

# FORMULATION AND EVALUATION OF A DUAL MULTIPARTICULATE DRUG DELIVERY SYSTEM CONTAINING FLOATING LEVOSULPIRIDE MINI-TABLETS AND ENTERIC-COATED EPLERENONE PELLETS

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## ABSTRACT

**Background:** Conventional immediate-release oral medication formulations of substances that are absorbed largely from the upper gastrointestinal tract, or that require protection from stomach fluid, generally exhibit variable bioavailability and require frequent dosing. The objective of the present work was to design a dual multiparticulate capsule containing a gastroretentive floating multiparticulate of levosulpiride, a prokinetic used in functional dyspepsia and gastroesophageal reflux disease, and a site-specific enteric-coated multiparticulate of eplerenone, a selective aldosterone-receptor antagonist used in hypertension and heart failure. The purpose was to co-administer two pharmacologically unrelated but commonly co-prescribed drugs in a single dosage form with independent release profiles optimized. **Methods:** Preformulation studies (solubility, melting point, UV spectrophotometry, FTIR compatibility) of both medicines were carried out. Floating levosulpiride mini-tablets (F1–F9) were made by direct compression with HPMC K100M and Carbopol 974P as release-

*retarding/gel-forming matrix and sodium bicarbonate–citric acid as effervescent floating system. The eplerenone core pellets (P1–P6) were prepared by extrusion–spheronization with microcrystalline cellulose and sodium alginate/HPMC E5 and enteric-coated with Eudragit L100 by fluidized-bed (Wurster) coating. The formulations were analyzed for micromeritic, mechanical, floating, swelling and dissolution behavior; the optimized units were filled in to hard gelatin capsules and evaluated for combined release and 3 months accelerated/long-term stability (ICH Q1A(R2)).* **Results:** *F9 (max polymer/gas-generant load) had the least floating lag time (25 s), floated >12 h, and continuous levosulpiride release (97.02% at 12 h; Higuchi-dominant, Korsmeyer–Peppas  $n \sim 1.0$ , indicating diffusion with polymer relaxation). The pellet formulation P6 (10% w/w coating weight gain, maximum sphericity 0.96) exhibited the lowest acid-stage release (4.18% in 2 h) and 97.52% eplerenone release at 12 h following transfer to pH 6.8 buffer (first-order dominating,  $n \approx 0.58$ ). The F9+P6 capsule combination was able to recreate the two release profiles without mutual interference and was within pharmacopeial limits after 3 months at 25 °C/60% RH and 40 °C/75% RH.* **Conclusion:** *A dual multiparticulate platform with floating and enteric-coated units in one capsule, providing a single, stable, reproducible oral dose form with two medicines with different gastrointestinal release requirements, can be achieved.*

**Keywords:** *Gastroretentive drug delivery Floating mini-tablets Enteric coated pellets Multiparticulate system Extrusion-spheronization Levosulpiride Eplerenone Korsmeyer-Peppas kinetics*

## 1. INTRODUCTION

The oral route is the most popular and most acknowledged form of systemic drugs administration due to ease of administration, non-invasive nature, inexpensive manufacturing and high patient acceptance <sup>[1,2,3]</sup>. But the contents of traditional immediate-release tablets and capsules are released rapidly and non-selectively throughout the gastrointestinal (GI) tract, which does not match up well with two well-known classes of drugs: those that are preferentially absorbed from the stomach and proximal small intestine, and those that are unstable, poorly tolerated, or better targeted to the intestine than to the stomach <sup>[4,5,6,7]</sup>. In the first type, quick stomach emptying reduces the time window for absorption and requires frequent doses. In the second, premature gastric exposure may affect drug stability, local tolerability or the desired site-specificity of

action. To overcome these mismatches between physicochemical/biopharmaceutical drug qualities and simple instantaneous release [8, 9, 10, 11, 12, 13, 14], modified-release technologies – sustained, controlled, delayed and targeted-release systems – were created.

The floating (buoyant) pharmaceutical delivery systems are one of the most suitable gastroretentive approaches for drugs with a narrow absorption window in the stomach and upper small intestine, since the bulk density of the dosage form is lower than that of the gastric fluid, allowing the dosage form to remain buoyant and to resist rapid gastric emptying, thus prolonging the time available for dissolution and absorption [15,16,17,18]. Effervescent floating systems have been studied most extensively. In this case, a gas-forming pair (usually sodium bicarbonate and an organic acid) reacts with gastric fluid, and the released CO<sub>2</sub> is trapped in a swelling polymer gel. The onset and duration of floating can be adjusted by means of the polymer and gas-generant load [19,20].

However, single-unit floating tablets are exposed to an all or none gastric emptying and a higher risk of dose dumping. Multiparticulate floating systems such as pellets, beads, microspheres or mini-tablets disperse the dose over a large number of small units which empty more slowly and reproducibly, minimize local irritation and are less sensitive to the variability of the pattern of gastric emptying [21,22,23,24]. Mini-tablets combine manufacturing robustness and dose-uniformity of conventional compression with biopharmaceutical advantages of multiparticulate system and are increasingly used in situations where numerous mini-units are integrated into a single capsule shell [25,26].

To achieve the opposite goal of gastric retention, i.e. to protect a drug from stomach fluid and to route its release to the small intestine, a complementary formulation technique is needed. The standard approach is enteric coating with pH dependent polymers such as Eudragit L100, hydroxypropyl methylcellulose phthalate or cellulose acetate phthalate and pellets produced by extrusion–spheronization are a particularly suitable core for such coating because their narrow size distribution, high sphericity and smooth surface promote a thin, uniform, mechanically robust film and consequently a reproducible lag time before release [27,28,29,30,31,32,33,34].

Levosulpiride is the levo-enantiomer of sulpiride, a selective dopamine D<sub>2</sub>-receptor antagonist with prokinetic activity utilized in functional dyspepsia, gastroesophageal reflux disease, diabetic gastroparesis and associated motility disorders [35,36]. It is absorbed mainly in the stomach and upper small intestine and has a relatively short elimination half-life (about 6-8 h), which usually

requires multiple daily doses. These features make it a rational candidate for a gastroretentive floating system to prolong gastric residence and sustain release over a prolonged period. Conversely, eplerenone is a selective mineralocorticoid (aldosterone) receptor antagonist indicated for the treatment of hypertension and heart failure following myocardial infarction, to minimize sodium and water retention and to mitigate the pro-fibrotic cardiovascular effects of aldosterone <sup>[37]</sup>. It is a BCS class II compound with very low aqueous solubility and extensive first pass metabolism via CYP3A4, so formulation approaches that avoid premature gastric release and promote controlled, site-specific liberation in the intestine are a reasonable strategy for improving the consistency of its release from a solid oral dosage form.

There is also a physiological basis for the combination of these two medications. Upper-GI motility disturbance (early satiety, bloating, nausea and delayed gastric emptying) is a known feature of chronic heart failure, partly due to splanchnic venous congestion, reduced gut perfusion and intestinal wall edema <sup>[38]</sup>; patients on cardiovascular therapy such as aldosterone-receptor antagonists also frequently require prokinetic management of coexisting upper-GI symptoms. Therefore, the single dosage form that can provide the sustained gastric-phase release of a prokinetic and the protected intestine-targeted release of a cardiovascular agent is a plausible platform-level proof of concept for reducing the pill burden in such patients regardless of any specific fixed-dose regulatory claim.

Building on this rationale, the present study set out to (i) develop and optimize floating levosulpiride mini-tablets by direct compression using an HPMC K100M/Carbopol 974P hydrophilic matrix and a sodium bicarbonate–citric acid effervescent couple; (ii) develop and optimize eplerenone core pellets by extrusion–spheronization and apply a Eudragit L100 enteric coat by fluidized-bed coating; (iii) combine the optimized units into a single hard gelatin capsule to obtain a dual multiparticulate system; and (iv) characterize the physicochemical, floating, dissolution, and release-kinetic behaviour of the individual and combined systems, together with their short-term stability under ICH-type long-term and accelerated storage conditions.

