

Original Research Article

Development of enteric-coated osmotic tablet for colon-targeted hydrocortisone delivery

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Abstract

Purpose: To formulate enteric-coated osmotic tablets for colon-targeted delivery of hydrocortisone.

Methods: Nine core tablet batches were prepared with varying amounts of potassium chloride (osmogen), polyethylene glycol 4000 (solubilizing agent), starch (wicking agent), and microcrystalline cellulose (binder). The core tablets, each containing 20 mg hydrocortisone, were coated sequentially with a cellulose acetate (semi-permeable) membrane and Eudragit S-12, 5-P/PEG 400 (enteric polymer) system. In vitro dissolution was assessed over a period of twelve hours across physiologically relevant pH conditions.

Results: The enteric coating suppressed drug release to approximately 3 % during the initial two hours (pH 1.2), with only 3.4 – 5.1 % cumulative release after four hours at pH 4.5. Substantial release was initiated at pH 7.2, with the majority of hydrocortisone released during the final six-hour phase. Formulations B6 (containing 20 % osmogen and 1.67 % binder) and B7 (containing 13.33 % osmogen and 8.33 % binder) exhibited optimal colon-targeting, achieving 95.20 % and 95.30 % total release respectively. Release kinetics were predominantly first-order, with transport governed by non-Fickian (anomalous) diffusion.

Conclusion: Enteric-coated osmotic tablets containing hydrocortisone provide a site-specific colonic delivery, with only minimal premature drug loss in the upper gastrointestinal tract.

Keywords: Hydrocortisone, Osmotic tablet, Enteric coating, Colon, Targeted delivery

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INTRODUCTION

Targeted-delivery systems aim to release the active ingredient at a specific site, thereby enhancing therapeutic efficacy and minimizing systemic side effects [1]. Despite its advantages, oral delivery for colon targeting faces multiple physiological barriers in the gastrointestinal tract, including pH variability, acid and enzymatic

degradations, and variable transit times [2,3]. Strategies developed to overcome these barriers include pH-dependent systems, time-controlled systems, pressure-controlled systems, coating, prodrug approaches, and microflora-activated systems [4]. Osmotically controlled drug delivery systems (OCDDS) represent an advanced form of time-controlled release, in which drug liberation is driven by osmotic pressure

gradients. Such systems can be adapted for colon targeting, particularly when combined with pH-sensitive enteric coatings such as Eudragit E100 [5]. Typical OCDDS components include the active drug, a solubilizing agent, a wicking agent, an osmogen, a semi-permeable membrane polymer, a pore former, a plasticizer and a coating solvent system [6].

Inflammatory bowel diseases (IBDs) are commonly treated with anti-inflammatory agents, corticosteroids, and antibiotics. Conventional oral corticosteroids are suboptimal for colon-specific therapy because they release the drug before reaching the target site, limiting local efficacy [7]. Rectal formulations, while capable of localized delivery, often fail to reach the proximal colon and are associated with poor patient compliance due to discomfort [8]. A colon-targeted system capable of protecting the drug during transit through the upper gastrointestinal tract and releasing it only upon arrival in the colon is therefore highly desirable for the management of colon disorders [9]. Hydrocortisone, a corticosteroid widely used in IBD therapy, exerts both immunosuppressive and anti-inflammatory effects [10]. Its mechanism of action involves inhibition of phospholipase A₂, preventing phospholipid hydrolysis and subsequent synthesis of pro-inflammatory cytokines [11]. The action underlies its capacity to induce rapid clinical remission of inflammation [12]. This present study was designed to develop an osmotically controlled, pH-regulated, colon-targeted hydrocortisone tablet for the effective management of inflammatory bowel diseases.

EXPERIMENTAL

Materials

Hydrocortisone powder was purchased from Dotcom Pharma, India. The chemicals used for the study include solid polyethylene glycol 4000 (Central Drug House, India), liquid polyethylene glycol 400 (Central Drug House, India), Eudragit

S-12 and Eudragit 5-P (Evonic Industries, Germany), pectin and potassium chloride (Merck, Germany), cellulose acetate, starch, titanium dioxide, orange colour powder and microcrystalline cellulose (BDH Chemicals, England), magnesium stearate and talc (Hopkin ad Williams Ltd., England), isopropyl alcohol and ethanol (Halewood Chemicals Ltd., England).

