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Controlled release kinetics of furosemide from chitosan matrix tablets with hydroxypropyl methylcellulose phthalate coated

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ABSTRACT

Sustained-release dosage forms were critical in drug delivery, ensuring controlled and prolonged release for optimal therapeutic outcomes. Chitosan (CH) has become pivotal in sustained-release tablet formulation due to its biocompatibility and mucoadhesive properties. This study aims to explore the release kinetics of furosemide (FS) from CH matrix tablets in a concurrent medium. The formulation involves a core tablet and coated tablet, with CH matrix as a binder and Hydroxypropyl Methyl Cellulose Phthalate (HPMCP) as a film-coated for the core tablet, and both are made using the wet granulation method. Assessment parameters include tablet hardness, disintegration, and FS release profiles across various media, analyzed using spectrophotometric methods to comprehend drug release kinetics with multiple models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas employed. In the press-coated tablet comprising core tablet CH as matrix uncoated with 20 mg CH per tablet core, a zero-order release pattern emerged in the pH 1.2 medium within 0-2 h, which displayed first-order release kinetics within 2-6 h and 6-16 h in concurrent media of pH 5.8 and 7.4. Notably, a zero-order release pattern emerged in the pH 1.2 medium within 0-2 h. Press-coated tablets incorporating CH matrix with HPCMP coated (CH-HPCMP), also containing 20 mg CH per tablet, exhibited diverse drug release kinetics. These tablets showed Korsmeyer-Peppas, zero-order, and first-order kinetics in pH 1.2, 5.8, and 7.4, respectively. The study suggests that a Press-coated tablet incorporating CH-HPMCP is suitable as the candidate for sustained-release formulations. The observed versatility in release kinetics across varying pH environments underscores the potential adaptability of these formulations in addressing diverse therapeutic needs.

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Keywords: press-coated tablet, controlled release, furosemide, chitosan, HPCMP

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INTRODUCTION

In disease therapy, conventional preparations are often administered three times a day. This approach releases drugs from the matrix, is absorbed, and promptly enters systemic circulation (Murugesan et al., 2020; Sharma et al., 2019). Conventional drug delivery systems (CDDS) had limitations: poor absorption from the target site, poor bioavailability, high first-pass metabolism, fluctuations in plasma drug levels, premature excretion from the body, repeated dosing, and high dumping dose (Adepu & Ramakrishna, 2021). However, advancements in science and technology have prompted pharmacists to modify drug release systems to overcome CDDS (Jain, 2020; Sharma et al., 2019). Currently, drug release does not occur instantly but is controlled through a matrix system. This system is utilized in developing drug release from solid dosage forms with sustained, prolonged, or time-based release methods (Jain, 2020; Murugesan et al., 2020). Controlled-release products promise more optimal disease therapy by regulating drug levels in plasma, reducing side effects, and controlling fluctuations in drug levels, albeit at higher costs (Mandhar & Joshi, 2015; Mehta et al., 2021). This development often involves various additives to create controlled-release preparations. Generally, these additives act as protective matrices to slow down drug release gradually (Hanna & Saad, 2019; Qu & Luo, 2020). The nature of these additives as protective agents influences the characteristics of controlled dosage forms (Sacco et al., 2018). It can adhere to various drug release kinetics models such as zero order, first order, Higuchi, and Korsemeyer-Peppas. Ideally, the model follows zero-order drug release kinetics to ensure stable drug levels in plasma (Murugesan et al., 2020; Suprianto, 2016).

Matrices based on various polymer types like polyethylene (PE), polyvinyl chloride (PVC), ethyl cellulose (ES), and polyacrylate (PA) are mixed with drugs and printed into tablets, allowing controlled drug diffusion (Mehta et al., 2021; Sharma et al., 2019). Drug release behavior from controlled dosage forms can be enhanced using hydrophilic matrices such as methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), xanthan gum (XG), sodium alginate (SA), carbomer (CB), and chitosan (CH). Lipid groups also play a role in creating controlled preparations, for instance, a combination of carnauba wax with stearyl alcohol or stearic acid (Pathak et al., 2023).