## **2. MATERIAL AND METHODS**

### **2.1. Materials**

Levosulpiride and eplerenone were gift samples and used as received. The mini-tablet formulations were composed of HPMC K100M, Carbopol 974P, sodium bicarbonate, anhydrous

citric acid, lactose DCL 21, low-substituted hydroxypropyl cellulose (L-HPC LH11), colloidal anhydrous silica and magnesium stearate. The pellet preparation was done using microcrystalline cellulose PH 101, sodium alginate, HPMC E5, lactose monohydrate and polyvinylpyrrolidone K30 (PVP K30). The enteric coating was done using Eudragit L100, polyethylene glycol 400 (plasticizer), talc, isopropyl alcohol and acetone (coating solvents). All chemicals were of analytical / pharmacopeial grade.

## **2.2. Pre-formulation Studies**

Organoleptic features (colour, odor, appearance) of both medicines were observed visually. Solubility was qualitatively determined (24 h, room temperature, intermittent mechanical shaking) in distilled water, methanol, ethanol, 0.1 N HCl and phosphate buffers pH 6.8 and 7.4. Melting points were determined using the capillary technique in triplicate. The maximum value was determined by UV spectrophotometric scanning (200-400 nm) of solutions in an appropriate solvent and calibration curves were plotted over 10-60 µg/mL (levosulpiride) and 5-30 µg/mL (eplerenone) by linear regression of absorbance on concentration. The drug-excipient compatibility was evaluated by FTIR (KBr pellet) on the pure pharmaceuticals and on 1:1 (w/w) physical mixes with the major formulation excipients, by comparing the position of characteristic bands before and after mixing.

## **2.3. Preparation of levosulpiride floating mini-tablets**

Nine formulations (F1-F9; Table 1) containing 25 mg of levosulpiride per unit were prepared by direct compression method by varying HPMC K100M (10-25 mg), Carbopol 974P (0-10 mg), sodium bicarbonate (8-12 mg) and citric acid anhydrous (2-3 mg) against a lactose DCL 21 diluent. L-HPC LH11, colloidal silica and magnesium stearate were kept constant. Drug and polymers were mixed, effervescent couple was introduced carefully avoiding moisture, lactose and L-HPC were combined and finally colloidal silica/magnesium stearate were incorporated as glidant/lubricant (2–3 min mixing). Powder mixtures were tableted on a rotary tablet press using 6.00 mm flat upper-scored circular punches to a target unit weight of 80 mg.

**Table 1. Quantitative composition of the floating levosulpiride mini-tablet formulations F1–F9 (mg/ unit).**

| <b>Ingredient<br/>(mg/unit)</b> | <b>F1</b>    | <b>F2</b>    | <b>F3</b>    | <b>F4</b>    | <b>F5</b>    | <b>F6</b>    | <b>F7</b>    | <b>F8</b>    | <b>F9</b>    |
|---------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Levosulpiride                   | 25.00        | 25.00        | 25.00        | 25.00        | 25.00        | 25.00        | 25.00        | 25.00        | 25.00        |
| HPMC K100M                      | 15.00        | 20.00        | 25.00        | 15.00        | 20.00        | 25.00        | 10.00        | 15.00        | 20.00        |
| Carbopol 974P                   | 0.00         | 0.00         | 0.00         | 5.00         | 5.00         | 5.00         | 10.00        | 10.00        | 10.00        |
| Sodium bicarbonate              | 8.00         | 8.00         | 8.00         | 10.00        | 10.00        | 10.00        | 12.00        | 12.00        | 12.00        |
| Citric acid<br>anhydrous        | 2.00         | 2.00         | 2.00         | 2.00         | 2.00         | 2.00         | 3.00         | 3.00         | 3.00         |
| Lactose DCL 21                  | 26.00        | 21.00        | 16.00        | 19.00        | 14.00        | 9.00         | 15.00        | 10.00        | 5.00         |
| L-HPC LH11                      | 2.00         | 2.00         | 2.00         | 2.00         | 2.00         | 2.00         | 2.00         | 2.00         | 2.00         |
| Colloidal anhydrous<br>silica   | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         |
| Magnesium stearate              | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         | 1.00         |
| <b>Total weight (mg)</b>        | <b>80.00</b> | <b>80.00</b> | <b>80.00</b> | <b>80.00</b> | <b>80.00</b> | <b>80.00</b> | <b>80.00</b> | <b>80.00</b> | <b>80.00</b> |

#### 2.4. Floating mini-tablets evaluation

Pre-compression blends were assessed for angle of repose (fixed-funnel method), bulk density, tapped density, Carr's index and Hausner ratio. Compressed mini-tablets (n=20 for weight variation, n=10 for other tests unless mentioned otherwise) were evaluated for weight variation, thickness, hardness (Monsanto-type tester), friability (100 revolutions, Roche friabilator) and drug content (10 tablets triturated, extracted and assayed by UV spectrophotometry). The floating lag time (FLT, time to emerge at the surface of the medium) and total floating time (TFT) were determined visually in 900 mL of 0.1 N HCl at  $37 \pm 0.5$  °C. Swelling index was evaluated gravimetrically in 0.1 N HCl at 1, 2, 4, 6 and 8 h as percentage weight rise compared to the original weight of tablets. In vitro release was carried out in 900 mL 0.1 N HCl,  $37 \pm 0.5$  °C, 50–75 rpm, samples of 5 mL were taken at 1, 2, 4, 6, 8, 10 and 12 h and replaced with new medium, cumulative release was estimated from the calibration curve and analysis was performed in triplicate (mean  $\pm$  SD). Release data of the optimized formulation were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models by linear regression; for the Korsmeyer–Peppas model, the exponent n was estimated from data points corresponding to  $\leq 60\%$  cumulative release as per the conventional restriction of this model to the early release phase.

## 2.5. Preparation of eplerenone core pellets by extrusion-spheronization

Six formulations (P1–P6; Table 2) containing 25 mg eplerenone per unit dose were prepared using microcrystalline cellulose PH 101 as a spheronization aid and sodium alginate (P1–P3) or HPMC E5 (P4–P6) as a pellet-forming polymer, with lactose monohydrate as a diluent and PVP K30 (dissolved in purified water) as a binder. The dry mix was blended with the binder solution to a cohesive, non-sticky plastic consistency and extruded through a die of 0.5–1 mm, spheronized (800–1200 rpm, 5–10 min), dried on trays at 40–50 °C, sieved to a size fraction of 0.5–1.5 mm and lubricated with talc and magnesium stearate.

## 2.6. Enteric coating in fluidized bed

Core pellets were coated with Eudragit L100 (8, 10 or 12% w/v in isopropyl alcohol : acetone) plasticized with PEG 400 (10 or 15% w/w of polymer) and talc (5% w/w of polymer) as anti-tack agent using bottom-spray fluidized-bed coater (inlet air 40–50 °C, controlled atomization pressure and spray rate) to target weight gains of 5%, 7.5% or 10% w/w (Table 2). Further drying was carried out to eliminate residual solvent, followed by cooling and storage in airtight containers.