Compatibility studies on the drug and the solubilizing agent

Potential interactions between hydrocortisone and polyethylene glycol 4000 were studied using Fourier transform infrared spectroscopy and differential scanning calorimetry. Fourier transform infrared spectra of the drug, solubilizing agent and physical mixture were taken over a scanning range of 500 to 4,000 cm⁻¹ using a spectrophotometer (Shimadzu Corporation, Kyoto-Japan). Thermograms of the drug, solubilizing agent and physical mixture of the two substances were also obtained using a differential scanning calorimeter (NETZSCH Co., Germany). Scanning was done at heating rate of 20 °C/min to 300 °C as described in the previous work of Olorunsola *et al* [13].

Preparation of granules for the core tablets

Granules for 100 tablets based on the core Tablet Formula in Table 1 were prepared by wet granulation technique. While the proportions of drug, wicking agent (starch), diluent (lactose), the lubricant (magnesium stearate) and the glidant (talc) were kept constant, those of the solubilizing agent (PEG 4000), the osmogen (potassium chloride) and the binder (microcrystalline cellulose) were varied. The required amounts of hydrocortisone and polyethylene glycol 4000 were transferred into a mortar and mixed thoroughly for 5 minutes. Starch, potassium chloride, lactose, and microcrystalline cellulose were weighed separately and mixed in another mortar.

Table 1: Composition of the various hydrocortisone core tablet formulations

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9
HCT (%)	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67
PEG 4000 (%)	10.00	11.67	11.67	3.33	3.33	1.67	1.67	6.67	3.33
KCl (%)	5.00	1.67	3.33	6.67	8.33	20.00	13.33	1.67	1.67
Lactose (%)	60.00	60.00	60.00	60.00	60.00	60.00	60.00	60.00	60.00
MCC (%)	8.33	10.00	8.33	13.33	11.67	1.67	8.33	15.00	18.33
Starch (%)	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
Mg Stearate (%)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Talc (%)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

HCT = hydrocortisone, PEG 4000 = polyethylene glycol 4000, KCl = potassium chloride, MCC= microcrystalline cellulose, Mg stearate = magnesium stearate

The two mixtures were blended together for another 5 minutes and moistened sufficiently with alcohol (90 % v/v) as the granulating solvent was added in 5 mL portions until the required level of moistness was achieved. The wet mass was screened through a 2 mm sieve. The resultant granules were dried at 45°C for 4 hours and then screened through a 1 mm sieve.

Pre-compression flow characterization

From each batch, 10 g of granules was transferred into a measuring cylinder, and the initial bulk volume was recorded. The cylinder was tapped 100 times, and the tapped volume was recorded. This process was repeated twice, and the bulk density (BD) and tapped density (TD) were calculated as mass/volume. Carr's Index (CI) and Hausner's Ratio (HR) were determined using Eq 1 and 2.

$$CI = \left(\frac{TD - BD}{BD} \right) 100 \dots\dots\dots (1)$$

$$HR = \frac{TD}{BD} \dots\dots\dots (2)$$

Compression

The required quantities of talc and magnesium stearate were weighed and gently mixed with the dried granules. The lubricated granules were compressed into tablets using 8 mm concave punches.

Microporous semi-permeable membrane coating

A modified method of Li *et al* [14] was used for the coating. A 2.0 g quantity of cellulose acetate was dissolved in 50 mL of acetone, and 0.8 g of pectin was dissolved in 50 mL of water. The two solutions were mixed on a magnetic stirrer for 5 minutes to obtain a homogeneous solution. Exactly 2 mL of polyethylene glycol 400 was added as a plasticizer to enhance the physico-mechanical strength of the polymer solution. The tablets were coated by spraying the solution on the core tablets using a pan coating apparatus, and the process was repeated until the core tablets were completely coated. The tablets were then allowed to dry at room temperature.