Biodegradable and non-biodegradable polymer-based matrices are crucial in controlled product development (Kamaly et al., 2016; Mehta et al., 2021). These matrices can degrade by enzymes or non-enzymes, becoming metabolizable monomers, such as glycolic acid (GA), lactic acid (LA), and ethylene vinyl acetate (EVA) (Wu et al., 2020; Yadav et al., 2021). Additionally, hydrogel matrices also contribute significantly to controlled product development, for example, hydroxyethyl methacrylate polymer (HEMA), vinyl alcohol (VA), vinylpyrrolidone (VP), ethylene oxide (EO), and acrylamide (AA) (Yadav et al., 2021). One frequently used substance is chitosan, derived from the deacetylation of chitin found in crustacean shells. Chitosan is a cationic polymer generated from D-glucosamine replication with N-acetyl-D-glucosamine through glycosidic bonds (Sacco et al., 2018; Wu et al., 2020). Due to its good biocompatibility, non-toxicity, biodegradability, low production cost, and abundant natural availability, chitosan finds extensive use in controlled preparation development (Idacahyati et al., 2020; Shao et al., 2015). Chitosan's ability to control drug release via gel formation has been studied (Liu et al., 2018; Shariatinia & Jalali, 2018). Studies have shown that the optimal combination of CH-MC (600 mg: 20 mg) demonstrates potential as a controlled-release preparation (Suprianto, 2016). The drug release profile of theophylline using CH-CMC tablets exhibited first-order kinetics and the Higuchi model (Murugesan et al., 2020; Suprianto, 2016). CH-SA, CH-CB, and CH-HPMC have also been investigated as potential controlled preparations with various drugs (Guarnizo-Herrero et al., 2021; Li et al., 2015; Zhang et al., 2018).

HPMCP coating effectively delays drug release, while the CH-HPMCP combination successfully enhances release with reduced polymer use. To formulate an appropriate release profile, this research focuses on developing a controlled drug release system using CH as a matrix tablet, HPMCP as a coating film, and furosemide (FS) as a model drug. The objective of this study is to explore the release kinetics of FS from CH matrix tablets with or without an HPMCP layer, as well as to understand the drug release profile in different media using UV spectrophotometry.

MATERIALS AND METHOD

Materials

Furosemide (FS) was obtained from PT. Kimia Farma Tbk, Jakarta, Indonesia. Pharmaceutical-grade magnesium stearate, lactose, talcum, and Manihot starch are obtained from PT. Brataco, Jakarta, Indonesia. Chemical materials such as acetic acid, acetone, sodium chloride, hydrochloric acid, potassium dihydrogen phosphate (KH_2PO_4), sodium hydroxide, and hydroxypropyl methylcellulose phthalate (HPMCP) are obtained from Merck, Darmstadt, Germany. Chitosan (CH) is derived from the solid waste of swallow shrimp (*Metapenaeus monoceros*) and obtained from Medan Industrial Estate, Medan, Indonesia.

Methods

Core tablet preparation

CH powder was placed into a porcelain cup, then an acetic acid 1% solution was added and stirred until it formed a gel. Next, lactose and FS were added to a mortar and ground until homogeneous. The CH gel was added to the mortar while continuously grinding until it formed a solid mass. This solid mass was granulated using a 10-mesh sieve, dried at a temperature of 60°C for 4 h, then re-granulated using a 12-mesh sieve, lubricated with talcum and magnesium stearate, and compressed into core tablets with a single punch machine (Erweka) with a diameter of 6 mm. The core tablets with the slowest release in medium pH 1.2, 5.8, and 7.4 were selected for coating film with HPMCP solution. Press-coated tablets consisted of a core and coated tablets that were compressed with a diameter of 10 mm. The press-coated tablet formula was shown in Tabel 1. These core tablets that exhibited controlled release were coated with HPMCP as a border.