**Table 2. Composition of core eplerenone pellets (extrusion-spheronization) and enteric coating parameters (fluidized-bed coating). P1–P6.**

| <b>Ingredient</b>                         | <b>P1</b> | <b>P2</b> | <b>P3</b> | <b>P4</b> | <b>P5</b> | <b>P6</b> |
|-------------------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Eplerenone (mg)                           | 25.00     | 25.00     | 25.00     | 25.00     | 25.00     | 25.00     |
| MCC PH 101 (mg)                           | 45.00     | 42.00     | 39.00     | 45.00     | 42.00     | 39.00     |
| Sodium alginate (mg)                      | 2.00      | 4.00      | 6.00      | -         | -         | -         |
| HPMC E5 (mg)                              | -         | -         | -         | 2.00      | 4.00      | 6.00      |
| Lactose monohydrate (mg)                  | 20.00     | 21.00     | 22.00     | 20.00     | 21.00     | 22.00     |
| PVP K30 (mg)                              | 6.00      | 6.00      | 6.00      | 6.00      | 6.00      | 6.00      |
| Talc (mg)                                 | 1.00      | 1.00      | 1.00      | 1.00      | 1.00      | 1.00      |
| Magnesium stearate (mg)                   | 1.00      | 1.00      | 1.00      | 1.00      | 1.00      | 1.00      |
| Purified water                            | q.s.      | q.s.      | q.s.      | q.s.      | q.s.      | q.s.      |
| <b>Enteric coating parameters</b>         |           |           |           |           |           |           |
| Eudragit L100 (% w/v of coating solution) | 8         | 10        | 12        | 8         | 10        | 12        |
| PEG 400 (% w/w of polymer)                | 10        | 10        | 10        | 15        | 15        | 15        |
| Talc (% w/w of polymer)                   | 5         | 5         | 5         | 5         | 5         | 5         |

## 2.7. Evaluation of core and enteric coated pellets

The core pellets were characterized in terms of size distribution (sieve analysis in the range of 0.5–1.5 mm), sphericity (image analysis of the pellet outline, as the ratio between minimum and maximum Feret diameter, 1.0 indicating a perfect sphere), friability (drum friabilator, percentage weight loss), drug content and in vitro release of the uncoated core (USP Apparatus I, basket, 900 mL 0.1 N HCl,  $37 \pm 0.5$  °C). Acid resistance of the enteric-coated pellets was determined according to USP (Apparatus I, 900 mL 0.1 N HCl,  $37 \pm 0.5$  °C, 50 rpm, 2 h, visual inspection for cracking, softening or disintegration). In vitro dissolution was carried out in two stages (2 h in 0.1 N HCl followed by transfer to phosphate buffer pH 6.8,  $37 \pm 0.5$  °C, 50–100 rpm, sampled to 12 h). The buffer-stage data, relative to the transfer time ( $\tau = t - 2$  h), were fitted to zero-order, first-order, Higuchi and Korsmeyer-Peppas models for the optimized coated pellet, because kinetic modeling of a lag-time containing delayed-release profile is only meaningful once the enteric barrier has dissolved and release has effectively begun. The Korsmeyer-Peppas exponent was estimated from the first three post-transfer time points ( $\tau = 1$ –4 h, cumulative release  $\leq 71\%$ ), which extends marginally beyond the conventional 60% cut-off due to the limited number of sampling points available below that threshold for this rapidly-releasing system.

## 2.8. Development and assessment of the dual multiparticulate system

The optimized floating mini-tablets and optimized enteric-coated pellets were put together into size appropriate hard gelatin capsules in a predetermined ratio corresponding to one unit dose of each drug. The filled capsules were visually inspected for appearance, fill uniformity, capsule/pellet/tablet integrity and then tested for combined in vitro release by the same two-stage protocol as described in Section 2.7 (0.1 N HCl for 2 h, then phosphate buffer pH 6.8) with samples analyzed for levosulpiride and eplerenone at their respective  $\lambda_{\max}$ .

## 2.9. Stability testing

The improved dual multiparticulate formulation was packaged and kept under long-term ( $25 \pm 2$  °C/ $60 \pm 5\%$  RH) and accelerated ( $40 \pm 2$  °C/ $75 \pm 5\%$  RH) conditions according to ICH Q1A(R2). The physical appearance, drug content (both drugs), floating behavior (FLT, TFT), acid resistance and in vitro release were evaluated for samples taken at 0, 1, 2 and 3 months.

## 2.10. Statistical processing

All evaluations were completed in triplicate except where noted and results are expressed as mean  $\pm$  standard deviation (SD). The regression parameters (slope, intercept and coefficient of

determination, R<sup>2</sup>) for the calibration and kinetic models were determined via least-squares linear regression.

### 3. RESULTS AND DISCUSSION

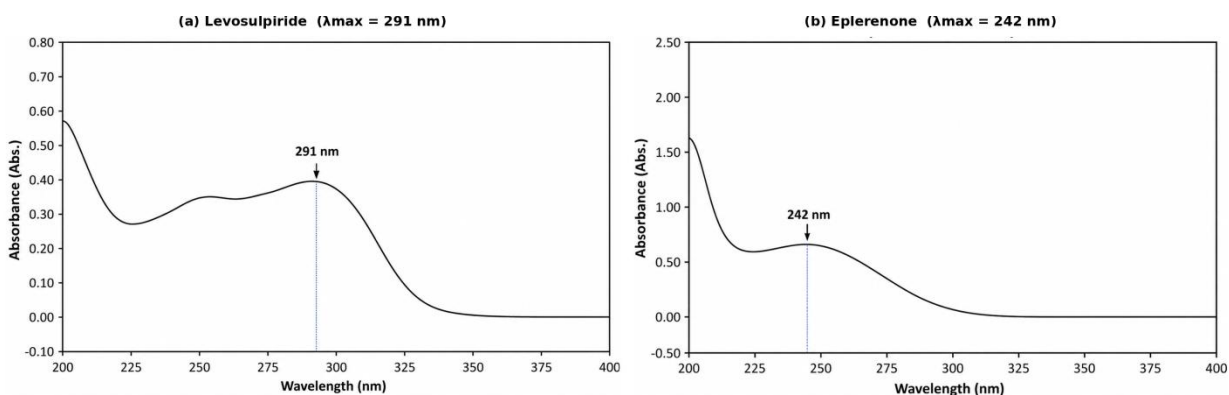
#### 3.1. Pre-formulation studies

The two medicines were obtained as odorless crystalline powders, white to off-white for levosulpiride and white to light yellow for eplerenone, in agreement with the description of the pharmacopeia and demonstrating the absence of significant degradation (Table 3). Levosulpiride showed limited solubility in water but high solubility in methanol and solubility in 0.1 N HCl which is consistent with the preferred dissolution and absorption in the acidic environment of the stomach and supports the adoption of a gastroretentive floating strategy. Eplerenone was essentially insoluble in water and sparingly soluble in aqueous buffers consistent with its known BCS class II character and offering a formulation rationale for pelletization and enteric coated delayed release instead of immediate gastric dissolving. The melting ranges (levosulpiride 178–182 °C; eplerenone 228–235 °C) were in agreement with published values, confirming the identity and purity of the drugs.

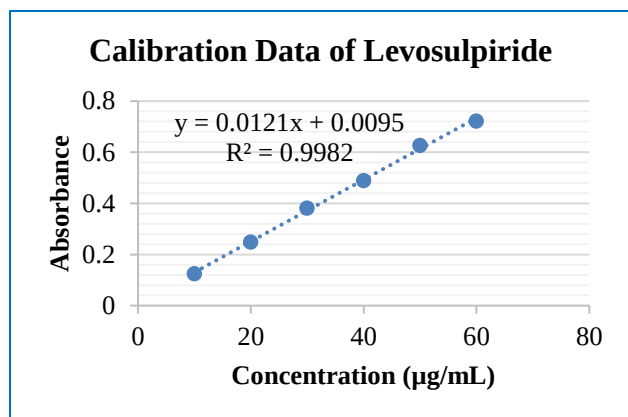
The  $\lambda_{\text{max}}$  of UV scan was found to be 291 nm for levosulpiride and 242 nm for eplerenone (Figure 1), and calibration plots were found to be linear in the investigated range at these wavelengths: absorbance =  $y = 0.012x + 0.009$ ,  $R^2 = 0.998$  for levosulpiride; absorbance  $y = 0.016x + 0.004$ ,  $R^2 = 0.999$  for eplerenone (Figure 2, Table 3). Hence, both approaches were adequate for quantitative estimation in the subsequent formulation and dissolving investigations [39,40,41,42].

