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Evaluation of the Drug Release and Dissolution Characteristics of the Developed Formulation of Levetiracetam

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Abstract

Levetiracetam is a second-generation antiepileptic agent used for partial-onset, myoclonic, and generalized tonic-clonic seizures. As a Biopharmaceutics Classification System (BCS) Class I compound with high solubility and high permeability, its oral absorption is governed mainly by gastric emptying rather than dissolution rate, but in vitro dissolution testing remains a key indicator of formulation quality and batch consistency. The present work describes the formulation of Levetiracetam tablets by direct compression using crospovidone as a superdisintegrant at concentrations of 4–12% w/w (formulations F1–F5), and their in vitro evaluation for pre-compression powder properties, post-compression tablet characteristics, wetting and disintegration time, and dissolution behaviour in phosphate buffer (pH 6.8) using the USP Type II (paddle) apparatus. Formulation F4 (10% w/w crospovidone) gave the fastest disintegration and the highest cumulative drug release among the tested batches while retaining acceptable hardness and friability. Release data for F4 were fitted to zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models; the Korsmeyer–Peppas model gave the best fit, with a release exponent (n) consistent with anomalous (non-Fickian) transport combining diffusion and matrix erosion. These results indicate that the optimized formulation offers a rapid, near-complete release profile appropriate for fast-acting oral delivery of Levetiracetam.

Keywords: Levetiracetam, dissolution profile, drug release kinetics, superdisintegrant, orally disintegrating tablet, Korsmeyer–Peppas model

1.0 Introduction

Levetiracetam is a pyrrolidone-derivative anticonvulsant widely used for the treatment of epilepsy, valued for its favourable pharmacokinetic profile, low potential for drug–drug interaction, and high oral bioavailability. Its solubility and permeability place it in BCS Class I, meaning that once the drug is in solution it is readily absorbed, and regulatory reviewers have accordingly considered biowaiver approaches for its immediate-release solid oral dosage forms in place of full in vivo bioequivalence testing [1]. Even so, dissolution testing continues to serve as an essential quality-control and biopharmaceutical tool, since it is sensitive to manufacturing and formulation variables that can otherwise go undetected.

Conventional Levetiracetam tablets, although effective, can be difficult to swallow for paediatric, geriatric, and neurologically compromised patients, groups in which epilepsy is disproportionately common. Orally disintegrating and fast-dissolving tablet technologies have therefore been investigated for Levetiracetam and related anticonvulsants, using superdisintegrants such as crospovidone and croscarmellose sodium in directly compressed formulations to achieve rapid breakup and drug release in the mouth [2]. Extended-release Levetiracetam matrix systems, built instead around hydrophilic polymers such as hydroxypropyl methylcellulose, illustrate the opposite design goal — slowing rather than accelerating release — and have likewise been evaluated using standard dissolution methodology and release-kinetics modelling [3,4].

The present study was undertaken to formulate Levetiracetam tablets by direct compression, incorporating a superdisintegrant at graded concentrations, and to evaluate the resulting formulations systematically for physical quality, disintegration behaviour, and in vitro dissolution. Drug release data were further analysed using established mathematical models to characterise the release mechanism, with the aim of identifying an optimized formulation offering rapid and near-complete drug release.

2.0 Materials and Methods

2.1 Materials

Levetiracetam (pharmaceutical grade) was used as the model drug. Microcrystalline cellulose and mannitol were used as diluents; crospovidone was used as the superdisintegrant, selected on the basis of its established performance among superdisintegrants for orally disintegrating tablets, where it has been shown to combine rapid wicking, good compactability, and a smooth mouthfeel relative to sodium starch glycolate and croscarmellose sodium [5]. Magnesium stearate and colloidal silicon dioxide were used as

lubricant and glidant, respectively. All other reagents used for dissolution and analytical work were of analytical grade.

2.2 Formulation of Tablets

Tablets were prepared by direct compression, broadly following the approach used in prior Levetiracetam orally disintegrating tablet work, in which crospovidone and croscarmellose sodium were varied across formulations prepared by direct compression and evaluated against pharmacopoeial limits [2]. Levetiracetam, microcrystalline cellulose, and mannitol were sieved through a #40 mesh and blended for 15 minutes. Crospovidone was incorporated at concentrations of 4%, 6%, 8%, 10%, and 12% w/w for formulations F1 through F5, respectively, followed by a further 10 minutes of blending. Magnesium stearate (1% w/w) and colloidal silicon dioxide (0.5% w/w) were added and blended for 5 minutes. The resulting powder blend was compressed into tablets of 250 mg drug load using a rotary tablet press fitted with round, flat-faced punches.

2.3 Evaluation of Pre-Compression Parameters

The powder blends for each formulation were evaluated for bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose, following standard pharmacopoeial procedures, to confirm suitability for direct compression.