Enteric coating

Using a modified form of the coating method described by Li *et al* [14], 15 g Eudragit S-12,5-P was dissolved in 100 mL isopropyl alcohol. Separately, 2 g of titanium dioxide and 0.5 g orange colour powder were mixed in a mortar, then 3 mL liquid (PEG 400) was added to form a

paste. The Eudragit S-12,5-P solution was added to this paste and mixed thoroughly. A 1:1 mixture of isopropyl alcohol and water (150 mL) was gradually added, and the volume was adjusted to 200 mL. The coating solution was applied using the pan coating method, and the tablets were dried at room temperature.

Weight uniformity test

The weight uniformity of 10 randomly selected tablets was assessed using an Adventurer analytical balance (Ohaus Corporation, United States). The mean weight and percent weight gain after coating were calculated.

Quantification for hydrocortisone

Hydrocortisone solutions of 0.5 – 7.0 µg/mL were prepared, and the absorbance of 5 mL samples was measured at 241 nm using a spectrophotometer (UNICO 2100 UV-Visible Spectrophotometer, Shanghai China) [15]. A calibration curve of absorbance versus concentration was plotted for subsequent quantification of drug release.

In vitro dissolution studies

Dissolution testing was carried out using a USP Type 1 apparatus (DDT-6C3, China) at 50 rpm and 37 ± 0.5 °C. A three-stage pH change was simulated to represent gastrointestinal transit. The dissolution system was initially made to simulate a pH of 1.2 in the stomach. This was prepared starting with 0.1 N hydrochloric acid and adjusting the pH to 1.2 using a portion of 2 N sodium hydroxide. Hence, the dissolution test commenced with 1000 mL of pH 1.2 solution for two hours. Thereafter, the pH was adjusted to 4.5 and the test continued for another four hours. Finally, the pH was increased to 7.2 and the dissolution continued for six hours. Changes in pH of the dissolution medium at all times were achieved by the addition of regulated amounts of 2 N sodium hydroxide, while the pH was being monitored. Aliquots (5 mL) were withdrawn at predetermined intervals (0.5 – 12 h), filtered, and replaced with fresh medium. The amount of drug released was determined at 241 nm [15], expressed as percent drug release, and plotted against time.

Drug release kinetics and transport mechanism

Drug release from 6 h onward (post-lag phase) were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models [16]. Regression coefficients (R²) were obtained for the zero-order,

first-order, and Higuchi plots, and the release exponent (n) was calculated from the Korsmeyer–Peppas model.

Statistical analysis

Data were analyzed using Analysis of Variance (ANOVA) followed by Tukey–Kramer multiple comparison tests with GraphPad Instat-3 software. Results are expressed as mean $\pm$ standard deviation (SD), and differences were considered significant at $p < 0.05$.

RESULTS

Fourier transform infrared (FTIR) spectra

The overlaid FTIR spectra of the drug, the solubilizer, and their simple mixture are shown in Figure 1. The spectrum of the drug–polymer mixture (Figure 1c) exhibited no new peaks, and all the characteristic peaks of the individual components (Figures 1a and 1b) were retained, indicating the absence of chemical interaction.