**Table 3. Preformulation studies of levosulpiride and eplerenone.**

| Parameter                              | Levosulpiride                         | Eplerenone                               |
|----------------------------------------|---------------------------------------|------------------------------------------|
| Colour                                 | White to off-white                    | White to pale yellow                     |
| Odour                                  | Odourless                             | Odourless                                |
| Appearance / nature                    | Crystalline powder, non-hygroscopic   | Crystalline powder, slightly hygroscopic |
| Solubility – distilled water           | Sparingly soluble                     | Practically insoluble                    |
| Solubility – methanol                  | Freely soluble                        | Soluble                                  |
| Solubility – ethanol                   | Soluble                               | Slightly soluble                         |
| Solubility – 0.1 N HCl (pH 1.2)        | Soluble                               | Very slightly soluble                    |
| Solubility – phosphate buffer pH 6.8   | Moderately soluble                    | Slightly soluble                         |
| Solubility – phosphate buffer pH 7.4   | Moderately soluble                    | Slightly soluble                         |
| Melting point, observed (°C)           | 178–182                               | 228–235                                  |
| Melting point, reported (°C)           | 180                                   | 233                                      |
| $\lambda_{\text{max}}$ (nm)            | 291                                   | 242                                      |
| Calibration range ( $\mu\text{g/mL}$ ) | 10–60                                 | 5–30                                     |
| Regression equation                    | $y = 0.012x + 0.009$<br>$R^2 = 0.998$ | $y = 0.016x + 0.004$<br>$R^2 = 0.999$    |

**Figure 1. UV absorption spectra of levosulpiride ( $\lambda_{\text{max}} = 291 \text{ nm}$ ) (a) and eplerenone ( $\lambda_{\text{max}} = 242 \text{ nm}$ ) (b).**

(a) Levosulpiride



(b) Eplerenone

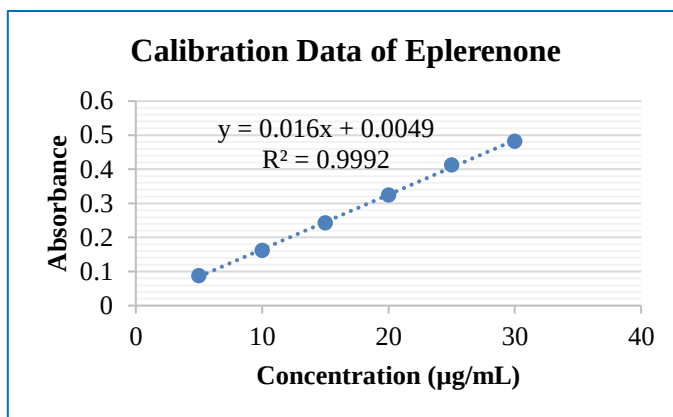


**Figure 2. Calibration curves of UV of (a) levosulpiride and (b) eplerenone with linear regression equations and coefficients of determination.**

The FTIR spectra of pure drugs exhibited all the expected characteristic bands (N–H and C=O/amide bands for levosulpiride; carbonyl/lactone and C–O bands for eplerenone), and these were retained without significant shift, broadening or loss in the physical mixtures with the selected excipients (Figure 3, Table 4), indicating the absence of major drug–excipient interaction and supporting the compatibility of the selected formulation components <sup>[43, 44]</sup>.

**Table 4. Comparison of characteristic FTIR spectra of the pure drug and physical combinations of drug–excipient.**

| Functional group        | Pure drug peak (cm <sup>-1</sup> ) | Physical-mixture peak (cm <sup>-1</sup> ) | Observation          |
|-------------------------|------------------------------------|-------------------------------------------|----------------------|
| N–H stretching          | 3345                               | 3340                                      | No significant shift |
| C=O stretching (amide)  | 1672                               | 1670                                      | No significant shift |
| Aromatic C=C stretching | 1580                               | 1578                                      | No significant shift |
| C–O stretching          | 1165                               | 1162                                      | No significant shift |

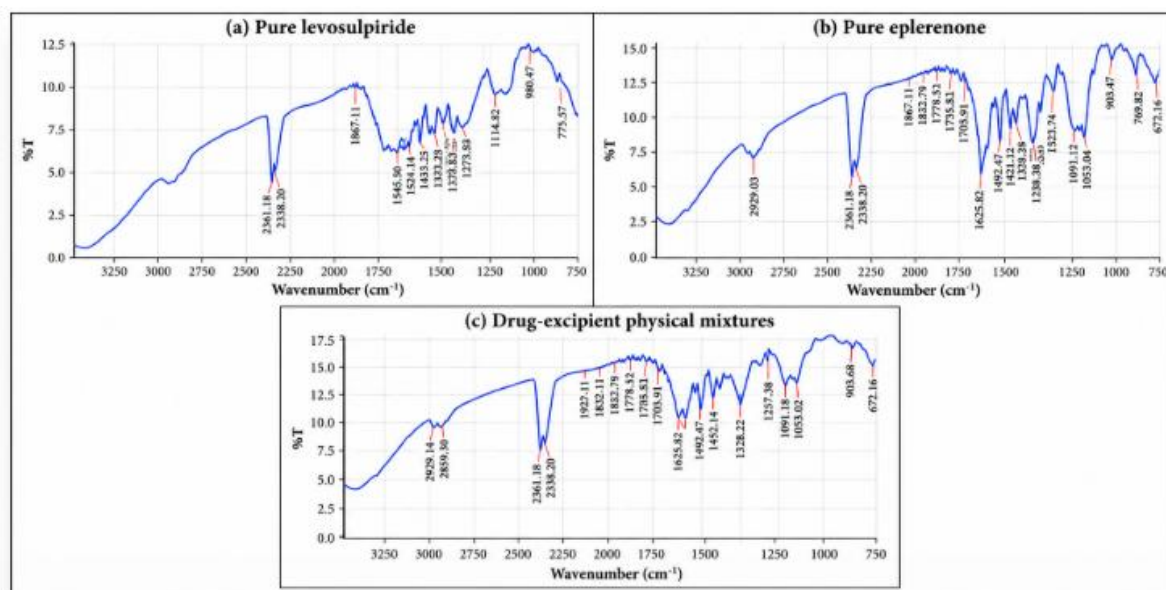


**Figure 3.** FTIR spectra of (a) pure levosulpiride, (b) pure eplerenone and (c) drug-excipient physical mixtures indicating absence of any major drug-excipient interaction.

### 3.2. Micromeritic and compression characteristics of mini-tablet mixes

The angle of repose decreased progressively from 32.5° (F1) to 25.6° (F9), and Carr's index and Hausner ratio decreased correspondingly from 16.0%/1.19 (F1) to 10.7%/1.12 (F9) (Table 5), indicating a trend toward improved flow with increasing polymer/effervescent load, most probably reflecting the more favorable particle packing conferred by the higher proportion of fine, cohesive polymer relative to lactose diluent at the higher-numbered formulations. All nine blends however fell in the “excellent” to “excellent” flow categories and none required any additional glidant over the fixed colloidal silica amount utilized throughout.

**Table 5.** Pre-compression (micromeritic) properties of floating mini-tablet powder blends F1–F9.

| Formulation | Angle of repose (°) | Bulk density (g/cm <sup>3</sup> ) | Tapped density (g/cm <sup>3</sup> ) | Carr's index (%) | Hausner ratio |
|-------------|---------------------|-----------------------------------|-------------------------------------|------------------|---------------|
| F1          | 32.5                | 0.42                              | 0.5                                 | 16               | 1.19          |
| F2          | 31.8                | 0.43                              | 0.51                                | 15.6             | 1.18          |
| F3          | 30.9                | 0.44                              | 0.51                                | 13.7             | 1.15          |
| F4          | 29.8                | 0.45                              | 0.52                                | 13.4             | 1.15          |
| F5          | 28.9                | 0.46                              | 0.53                                | 13.2             | 1.15          |
| F6          | 28.2                | 0.47                              | 0.54                                | 12.9             | 1.14          |
| F7          | 27.5                | 0.48                              | 0.55                                | 12.7             | 1.14          |
| F8          | 26.8                | 0.49                              | 0.56                                | 12.5             | 1.13          |
| F9          | 25.6                | 0.5                               | 0.56                                | 10.7             | 1.12          |

### 3.3. Floating and swelling properties of mini-tablets after compression

All formulations met pharmacopeial limits for weight variation. Hardness increased from 3.2 kg/cm<sup>2</sup> (F1) to 4.8 kg/cm<sup>2</sup> (F9) with a concomitant decrease in friability from 0.89% to 0.48%. Drug content varied from 96.5–99.8% (Table 6) in agreement with progressively firmer compacts at the higher polymer levels without loss of content uniformity.