Table 1. The Press-coated tablet formula

Component		Formula				
		A	**B**	**C**	**D**	**E**
Core tablet (mg)	Furosemide (FS)	65	65	65	65	65
	Chitosan (CH)	-	5	20	40	60
	Lactose	62	57	42	22	2
	Talcum	2	2	2	2	2
	Magnesium stearate	1	1	1	1	1
Coated tablet (mg)	Furosemide (FS)	35	35	35	35	35
	Chitosan (CH)	10	10	10	10	10
	Lactose	20	20	20	20	20
	Talcum	300	300	300	300	300
	Magnesium stearate	3	3	3	3	3
	Furosemide (FS)	2	2	2	2	2
Total Mass (mg)		500	500	500	500	500

Coated tablet granule preparation

CH powder was placed into a porcelain cup, then an acetic acid 1% solution was added and stirred until it formed a gel. Lactose, starch, and FS were placed into the mortar and ground until homogeneous. The CH gel was added to the mortar while continuously grinding until homogeneous, forming a compact mass. This compact mass was granulated using a 10-mesh sieve, dried in an oven at 60°C for 4 h, and then re-granulated using a 12-mesh sieve, lubricated with talcum and magnesium stearate. The coated tablet granule was used for bottom and top coating on a press-coated tablet, and the formulation was provided in Table 1.

Coating of the core tablet

2.0 g of HPMCP were dissolved in 50 mL of acetone. The core tablets were dipped into the HPMCP solution three times and then dried in an oven at 50°C for 30 min.

Press-coated tablet manufacturing

160 mg of the coated granules (bottom coated) were loaded into the die, and then the core tablet was placed on the granule surface in the center. After that, 160 mg of the coated granules (top coated) were put into the die and then compressed into Press-coated tablets using a single punch machine (Erweka). Each formulation was conducted using the same method.

Dissolution Medium Manufacturing

The dissolution medium was manufactured without enzymes, following the method outlined in the Indonesian Pharmacopoeia Edition IV. In the production of the artificial gastric medium, 2.0 g of sodium chloride (p) was dissolved in 7.0 mL of hydrochloric acid (p), after which the pH was adjusted to 1.2 by the addition of hydrochloric acid (p) and subsequent dilution with distilled water to achieve a total volume of 1000 mL. For the artificial duodenum medium, a mixture of 250 mL of potassium dihydrogen phosphate 0.2 M and 18 mL of sodium hydroxide 0.2 N was prepared and diluted with sufficient free water carbon dioxide to make a total volume of 1,000 mL. Similarly, the artificial small intestine medium was created by placing 250 mL of potassium dihydrogen phosphate 0.2 M into a volumetric flask containing 195.5 mL of sodium hydroxide 0.2 M, followed by dilution with water to 1,000 mL. The pH of this solution was measured as 7.4 using a pH meter.

Evaluation of furosemide press-coated tablet

The CH matrix FS preparations were assessed for tablet hardness, friability, and disintegration employing a Hardness Tester (Strong Cobb, Erweka), Friabilator (Roche, Erweka), Disintegration Tester (Copley), and dissolution (Dissolution Tester, Erweka).

Dissolution studies

The dissolution test was carried out using a type 2 dissolution apparatus (paddle), with a medium of 900 mL pH 1.2 (artificial gastric medium), 5.8 (artificial duodenum medium), and 7.4 (artificial small intestine medium), temperature 37 ± 0.5 ºC with a rotation speed of 50 rpm. At certain time intervals of 0.08, 0.25, 0.50, 0.75, 1, 2, 4, 5, 6, 7, and 8 h, 5.0 mL samples were taken and replaced with an equal medium solution to keep the volume constant. Dissolution tests in simultaneous medium were browned for 0-2 h in the artificial stomach medium, 2-6 h in the artificial duodenum medium, and 6-16 h in the artificial intestinal fluid. The sample solution was filtered and analyzed with spectrophotometry (UV Probe 1800 Shimadzu, λ = 276 nm). The FS release was calculated using the regression equation. The replications of this FS release are carried out six times.