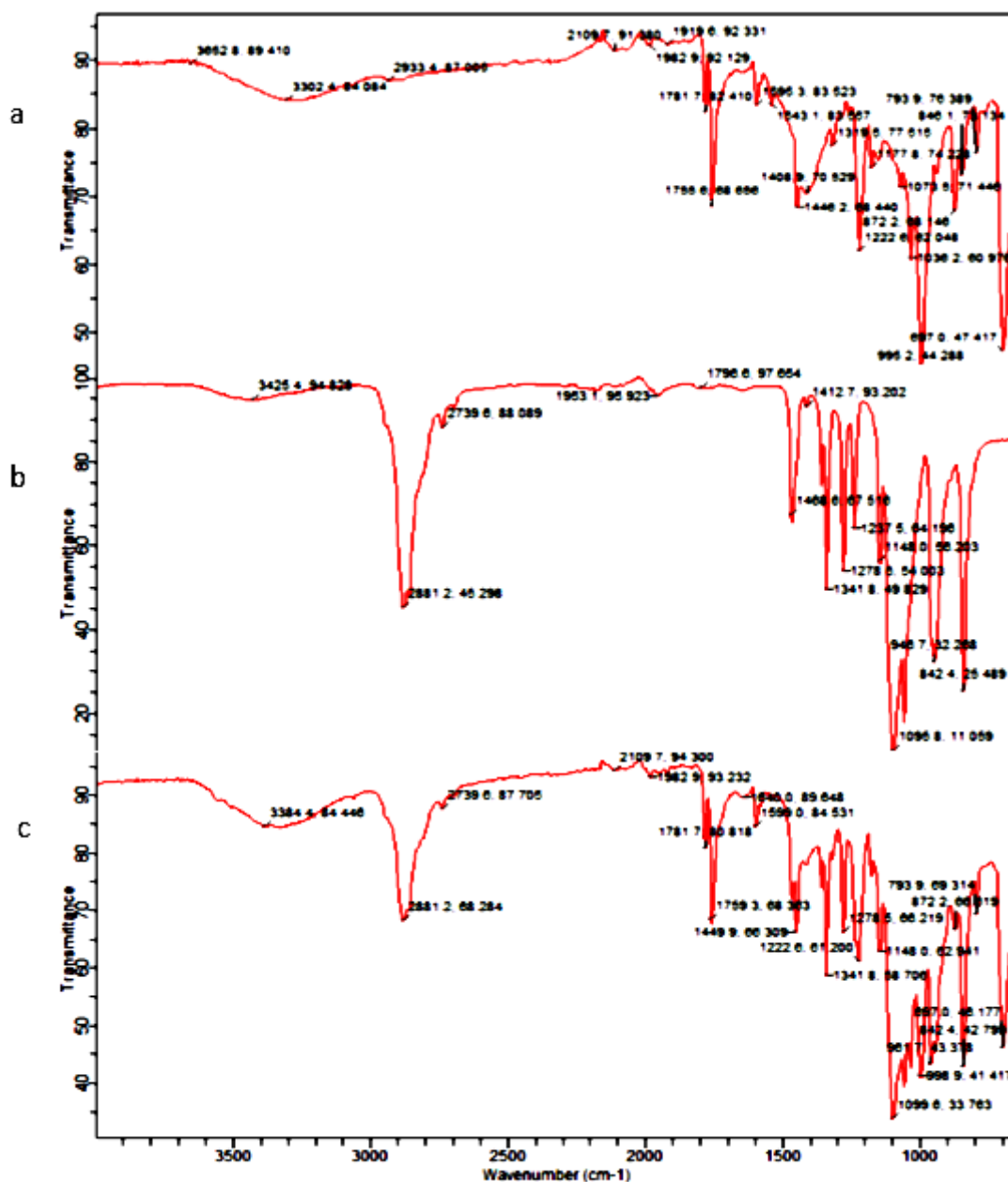


Figure 1: FTIR spectra of (a) hydrocortisone, (b) polyethylene glycol 4000 and (c) their simple mixture