The floating lag time dropped and total floating time increased monotonically with increasing HPMC K100M/Carbopol 974P and gas-generant concentration, from FLT 120 s/TFT 6 h (F1) to FLT 25 s/TFT >12 h (F9) (Table 6). This pattern is consistent with more rapid CO<sub>2</sub> generation and more effective gas trapping in a more extensively hydrated, higher-viscosity gel layer at higher polymer levels. The swelling index followed the same rank order, increasing from 90% (F1) to 145% (F9) at 8 h (Figure 4b), providing support for a mechanical relationship between polymer hydration/gel strength, gas entrapment and buoyancy.

**Table 6. Post-compression parameters and floating behavior of floating mini-tablets F1 - F9.**

| Formulation | Weight (mg) | Hardness (kg/cm <sup>2</sup> ) | Friability (%) | Thickness (mm) | Drug content (%) | Floating lag time (s) | Total floating time (h) |
|-------------|-------------|--------------------------------|----------------|----------------|------------------|-----------------------|-------------------------|
| F1          | 79.2 ± 0.5  | 3.2                            | 0.89           | 2.1            | 96.5             | 120                   | 6                       |
| F2          | 79.5 ± 0.4  | 3.4                            | 0.82           | 2.12           | 97.2             | 105                   | 7                       |
| F3          | 79.8 ± 0.3  | 3.6                            | 0.78           | 2.14           | 97.8             | 95                    | 8                       |
| F4          | 80.1 ± 0.5  | 3.8                            | 0.72           | 2.16           | 98.4             | 80                    | 9                       |
| F5          | 80.3 ± 0.4  | 4                              | 0.68           | 2.18           | 98.9             | 70                    | 10                      |
| F6          | 80.5 ± 0.3  | 4.2                            | 0.64           | 2.2            | 99.1             | 60                    | 11                      |
| F7          | 80.6 ± 0.5  | 4.4                            | 0.6            | 2.22           | 99.4             | 50                    | 12                      |
| F8          | 80.7 ± 0.4  | 4.6                            | 0.55           | 2.24           | 99.6             | 40                    | 12                      |
| F9          | 80.8 ± 0.3  | 4.8                            | 0.48           | 2.26           | 99.8             | 25                    | >12                     |

### 3.4. Mini-tablets in vitro release and release kinetics

The cumulative levosulpiride release after 12 h was narrow (97.0–99.1%) for all nine formulations but the rate of release decreased progressively with increasing polymer content: 1 h release fell from 29.3% (F1) to 11.3% (F9) and formulations F7–F9 showed the most gradual, sustained profile without an early burst (Figure 4a). Formulation F9 was selected as the optimum mini-tablet based on the combined premise of minimum FLT, maximum TFT, maximum

swelling capacity, maximum hardness/lowest friability and maximum gradual, burst-free release profile.

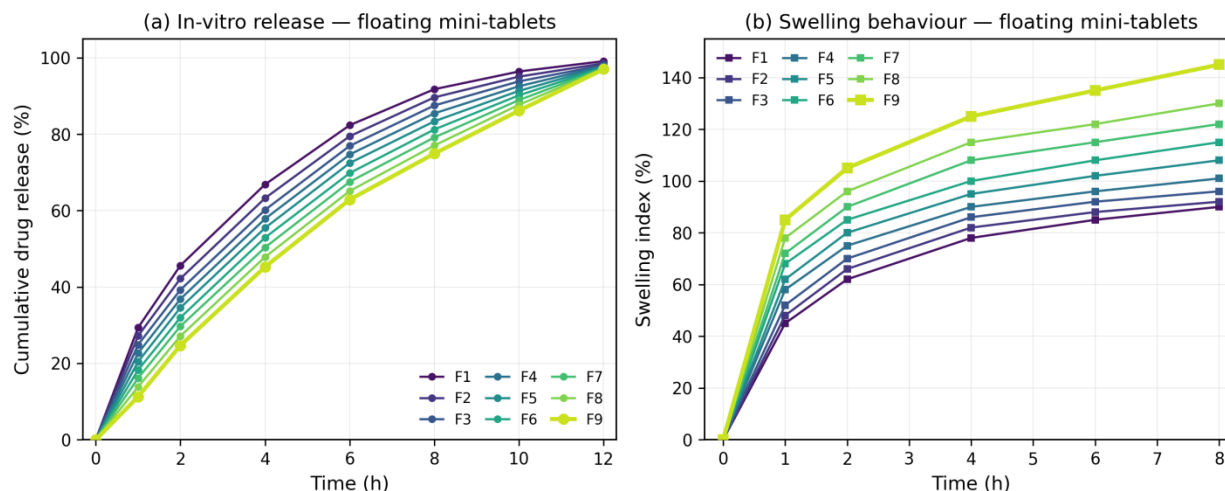


**Figure 4. (a) In-vitro cumulative drug release and (b) swelling index of floating levosulpiride mini-tablets F1–F9 in 0.1 N HCl ( $37 \pm 0.5$  °C); heavier trace for formulation F9.**

F9 release profile kinetic modeling (Table 7; Korsmeyer–Peppas plot in Figure 6) revealed the Higuchi model ( $R^2 = 0.9995$ ) had the highest coefficient of determination, consistent with diffusion-controlled release through the hydrated polymer matrix, while the Korsmeyer–Peppas exponent ( $n = 1.00$ ,  $R^2 = 0.9945$ , three points  $\leq 60\%$  release) was greater than the  $n = 0.89$  threshold conventionally used to divide super case-II transport in cylindrical matrices. These findings together suggest that release from F9 was dictated by a combination of Fickian diffusion through the swollen gel layer and polymer chain relaxation/erosion, a mechanism typical of high viscosity HPMC/Carbopol matrices which undergo significant swelling and consistent with the significant swelling behavior observed directly for this formulation.

**Table 7. Release-kinetic model parameters of the optimized floating mini-tablet (F9) and the optimized enteric-coated pellet (P6, buffer-stage data,  $\tau = t - 2$  h).**

**Formulation F9 (levosulpiride)**

| Kinetic model    | Regression equation               | $R^2$  | Rate constant / exponent             |
|------------------|-----------------------------------|--------|--------------------------------------|
| Zero-order       | $Q = 7.672t + 10.330$             | 0.9758 | $k_0 = 7.67 \% h^{-1}$               |
| First-order      | $\log(100-Q) = -0.1187t + 2.1785$ | 0.8999 | $k_1 = 0.273 h^{-1}$                 |
| Higuchi          | $Q = 35.019\sqrt{t} - 24.180$     | 0.9995 | $kH = 35.02 \% h^{-0.5}$             |
| Korsmeyer–Peppas | $\log Q = 1.004 \log t + 1.064$   | 0.9945 | $n = 1.00$ (super case-II transport) |

**Formulation P6 (eplerenone, post-coating-dissolution phase)**

| Kinetic model    | Regression equation                  | R <sup>2</sup> | Rate constant / exponent         |
|------------------|--------------------------------------|----------------|----------------------------------|
| Zero-order       | $Q = 7.099\tau + 35.741$             | 0.8995         | $k_0 = 7.10 \% h^{-1}$           |
| First-order      | $\log(100-Q) = -0.1611\tau + 2.0318$ | 0.9931         | $k_1 = 0.371 h^{-1}$             |
| Higuchi          | $Q = 30.864\sqrt{\tau} + 6.296$      | 0.9673         | $k_H = 30.86 \% h^{-0.5}$        |
| Korsmeyer–Peppas | $\log Q = 0.583 \log \tau + 1.531$   | 0.9853         | $n = 0.58$ (anomalous transport) |

**3.5. Physicochemical characterisation of eplerenone pellets**

The higher content of pellet-forming polymer (sodium alginate 2 → 6 mg in P1 → P3; HPMC E5 2 → 6 mg in P4 → P6, with reciprocal decrease in MCC PH 101) and, more importantly, the substitution of HPMC E5 for sodium alginate (P4 → P6 vs. P1 → P3) were correlated with a higher yield of pellets in the target 0.5–1.5 mm size range (up to 97% combined, P6), higher sphericity (0.82 to 0.96, P1 → P6), and lower friability (1.2% to 0.60%) (Table 9), in line with the more plastic, cohesive wet mass that HPMC E5 confers during extrusion–spheronization relative to sodium alginate at the levels studied. The core pellets contained 95.2–99.6% of the drug and the content increased with the formulation number. The dissolution of the uncoated cores was rapid and essentially complete within 4 h for all batches (95.8–97.7%), indicating that the core matrix per se did not exert any release-controlling function and that all six core formulations were suitable substrates for subsequent enteric coating. P6 was selected as optimum core based on size distribution, sphericity, friability and drug content.

