *et al.*2022 Using prosolv SMCC 90, which contain MCC, showed increasing in itopride HCl bioavailability, friability of 0.15, *In vitro* disintegration time 4±0.12 sec and wetting time 4±0.35 sec [21].

This may be due to difference in drug type, compression force or amount of silicified microcrystalline cellulose in prosolv SMCC 90 and prosolv 50 SMCC; the products differ in average of particle size and bulk density. Since moisture content affects MCC's compressibility, compressing MCC with different moisture contents at the same pressure might not produce the same compact porosity [22].

In general, the wetting time generally decreases with an increased MCC content. However, When the MCC content exceeded 90%, the wetting time showed a reverse tendency. This suggested that the inner structure of these tablets underwent some change at a high MCC concentration Moqbel *et al.* [10].

Formulae containing mannitol and sorbitol contain axial (mannitol) and equatorial (sorbitol) OH groups on C-2 atoms that allow hydrogen bonding upon hydration which decreases the DT. The absence of sorbitol and the presence of MCC, which decreased the water uptake leading to the increase of DT. The presence of (2-9%) relatively water-insoluble dibasic calcium phosphate contributed to the high DT.

The increase of drug release from ODTs is due to the presence of Pharmaburst 500 contains extra sorbitol; these hydrophilic substances aid in wetting, solubilization. The hydrophilicity of the drug particles facilitated their dispersion upon contact with the dissolution medium which is similar to the findings results acquired by Moqbel HA *et al.*2017 in their study on chlorzoxazone ODTs [10].

After comparing different excipients, results showed that formulas with MCC in their composition reported different results according to type of drug used, particles size variation, drug: excipients ratio or the applied pressure of compression and the type of drug that we are dealing with.

The values of Levetiracetam plasma mean residence time (MRT) indicate that the molecules of the drug in the ODT formula are not suffering from first-pass metabolism, so they stay in the body more than the commercial solution resulting in a higher effect. It is clear that the optimized formula represented a significant improvement over the commercial solution in the extent of absorption as exhibited by Cmax and AUC values ($p < 0.05$); the optimized formula showed a high absorption rate but non statistically significant ($p>0.05$).

CONCLUSION

In this study, ODTs of LVT were successfully made utilizing co-processed excipients by the direct compression method. The selected formula (F5), which contains 150 mg LVT and 100 mg pharmaburst®, demonstrated the best *in vitro* evaluation results among other circumstances for meeting the required quality as mentioned in the pharmacopeia. It showed the highest dissolution value, acceptable disintegration time, and suitable hardness. The *in vivo* study showed that the Cmax of F5 ODT was significantly higher than the commercial oral solution. Overall, Levetiracetam was the drug of choice in epilepsy as it has a high safety profile and is used widely in children and adults. So, ODT is considered a preferred dosage form with increased patient compliance; this dosage form increases patient satisfaction as it has a rapid effect, is easily administrated without water and avoiding first-pass metabolism.

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Nil

AUTHORS CONTRIBUTIONS

The article comprises original, unpublished material that is not published elsewhere, in any language, and is not under consideration for publication elsewhere. All authors have read and approved the text and consent to its publication.

CONFLICT OF INTERESTS

Authors declared no conflict of interests.

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