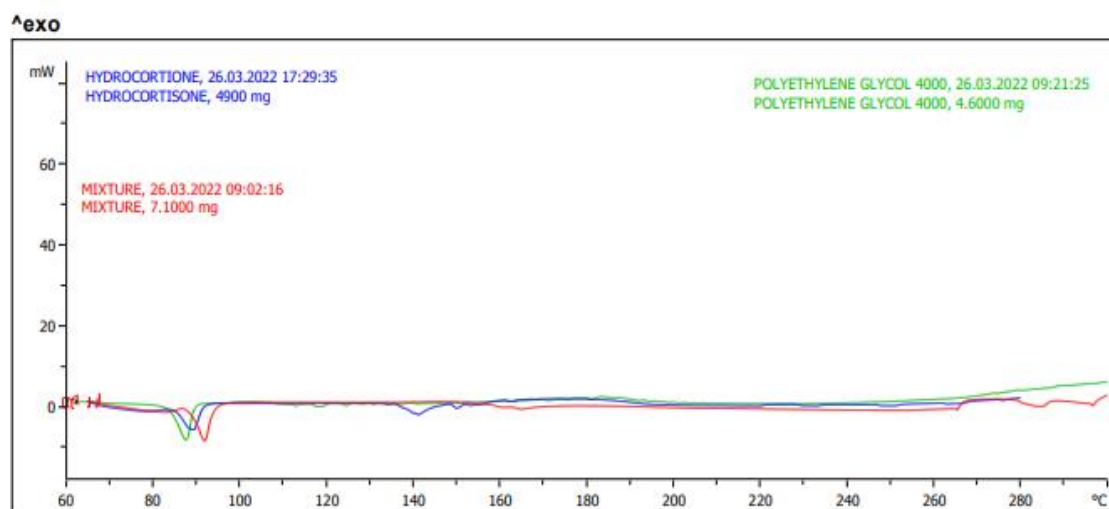


Figure 2: DSC overlay thermograms of hydrocortisone, polyethylene glycol 4000 and hydrocortisone - polyethylene glycol 4000 mixture

Differential scanning calorimetry (DSC) thermograms

The DSC thermograms (Figure 2) showed a sharp endothermic peak for the drug at 87.5 °C (blue-coloured thermogram) and for the polymer at 86.7 °C (green-coloured thermogram). The thermogram of the drug-polymer mixture exhibited a slightly shifted endothermic peak at 91 °C (red-coloured thermogram), suggesting physical mixing without significant interaction.

Granule flowability

Flow properties of Batches B1–B9 are summarized in Table 2. Carr's Index ranged from 20.95 % to 34.07 %, while Hausner's ratio ranged from 1.27 to 1.52. Batches B6 and B7 demonstrated the poorest flow characteristics.

Table 2: Pre-compression parameters

Batch	Carr's Index (%)	Hausner's Ratio
B1	20.95 ± 1.23	1.27 ± 0.22
B2	28.57 ± 2.23	1.40 ± 0.31
B3	22.86 ± 1.14	1.30 ± 0.23
B4	21.78 ± 2.32	1.28 ± 0.33
B5	29.81 ± 2.11	1.42 ± 0.32
B6	33.98 ± 1.23	1.51 ± 0.26
B7	34.07 ± 2.31	1.52 ± 0.34
B8	29.20 ± 1.65	1.41 ± 0.28
B9	21.29 ± 2.15	1.27 ± 0.31

Tablet weight

Table 3 presents the results for uniformity of weight and percent weight gain after coating. Average tablet weight ranged from 327.90 to

346.00 mg, while coating weight gain ranged from 9.30 % (B1) to 15.33 % (B5).

Drug release from tablets

Dissolution profiles (Figure 3) showed < 3 % drug release in the first two hours for all batches. At pH 4.5, cumulative release over the four hours remained below 6 % (3.40 – 5.10 %). There was a pronounced increase in drug release rate after the initial lag in the first six hours, with Batches B6 and B7 achieving complete release by 12 hours, and delivering 95.20 and 95.30 % drug, respectively.

Table 3: Physical attributes of the coated tablets

Batch	Average weight (mg)	Increase in weight after coating (%)
B1	327.90	9.30
B2	339.20	13.07
B3	340.70	13.47
B4	336.30	12.10
B5	346.00	15.33
B6	328.20	9.40
B7	334.30	11.43
B8	332.90	10.96
B9	332.90	10.96

Release kinetics and transport mechanism

Regression coefficients (R^2) from zero-order, first-order, and Higuchi models, as well as release exponents (n) from the Korsmeyer–Peppas model, are summarized in Table 4. The highest R^2 (0.9173) was observed for B2 in the zero-order model, closely followed by B6 in the first-order model (0.9171). The release exponents ranged from 0.53 to 0.73, indicating anomalous (non-Fickian) transport mechanisms.