**3.6. Acid resistance and disintegration of enteric coated pellets**

Increasing the Eudragit L100 coating level from 5% to 10% w/w weight gain (Table 8) decreased the acid-stage drug release (2 h, 0.1 N HCl) from a range of 11–12% at the 5% coating level to 4.18–6.48% at the 10% level. Visual inspection showed intact, undamaged coats for the higher coating levels, while the 5% level showed slight cracking in one formulation. P6 (12% w/v Eudragit L100 coating dispersion, 15% w/w PEG 400, coated to a 10% w/w target weight gain) exhibited the lowest acid-stage release (4.18%) and, after transfer to pH 6.8 buffer, released 97.52% of eplerenone by 12 h, displaying a typical biphasic profile with negligible release during the acid stage and then a rapid increase once the enteric film dissolved (Figure 5). This was confirmed with Eudragit L100 that protected the drug effectively in the stomach in a pH-

dependent manner, and allowed rapid and basically complete drug release in the intestinal pH environment.

**Table 8. Physicochemical characteristics of core eplerenone pellets and acid resistance of enteric-coated pellets, formulations P1–P6.**

| Batch | % Retained 0.5–1 mm | % Retained 1–1.5 mm | Sphericity | Friability (%) | Core drug content (%) | Core release at 4 h (%) | Coating weight gain (%) | Acid-stage release, 2 h (%) | Coat appearance after acid exposure |
|-------|---------------------|---------------------|------------|----------------|-----------------------|-------------------------|-------------------------|-----------------------------|-------------------------------------|
| P1    | 60                  | 30                  | 0.82       | 1.2            | 95.2                  | 97.68                   | 5                       | 12.34                       | Slight coating damage               |
| P2    | 65                  | 28                  | 0.85       | 1.05           | 96.5                  | 97.24                   | 7.5                     | 9.82                        | Minor swelling                      |
| P3    | 68                  | 27                  | 0.88       | 0.95           | 97.8                  | 96.82                   | 10                      | 6.48                        | Intact                              |
| P4    | 70                  | 25                  | 0.9        | 0.82           | 98.4                  | 96.46                   | 5                       | 11.18                       | Slight cracks                       |
| P5    | 72                  | 24                  | 0.93       | 0.75           | 99.1                  | 96.18                   | 7.5                     | 8.42                        | Intact                              |
| P6    | 75                  | 22                  | 0.96       | 0.6            | 99.6                  | 95.84                   | 10                      | 4.18                        | Intact, no damage                   |

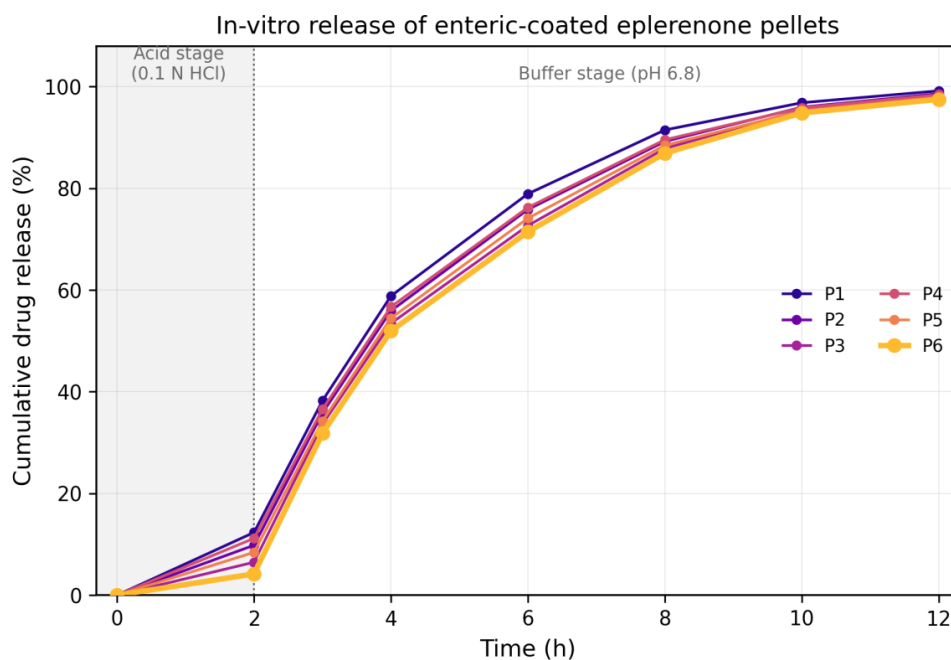


**Figure 5. In vitro release of enteric-coated eplerenone pellets P1–P6: 2 h acid stage (0.1 N HCl) followed by transfer to phosphate buffer pH 6.8; formulation P6 shown with heavier trace.**

Kinetic analysis of the P6 buffer-stage release (Table 8) gave the highest  $R^2$  for the first-order model ( $R^2 = 0.9931$ ) of all the classical models, although the Higuchi model also gave a reasonable fit ( $R^2 = 0.9673$ ). The Korsmeyer–Peppas exponent ( $n = 0.58$ , buffer-stage data  $\leq \sim 71\%$  release) was within the range of anomalous (non-Fickian) transport conventionally used for spherical matrices ( $0.43 \leq n < 0.85$ ). This suggested that release was controlled by a combination of diffusion through and erosion/disintegration of the residual pellet matrix once the enteric barrier had dissolved, rather than just simple first-order diffusion alone. The scarcity of data points below the usual 60% cut-off for this fast-dissolving system is recognized as a limitation on the accuracy of the exponent estimation.

### 3.7. Dual multiparticulate system: physical evaluation and combined release

The mini-tablets F9 and pellets P6 in optimal formulation were homogeneous in appearance, showed no pellet–tablet incompatibility, no breaking or leaking and were reproducibly filled (Table 9). The combined in vitro dissolution profile (Figure 6) successfully reproduced the release characteristics of each individual component: levosulpiride release from the floating mini-tablets started from the beginning of the test and reached 97.02 % at 12 h, in a manner that was essentially superimposable on the profile obtained for F9 alone, while eplerenone release from the enteric-coated pellets remained below 5% throughout the 2 h acid stage before increasing rapidly after the transfer to pH 6.8 buffer to reach 97.52 % at 12 h, again closely matching the profile of P6 tested alone. This concordance indicates that co-formulation in a single capsule did not significantly affect the release behavior of either component, i.e. the floating and enteric-coated units behaved independently, without evidence of dose dumping, mutual interference or cross-contamination of release mechanism, and the platform successfully delivered two temporally and spatially distinct release profiles (sustained gastric release versus delayed intestinal release) from a single oral dosage form.