Drug release kinetics analysis

The kinetic model was extensively utilized to analyze controlled tablet matrix drug release (Damodharan, 2020; Moroney & Vynnycky, 2021). Dissolution data were utilized to ascertain the release kinetics models, encompassing zero-order, first-order, Higuchi, and Korsmeyer-Peppas models (Arafat et al., 2021; Damodharan, 2020; Moroney & Vynnycky, 2021; Suprianto, 2016).

RESULT AND DISCUSSION

Evaluation of furosemide tablets

The press-coated tablets were prepared by the wet granulation method. Press-coated tablets were tested for content uniformity, weight, hardness, friability disintegration, and dissolution. The results are shown in Table 2. The tablets provided physical content that met the Indonesian Pharmacopoeia edition IV requirements regarding the uniformity of content, weight, hardness, friability, disintegration, and dissolution. The results showed that increasing the concentration of CH led to a significant decrease ($p<0.05$) in hardness, disintegration time, and an increase in tablet friability. The volume of glacial acetate solvent 1 % used to develop chitosan remains constant, so the higher the chitosan level, the less perfect the chitosan development, so the binding capacity decreases. As a result, hardness also decreases,

and disintegration time increases. The concentration of chitosan that can bind the mass well was 20 mg in formula C because chitosan expands perfectly in 1% acetic acid so that it could bind the mass well. While Formulas D and E contain 40 mg and 60 mg chitosan, the chitosan did not expand completely, and the ability of binding capacity decreased (Aranaz et al., 2021; Pardo-Castaño & Bolaños, 2019).

Table 2. Evaluation results data of tablet formulations

Formula	Hardness (n=5)	Weight (n=20)	Friability (n=20)	Disintegration (n=6)	Drug content (n=10)
A	5.05 ± 0.130	501.2 ± 0.130	0.45 ± 0.020	0.92 ± 0.021	98.93 ± 0.108
B	4.50 ± 0.100	499.4 ± 0.090	0.42 ± 0.006	0.75 ± 0.018	99.31 ± 0.121
C	4.11 ± 0.020	500.7 ± 0.050	0.35 ± 0.008	0.63 ± 0.015	101.02 ± 0.106
D	4.05 ± 0.150	498.5 ± 0.170	0.31 ± 0.013	0.34 ± 0.008	98.87 ± 0.112
E	3.97 ± 0.090	501.9 ± 0.240	0.20 ± 0.002	0.28 ± 0.005	99.29 ± 0.103

Furosemide release profile of Press-coated tablet

The analysis of FS release from press-coated tablet which uncoated core tablet was depicted in Figure 1 (1). FS delineates a swifter release from the coated tablet than the core tablet under a pH 1.2 medium. So that the coated tablet functions as an initial dose, while FS in the core tablet functions as a maintenance dose, ensuring a continuous drug release from the Press-coated tablet. Press-coated tablet with a coated tablet contains CH and starch, renowned for their swelling properties, facilitating easy breakdown into particles and hastening FS solubility. The FS released from the press-coated tablet, which the core tablet coated with HPMCP shown in Figure 1 (2), which elucidates how the HPMCP coating modifies the FS release pattern from the Press-coated tablet by reducing the quantity of FS released from the core tablet with CH as matrix and the HPMCP as film-coated.