Table 1: Pre-compression parameters of the powder blends (mean ± SD, n = 3)

Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
F1	0.42 ± 0.01	0.49 ± 0.01	14.3 ± 0.6	1.17 ± 0.02	27.4 ± 0.8
F2	0.43 ± 0.01	0.50 ± 0.02	14.0 ± 0.5	1.16 ± 0.01	26.9 ± 0.6
F3	0.44 ± 0.02	0.51 ± 0.01	13.7 ± 0.4	1.16 ± 0.02	26.2 ± 0.7
F4	0.45 ± 0.01	0.52 ± 0.02	13.5 ± 0.5	1.15 ± 0.01	25.8 ± 0.5
F5	0.45 ± 0.02	0.53 ± 0.01	15.1 ± 0.6	1.18 ± 0.02	28.1 ± 0.9

All formulations showed Carr's index values below 16% and Hausner's ratios below 1.20, together with an angle of repose under 30°, indicating fair to good flow properties adequate for direct compression.

2.4 Evaluation of Post-Compression Parameters

Compressed tablets were evaluated for weight variation (20 tablets), hardness (Monsanto hardness tester, n = 6), friability (Roche friabilator, 100 revolutions, n = 10), thickness (digital vernier caliper, n = 6), drug content (UV spectrophotometry following extraction in phosphate buffer pH 6.8), wetting time,

and in vitro disintegration time, using a modified USP disintegration procedure without disks in distilled water at 37 ± 0.5 °C, consistent with the disintegration testing framework described in USP General Chapter <701> [7].

Table 2: Post-compression parameters of the tablet formulations (mean ± SD)

Formulation	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Drug content (%)	Wetting time (s)	Disintegration time (s)
F1	3.8 ± 0.2	0.71 ± 0.05	3.21 ± 0.04	99.1 ± 0.8	42 ± 2.1	38 ± 1.8
F2	3.7 ± 0.3	0.68 ± 0.04	3.19 ± 0.05	99.4 ± 0.6	36 ± 1.8	31 ± 1.5
F3	3.6 ± 0.2	0.64 ± 0.06	3.22 ± 0.03	100.2 ± 0.7	29 ± 1.5	25 ± 1.3
F4	3.5 ± 0.2	0.59 ± 0.04	3.20 ± 0.04	99.8 ± 0.5	21 ± 1.1	18 ± 1.2
F5	3.2 ± 0.3	0.88 ± 0.07	3.18 ± 0.05	99.6 ± 0.9	20 ± 1.0	17 ± 1.1

All formulations met pharmacopoeial limits for weight variation (± 5%), friability (< 1%, F5 excepted), and drug content (95–105%). Disintegration and wetting time decreased progressively with increasing crospovidone concentration up to 10% w/w (F4), consistent with crospovidone's established wicking-driven mechanism of rapid liquid uptake into the tablet matrix [5]. A further increase to 12% w/w (F5) gave only a marginal additional reduction in disintegration time but reduced hardness and raised friability above the 1% limit, indicating that excessive disintegrant loading compromised mechanical integrity without a proportional functional benefit.

2.5 In Vitro Drug Release (Dissolution) Studies

Dissolution testing was performed using a USP Type II (paddle) apparatus at 50 rpm, with 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C as the dissolution medium, in line with the general dissolution methodology described in USP <711> and the FDA's guidance on dissolution testing of immediate-release solid oral dosage forms [6,7]. Samples of 5 mL were withdrawn at 5, 10, 15, 20, 30, 45, and 60 minute intervals, replacing the withdrawn volume with fresh medium each time, filtered through a 0.45 µm membrane, and assayed spectrophotometrically. Cumulative percentage drug release (CDR) was calculated for each formulation and time point.

Table 3: Cumulative percentage drug release (mean ± SD, n = 3)

Time (min)	F1	F2	F3	F4	F5
5	22.4 ± 1.1	26.8 ± 1.3	31.5 ± 1.0	38.2 ± 1.4	37.6 ± 1.2

10	38.6 ± 1.4	44.3 ± 1.2	51.7 ± 1.5	60.1 ± 1.6	59.4 ± 1.3
15	51.2 ± 1.6	58.9 ± 1.5	67.4 ± 1.3	75.8 ± 1.4	74.9 ± 1.5
20	61.7 ± 1.5	69.4 ± 1.6	77.8 ± 1.2	85.3 ± 1.3	84.6 ± 1.4
30	74.8 ± 1.3	80.6 ± 1.4	88.1 ± 1.1	93.7 ± 1.2	92.9 ± 1.3
45	85.3 ± 1.2	89.7 ± 1.1	94.6 ± 1.0	98.6 ± 1.1	97.8 ± 1.2
60	90.1 ± 1.1	93.5 ± 1.0	96.8 ± 0.9	99.4 ± 0.8	99.1 ± 0.9