**Table 9. Physical assessment of the dual multiparticulate capsule (optimized F9 mini-tablets + P6 pellets).**

| Parameter                | Observation                                 |
|--------------------------|---------------------------------------------|
| Appearance               | Intact, uniform capsules                    |
| Fill uniformity          | Uniform across capsules                     |
| Capsule / unit integrity | No cracks, leakage, or pellet–tablet damage |

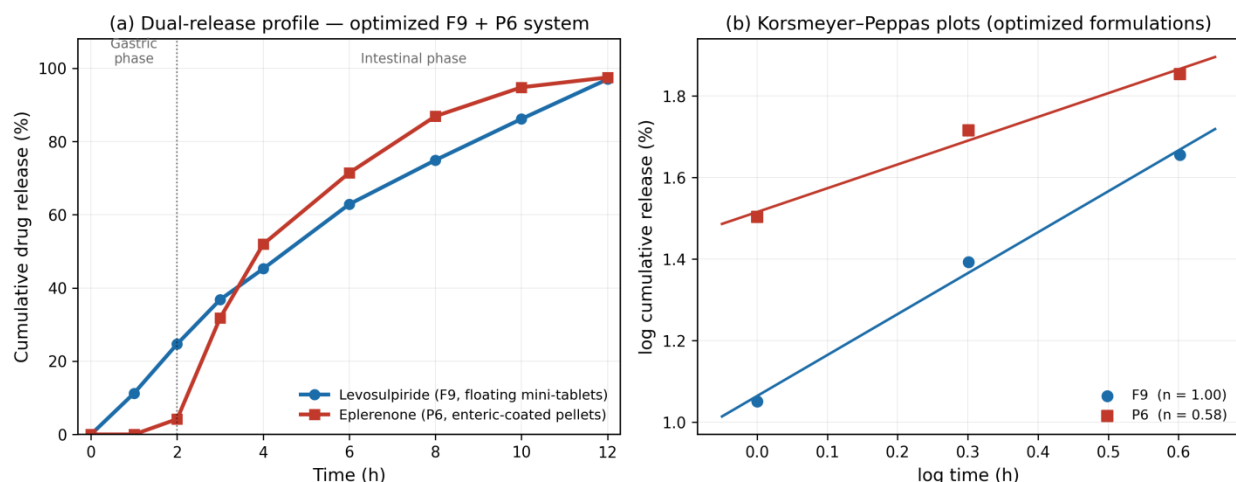


**Figure 6. (a) Comparative release profile of levosulpiride (F9) and eplerenone (P6) from the improved dual multiparticulate system in vitro. (b) Korsmeyer-Peppas plots for the improved formulations (F9,  $n = 1.00$ ; P6,  $n = 0.58$ ).**

### 3.8. Studies of stability

Under long term conditions, the optimized dual multiparticulate capsules showed no significant change in physical appearance over 3 months storage, and only a little dulling/softening of the capsule shell under accelerated conditions, without cracking or leaking under either condition (Table 10). The drug content of levosulpiride and eplerenone was well within the 90–110% pharmacopeial acceptability range at both storage settings and decreased very slightly by month 3 (levosulpiride: 98.58% at 25 °C, 98.06% at 40 °C; eplerenone: 98.34% at 25 °C, 97.82% at 40 °C) (Figure 7a). The floating lag time was increased by a small amount (from 25 s to 30 s) while the total floating time was >12 h throughout. The acid stage release of the pellet component was within the 10% acceptance limit at all time points (4.18% to 5.08%). The cumulative 12 h release of both drugs was decreased by small amount (levosulpiride 97.02% to 96.08%; eplerenone 97.52% to 96.52%) (Table 10, Figure 7b). The results indicate that the mechanical, floating, coating and release-controlling properties of the optimized dual multiparticulate system were not significantly affected by 3 months of long-term or accelerated storage and support the short-term physical and functional stability of the platform, but confirmation of a definitive shelf life would require stability data for the entire ICH-recommended period.

**Table 10. Stability profile of improved dual multiparticulate formulation (F9 + P6) under long term ( $25 \pm 2$  °C/60 ± 5 % RH) and accelerated ( $40 \pm 2$  °C/75 ± 5 % RH) conditions.**

| Parameter                          | 0 month         | 1 month   | 2 months        | 3 months                  |
|------------------------------------|-----------------|-----------|-----------------|---------------------------|
| Physical appearance — 25 °C/60% RH | Intact capsules | No change | No change       | No change                 |
| Physical appearance — 40 °C/75% RH | Intact capsules | No change | Slight dullness | Slight softening of shell |
| Levosulpiride content — 25 °C (%)  | 99.62           | 99.28     | 98.92           | 98.58                     |
| Levosulpiride content — 40 °C (%)  | 99.62           | 98.96     | 98.52           | 98.06                     |
| Eplerenone content — 25 °C (%)     | 99.48           | 99.14     | 98.76           | 98.34                     |
| Eplerenone content — 40 °C (%)     | 99.48           | 98.84     | 98.26           | 97.82                     |
| Floating lag time (s)              | 25              | 26        | 28              | 30                        |
| Total floating time (h)            | >12             | >12       | >12             | >12                       |
| Acid-stage release, pellets (%)    | 4.18            | 4.36      | 4.72            | 5.08                      |
| 12 h release — levosulpiride (%)   | 97.02           | 96.74     | 96.42           | 96.08                     |
| 12 h release — eplerenone (%)      | 97.52           | 97.18     | 96.86           | 96.52                     |

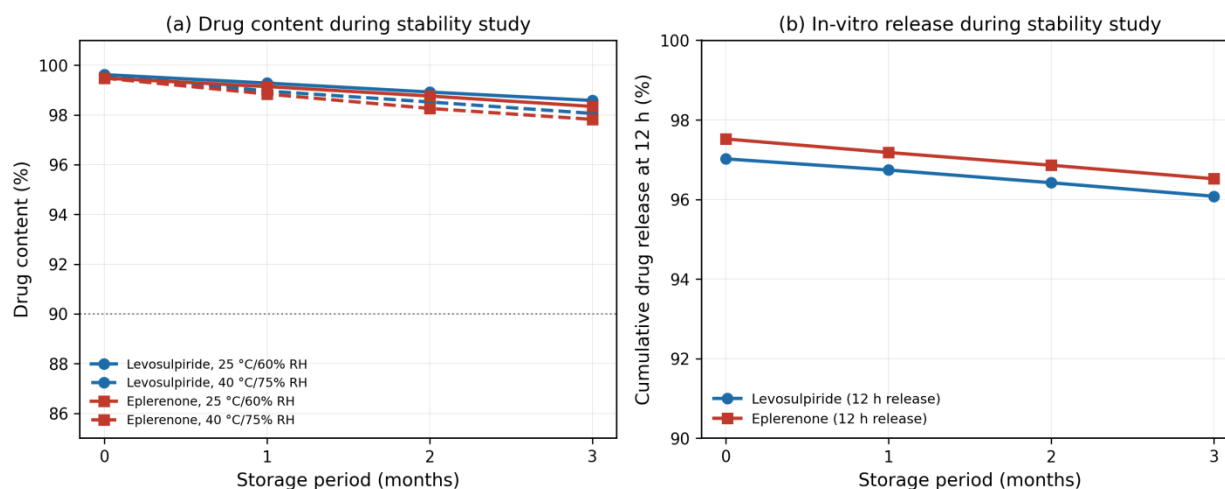


**Figure 7. Stability of the improved dual multiparticulate formulation (F9 + P6) for 3 months: (a) drug content and (b) cumulative in vitro release at 12 h, under long-term (25 °C/60% RH) and accelerated (40 °C/75% RH) conditions.**

#### 4. SUMMARY AND CONCLUSION

The dual multiparticulate oral drug administration system containing gastroretentive floating levosulpiride mini-tablets and enteric-coated eplerenone pellets was effectively conceived, optimized and characterized. The optimized mini-tablet (F9; 25 mg levosulpiride, 20 mg HPMC

K100M, 10 mg Carbopol 974P, 12 mg sodium bicarbonate, 3 mg citric acid) floated within 25 s, remained buoyant for more than 12 h and released 97.02% of its levosulpiride content over 12 h by a diffusion/relaxation regulated mechanism. The optimized enteric-coated pellet (P6; HPMC E5 core coated to 10% w/w weight gain with 12% w/v Eudragit L100 dispersion plasticized with 15% PEG 400) restricted eplerenone release in the gastric phase to 4.18% over 2 h and attained 97.52% release within 12 h of transfer to intestinal pH, by diffusion/erosion-controlled mechanism after coat dissolution. When combined in a single hard gelatin capsule, the two components maintained their own release properties without any interference and the completed system was physically and functionally robust for 3 months under long term and accelerated ICH-type circumstances. The results suggest that combining floating and enteric coated multiparticulate technologies in a single oral dosage form as a platform strategy for co-administration of drugs with divergent release requirements in the gastrointestinal tract is technically feasible and provide a formulation basis for additional pharmacokinetic and longer duration stability evaluation of the approach.