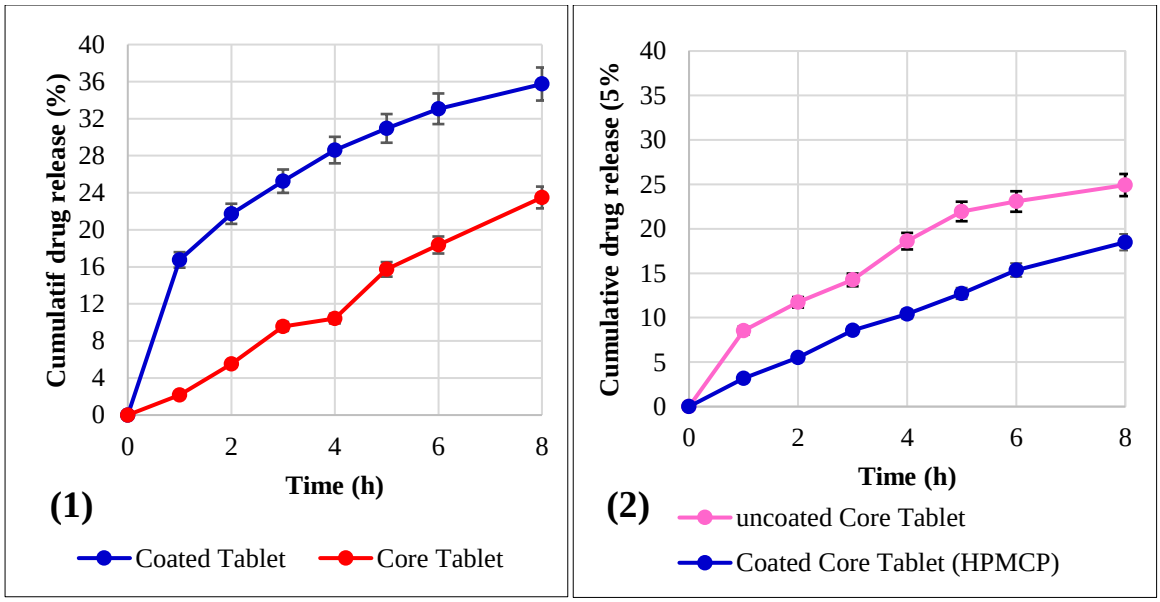

Figure 1. FS release from coated and core tablets uncoated (1), uncoated and coated core tablets (2)

The press-coated tablet consists of a core and a coated tablet. The core tablet was uncoated and coated with HPMCP. The core tablet in formula C showed the best-controlled release at pH 1.2 (Figure 2 (1)), 5.8 (Figure 3 (1)), and 7.4 (Figure 4 (1)), so it was chosen to be film coated with HPMCP.

Figure 2 (1) and Figure 2 (2) delineate the FS release profile from the CH matrix in a pH 1.2 medium. These figures explicate that with an elevation in CH concentration, FS release intensifies owing to the expansion of CH in the acidic pH 1.2 environment (Li et al., 2021; Moradi et al., 2023). Figure 2 (2) exhibits a relatively higher FS release than Figure 2 (1), attributed to the presence of FS in the coating formula, prompting immediate tablet disintegration and FS dissolution. The escalated CH concentration in the core tablets accelerates FS release as CH swells in the acidic pH 1.2 medium.