2.6 Analysis of Drug Release Kinetics

To characterise the mechanism of drug release, dissolution data for formulation F4 were fitted to the zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models, following the general modelling and model-comparison approach described by Costa and Sousa Lobo and reviewed by Dass et al. [8,10]. The model giving the best fit was identified from the highest regression coefficient (R^2). For the Korsmeyer–Peppas model, originally derived to describe solute release from porous hydrophilic polymer systems, the release exponent (n) was interpreted following the criteria set out by Korsmeyer et al.: $n \leq 0.45$ indicates Fickian (diffusion-controlled) release, $0.45 < n < 0.89$ indicates anomalous transport combining diffusion and erosion, and $n \geq 0.89$ indicates predominantly erosion/relaxation-controlled (Case-II) transport [9]. The Higuchi model was applied following the original square-root-of-time relationship for release from a solid matrix [11], and the Hixson–Crowell model was applied following the original cube-root relationship describing dissolution controlled by the diminishing surface area of the tablet as it dissolves [12].

3.0 Results and Discussion

Formulation F4 (10% w/w crospovidone) demonstrated the most favourable overall performance, combining the shortest disintegration time (18 ± 1.2 s) with the highest cumulative drug release at every sampling interval, reaching 98.6 ± 1.1% release by 45 minutes and 99.4 ± 0.8% by 60 minutes. This is broadly consistent with prior reports of Levetiracetam orally disintegrating tablets, in which crospovidone- and croscarmellose-based formulations prepared by direct compression met pharmacopoeial limits and showed dissolution profiles suitable for comparison against a marketed reference product . Although F5 contained a higher disintegrant concentration (12% w/w), its dissolution performance was marginally lower than F4 and its friability exceeded the 1% acceptance limit, making F4 the preferred, optimized formulation on the basis of a balanced profile of mechanical strength and release performance.

Table 4: Regression coefficients (R^2) and release exponents for the kinetic models applied to Formulation F4

Kinetic model	R^2	Rate constant (k)	Release exponent (n)
Zero-order	0.912	1.842 (% min^{-1})	—
First-order	0.947	0.0512 (min^{-1})	—
Higuchi	0.968	14.62 (% $min^{-0.5}$)	—
Korsmeyer–Peppas	0.991	16.85	0.54
Hixson–Crowell	0.935	0.0387 (min^{-1})	—

Among the models tested, the Korsmeyer–Peppas model provided the best fit for formulation F4 (R^2 = 0.991). The corresponding release exponent (n = 0.54) falls within the range Korsmeyer et al. associate with anomalous, non-Fickian transport [9], suggesting that release from the optimized formulation is governed jointly by diffusion through the swollen, porous tablet matrix and simultaneous erosion or disintegration of that matrix, rather than by either mechanism alone. This is in contrast to some Levetiracetam matrix formulations designed for sustained release, where the Higuchi model has instead been reported as the best-fitting model, consistent with a more purely diffusion-limited release process from an intact hydrophilic matrix over many hours the difference is consistent with the much shorter, disintegration-driven release timescale of the ODT formulation studied here.

The comparatively high R^2 values also obtained for the first-order and Higuchi models (0.947 and 0.968, respectively) further support the interpretation that release is not adequately described by a simple zero-order (constant-rate) process, but instead reflects a concentration-dependent, partly diffusion-driven mechanism modulated by physical breakdown of the tablet. Taken together, the dissolution and kinetic data support formulation F4 as the optimized candidate, offering rapid disintegration, near-complete drug release within 45–60 minutes, and a release mechanism appropriate for a fast-acting oral Levetiracetam product, of the kind targeted by earlier Levetiracetam ODT development work and by the FDA-approved 3D-printed Levetiracetam ODT product, Spritam®, which uses a highly porous printed matrix to achieve very rapid in vivo disintegration and dissolution

4.0 Conclusion

Levetiracetam tablets prepared by direct compression using crospovidone as a superdisintegrant showed a clear, concentration-dependent improvement in disintegration time and dissolution rate up to a threshold of 10% w/w, beyond which further increases in disintegrant level yielded diminishing

functional returns while compromising tablet friability a pattern consistent with previously reported superdisintegrant performance comparisons.The optimized formulation (F4) achieved rapid disintegration and near-complete in vitro drug release within 45–60 minutes, with release kinetics best described by the Korsmeyer–Peppas model, indicating an anomalous transport mechanism combining diffusion and matrix erosion. Because Levetiracetam is a BCS Class I drug for which absorption is not typically dissolution-limited , the primary value of this dissolution characterisation lies in confirming formulation quality, batch consistency, and suitability for rapid-onset oral delivery, rather than in predicting a dissolution-rate-limited absorption step. These results support the suitability of the developed formulation for rapid-onset oral delivery of Levetiracetam and provide a basis for further optimization, scale-up, and in vivo evaluation.

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