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## **REFERENCES:**

1. Colombo P, Sonvico F, Colombo G, Bettini R. Novel platforms for oral drug delivery. *Pharm Res.* 2009;26(3):601-11.
2. Jain KK. Drug delivery systems—an overview. In: Jain KK, editor. *Drug Delivery Systems*. Totowa (NJ): Humana Press; 2008. p. 1-50.
3. Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in oral drug delivery. *Front Pharmacol.* 2021;12:618411.
4. Mørnø RJ. Oral drug delivery research in Europe. *J Control Release.* 2012;161(2):247-53.
5. Murugesan S, Gowramma B, Lakshmanan K, Karri VVSR, Radhakrishnan A. Oral modified drug release solid dosage form with special reference to design: an overview. *Curr Drug Res Rev.* 2020;12(1):16-25.

6. Loke YH, Jayakrishnan A, Razif MR, Yee KM, Kee PE, Goh BH, et al. A comprehensive review of challenges in oral drug delivery systems and recent advancements in innovative design strategies. *Curr Pharm Des.* 2025;31(5):360-76.
7. Lou J, Duan H, Qin Q, Teng Z, Gan F, Zhou X, et al. Advances in oral drug delivery systems: challenges and opportunities. *Pharmaceutics.* 2023;15(2):484.
8. Adepu S, Ramakrishna S. Controlled drug delivery systems: current status and future directions. *Molecules.* 2021;26(19):5905.
9. Charman SA, Charman WN. Oral modified-release delivery systems. In: Rathbone MJ, Hadgraft J, Roberts MS, editors. *Modified-Release Drug Delivery Technology.* New York: Marcel Dekker; 2002. p. 1-9.
10. Lane ME. In: Rathbone MJ, Hadgraft J, Roberts MS, editors. *Modified-Release Drug Delivery Technology.* New York: Marcel Dekker; 2003.
11. Jantzen GM, Robinson JR. Sustained- and controlled-release drug delivery systems. In: Banker GS, Rhodes CT, editors. *Modern Pharmaceutics. Drugs and the Pharmaceutical Sciences*, vol 121. New York: Marcel Dekker; 2002. p. 501-28.
12. Dixit N, Maurya SD, Sagar BP. Sustained release drug delivery system. *Indian J Res Pharm Biotechnol.* 2013;1(3):305-10.
13. Heng PWS. Controlled release drug delivery systems. *Pharm Dev Technol.* 2018;23(9):833.
14. Huynh CT, Lee DS. Controlled release. In: *Encyclopedia of Polymeric Nanomaterials.* Berlin: Springer; 2014. p. 1-12.
15. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. *Drug Deliv.* 2011;18(2):97-110.
16. Ishak RAH. Buoyancy-generating agents for stomach-specific drug delivery: an overview with special emphasis on floating behavior. *J Pharm Pharm Sci.* 2015;18(1):77-100.
17. Dixit N. Floating drug delivery system. *J Curr Pharm Res.* 2011;7(1):6-20.
18. Reddy LH, Murthy RSR. Floating dosage systems in drug delivery. *Crit Rev Ther Drug Carrier Syst.* 2002;19(6):553-85.
19. Prinderre P, Sauzet C, Fuxen C. Advances in gastro retentive drug-delivery systems. *Expert Opin Drug Deliv.* 2011;8(9):1189-203.
20. Dhiman S, Philip N, Singh TG, Babbar R, Garg N, Diwan V, et al. An insight on novel approaches & perspectives for gastro-retentive drug delivery systems. *Curr Drug Deliv.* 2023;20(6):708-29.
21. Nayak AK, Malakar J, Sen KK. Gastroretentive drug delivery technologies: current approaches and future potential. *J Pharm Educ Res.* 2010;1(2):1-12.
22. Das S, Kaur S, Rai VK. Gastro-retentive drug delivery systems: a recent update on clinical pertinence and drug delivery. *Drug DelivTransl Res.* 2021;11(5):1849-77.
23. Mishra S, Shukla P, Chumbhale DS, Dutta P, Vellingiri D, Tiwari R. Exploring the potential of gastro retentive drug delivery systems: an insightful perspective. *Int J Pharm Investig.* 2025;15(3).

24. Rajabi-Siahboomi AR, editor. Overview of multiparticulate systems for oral drug delivery. In: Multiparticulate Drug Delivery: Formulation, Processing and Manufacturing. New York: Springer; 2017. p. 1-4.
25. Seitz A. Mini-tablets as an alternative galenic formulation for neonates [dissertation]. Düsseldorf: Heinrich-Heine-Universität.
26. Münch J. Acceptability, swallowability, and palatability of three oral placebo formulations in young children [dissertation]. Düsseldorf: Heinrich-Heine-Universität; 2022.
27. Muley S, Nandgude T, Poddar S. Extrusion-spheronization a promising pelletization technique: in-depth review. Asian J Pharm Sci. 2016;11(6):684-99.
28. Kandukuri JM, Allenki V, Eaga CM, Keshetty V, Jannu KK. Pelletization techniques for oral drug delivery. Int J Pharm Sci Drug Res. 2009;1(2):63-70.
29. Hirjau M, Nicoara AC, Hirjau V, Lupuleasa D. Pelletization techniques used in pharmaceutical fields. Farmacia. 2011;4(3):4.
30. Ghebre-Sellassie I. Pellets: a general overview. In: Pharmaceutical Pelletization Technology. Boca Raton: CRC Press; 2022. p. 1-13.
31. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed-release system for colonic specific delivery. Int J Pharm. 1994;108(1):77-83.
32. Maroni A, Moutaharrik S, Zema L, Gazzaniga A. Enteric coatings for colonic drug delivery: state of the art. Expert Opin Drug Deliv. 2017;14(9):1027-9.
33. Loh YY, Enose AA, Garg V. Enteric-coated polymers past and present—a review. Drug Deliv Lett. 2022;12(2):85-95.
34. Thakral S, Thakral NK, Majumdar DK. Eudragit: a technology evaluation. Expert Opin Drug Deliv. 2013;10(1):131-49.
35. Lozano R, Concha MP, Montealegre A, de Leon L, Villalba JO, Esteban HL, et al. Effectiveness and safety of levosulpiride in the treatment of dysmotility-like functional dyspepsia. Ther Clin Risk Manag. 2007;3:149-55.
36. Gupta S, Garg GR, Halder S, Sharma KK. Levosulpiride: a review. Delhi Psychiatry J. 2007;10:144-6.
37. Moore TD, Nawarskas JJ, Anderson JR. Eplerenone: a selective aldosterone receptor antagonist for hypertension and heart failure. Heart Dis. 2003;5(5):354-63.
38. Polsinelli VB, Sinha A, Shah SJ. Visceral congestion in heart failure: right ventricular dysfunction, splanchnic hemodynamics, and the intestinal microenvironment. Curr Heart Fail Rep. 2017;14(6):519-28.
39. Gopinath R, Naidu RA. Pharmaceutical preformulation studies—current review. Int J Pharm Biol Arch. 2011;2(5):1391-400.
40. Bharate SS, Vishwakarma RA. Impact of preformulation on drug development. Expert Opin Drug Deliv. 2013;10(9):1239-57.
41. Singh A, Avupati VR. Development and validation of UV-spectrophotometric method for the estimation of curcumin in standardised polyherbal formulations. J Young Pharm. 2017;9(4):574-7.

42. Jain PS, Chaudhari AJ, Patel SA, Patel ZN, Patel DT. Development and validation of UV-spectrophotometric method for determination of terbinafine hydrochloride in bulk and in formulation. Pharm Methods. 2011;2(3):198-202.
43. Chadha R, Bhandari S. Drug-excipient compatibility screening—role of thermoanalytical and spectroscopic techniques. J Pharm Biomed Anal. 2014;87:82-97.
44. Patel P, Ahir K, Patel V, Manani L, Patel C. Drug-excipient compatibility studies: first step for dosage form development. PharmaInnov J. 2015;4(5 Pt A):14-20.