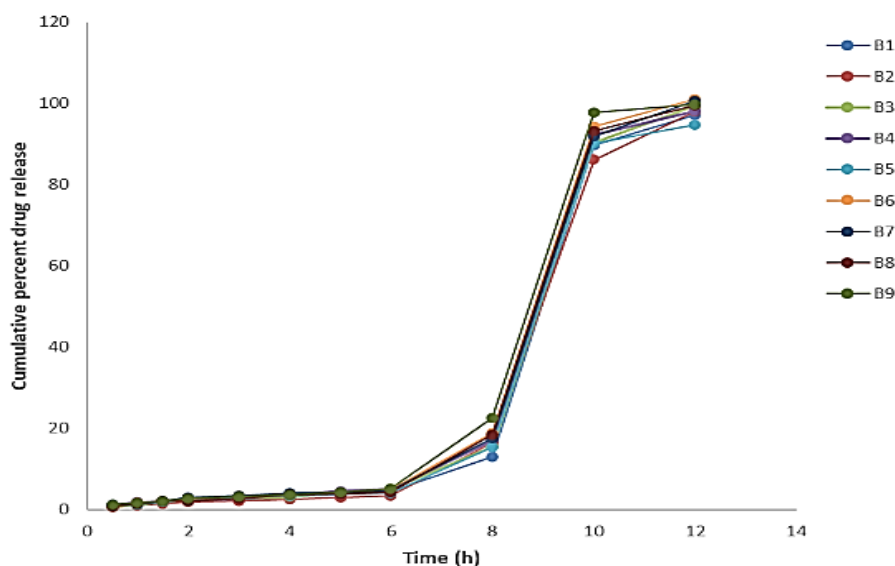


Figure 3: Dissolution curves of the various formulations

Table 4: Regression coefficients and release exponents

Batch	Zero-order plot		First-order plot		Higuchi plot		Korsmeyer-Peppas plot
	R ²	Error %	R ²	Error %	R ²	Error %	N
B1	0.8695	5.21	0.9120	0.56	0.7549	6.40	0.64
B2	0.9173	0.00	0.8982	2.06	0.8065	0.00	0.53
B3	0.8835	3.68	0.8907	2.87	0.7715	4.34	0.71
B4	0.8769	4.40	0.9159	0.13	0.7776	3.58	0.69
B5	0.8684	5.33	0.8928	2.65	0.7702	4.50	0.61
B6	0.8816	3.89	0.9171	0.00	0.7879	2.30	0.68
B7	0.8878	3.22	0.9085	0.94	0.7855	2.60	0.67
B8	0.8846	3.56	0.8958	2.32	0.7906	1.97	0.63
B9	0.8764	4.46	0.8972	3.17	0.8019	0.57	0.73
Mean		3.75±0.53		1.63±0.41		2.92±0.67	

R² = regression coefficient, n = release exponent

DISCUSSION

The FTIR spectrum of hydrocortisone exhibited absorption peaks at 3302, 2933, and 1755 cm⁻¹, corresponding to O–H, C–H, and C=O functional groups. These match the characteristic peaks reported by Altamini *et al* [17] and are consistent with the cyclopentano-perhydrophenanthrene nucleus and the 17,21-dihydroxy-20-keto side chain of the drug [18]. Similar peaks (3384, 2881, and 1759 cm⁻¹) were observed in the drug–PEG 4000 mixture, with no new peaks emerging. This, along with the persistence of the original peaks, indicates chemical compatibility between the drug and the polymer.

The DSC thermograms revealed no significant change in melting point after mixing, apart from a slight rightward shift suggestive of a marginal increase in thermal stability. Such compatibility is essential in colon-targeted formulations, where PEG 4000, used as a solubilizing agent, remains

in intimate contact with the drug in the tablet core.

Carr's index (above 20 %) and Hausner's ratio (above 1.25) suggested fair flow [19]. Batches B6 and B7 demonstrated the poorest flow, likely due to their high potassium chloride content with high osmogen load. The addition of talc and magnesium stearate before compression ensured acceptable processing. Coating weight gain ranged from 9.30 % to 15.33 %. The wide variation in the amounts of coat in the various batches can be attributed to the wide variation in the composition of the batches.

Drug release during the first two hours at pH 1.2 remained below 3 %, confirming effective gastric protection by the Eudragit enteric coat. Minimal release over the next four hours at pH 4.5 suggests that the cellulose acetate semi-permeable layer and the osmotic lag time effectively delayed the release during the small intestinal transit (3 – 4 h) [20]. The fast release of

the drug after 6 hours, which was at pH 7.2, is consistent with colon-targeted delivery. However, the formulations exhibited varying release rates due to the varying composition of the tablet core.

While all the formulations can be said to provide substantial colon-targeted delivery, Batch B1, with the lowest osmogen content (5 % potassium chloride) and moderate solubilizer (10 % PEG 4000), released only 12.9 % at eight hours and failed to achieve complete release at 12 hours, making it more suitable for individuals with prolonged upper-GI transit. In contrast, Batches B6 and B7, both containing higher osmogen levels (20 % and 13.33 %, respectively) and lower binder content, achieved complete release with a high proportion being delivered after 6 hours and before 12 hours, aligning with optimal colon-targeted delivery. The complete drug release from Batches B6 and B7 is in alignment with the oral bioavailability of hydrocortisone being 96 - 100 % [21,22].

Kinetic modelling showed similar regression coefficients for zero-order (0.9173) and first-order (0.9171) fits. Hence, there was a need to consider the values of the prediction error in determining the best-fit model. The prediction error analysis favoured the first-order model, the value being lower (1.63 % versus 3.75 %), indicating concentration-dependent release. Notably, Batches B2 and B3, with the highest PEG 4000 content, aligned more closely with zero-order kinetics, consistent with literature reports that polymer inclusion promotes constant-rate release [6,23].

There are basically four mechanisms of drug transport based on the release exponent 'n' derivable from Korsmeyer-Peppas plot. These are: (i) Fickian diffusion (Case I) with $n = 0.45$; (ii) non-Fickian diffusion with $0.45 < n < 0.89$; (iii) Case II transport with $n = 0.89$ and (iv) Super Case II transport with $n > 0.89$ [16,23]. In this work, the release exponent was found to range from 0.53 to 0.73, indicating the non-Fickian diffusion mechanism, in which case the drug transport was not just by diffusion, but is solely based on concentration gradient.

The non-Fickian diffusion mechanism observed with all the formulations is a pointer to the presence of an osmotic system that promotes constant-rate drug release. The lag time due to the enteric coating coupled with the solubilizer content of the core tablet and the zero-order kinetics characterizing the osmotic system, is responsible for the effective colon-targeted delivery of the drug [24].

CONCLUSION

Hydrocortisone blends well with PEG 4000 without any detectable chemical interaction. The second six-hour phase represents the major period of drug release for all the formulations, with the release predominantly following first-order kinetics and the transport mechanism being non-Fickian diffusion. Enteric-coated osmotic tablets containing 13.33 – 20.00 % potassium chloride as the osmogen and 1.67 – 8.33 % microcrystalline cellulose as the binder in the tablet core are suitable for colon-targeted delivery of hydrocortisone. Zero-order kinetics can be enhanced by incorporating a high concentration of the solubilizer into the formulation.

DECLARATIONS

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Ethical approval

Not applicable.

Use of Artificial intelligence/Large language models

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contributions of Authors

We declare that this work was done by the authors named in this article and all liabilities

pertaining to claims relating to the content of this article will be borne by the authors. Grace Ebiekpi: Conceptualization, design, data collection and analysis, drafting of the manuscript. Emmanuel Otakagu: Data validation and critical review of the manuscript. Mbang Femi-Oyewo: Data validation and critical review of the manuscript. Stephen Majekodunmi: Supervision and critical review of the manuscript. Ema Uduk: Data collection and analysis. Emmanuel Olorunsola: Supervision, design and writing of the manuscript. All authors read and approved the manuscript for publication.

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