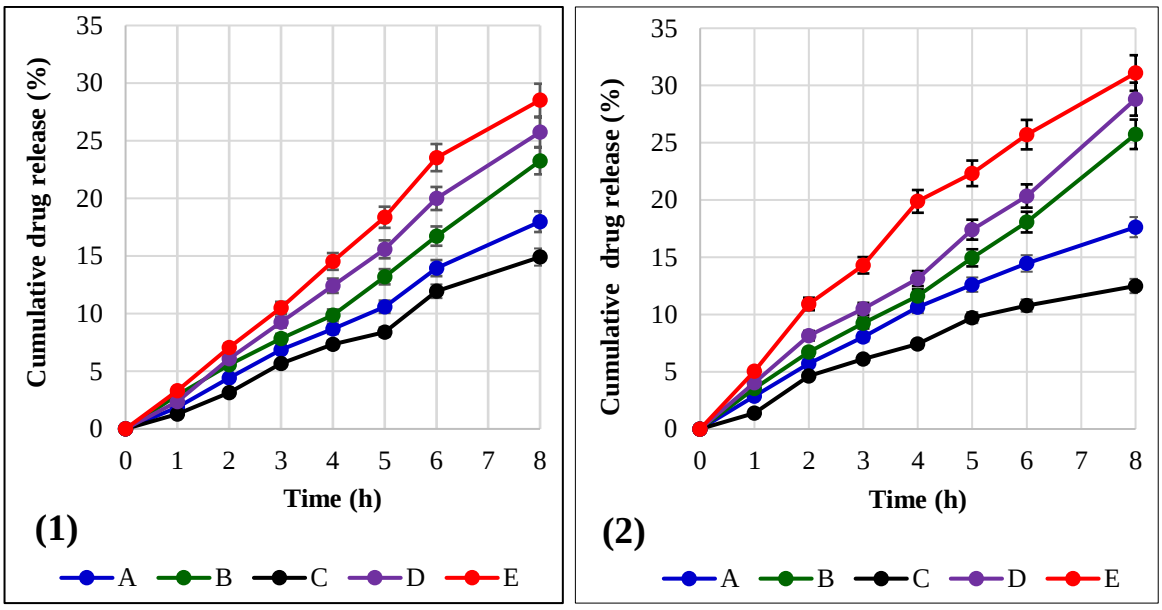

Figure 2. FS release of core tablet (1) and press-coated (2) in medium pH 1.2

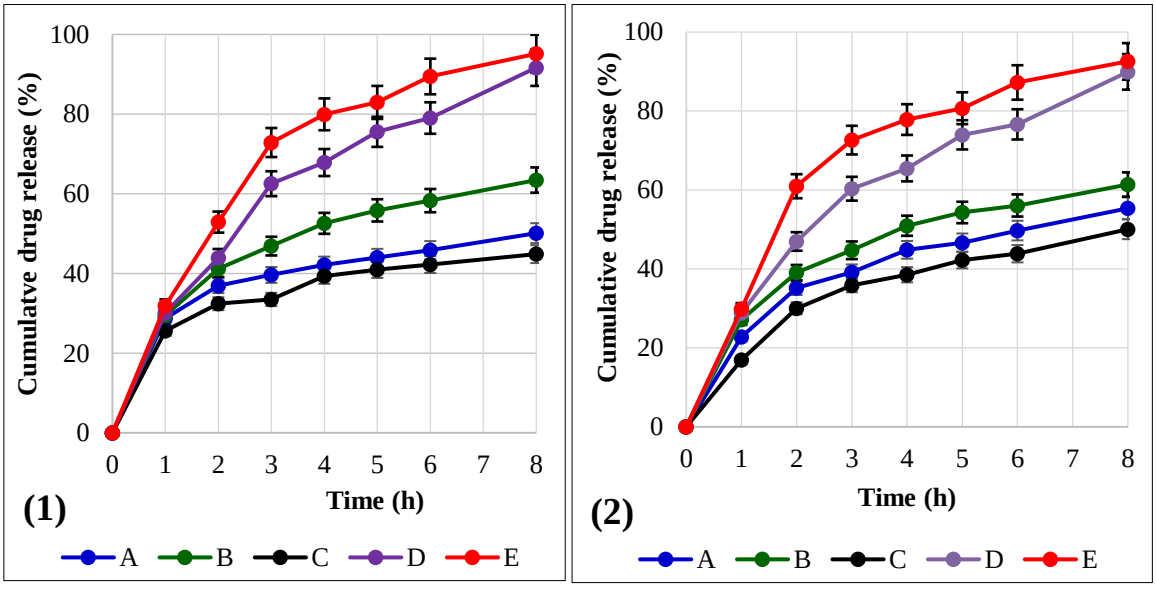

Figure 3. FS release of core tablet (1) and press-coated (2) in medium pH 5.8

Figure 3 (1) and Figure 3 (2) portray the FS release pattern from the CH matrix in a pH 5.8 medium. These figures manifest that higher CH concentrations correspond to faster FS release at pH 5.8 compared to pH 1.2. Elevated CH concentrations expedite FS release due to augmented swelling power, resulting in rapid tablet disintegration into particles and FS liberation. Prior studies have also highlighted CH's disintegrating properties (Moradi et al., 2023; Shiyan et al., 2021), underscoring that increased CH content augments tablet disintegration into particles, facilitating FS release into the dissolution medium. Conversely, formula A core tablets lacking CH and developer exhibit slower FS dissolution due to limited fluid penetration. Formula C core tablets coated with HPMCP exhibit the slowest dissolution rate. HPMC effectively constrains FS release from the CH matrix employed in the formula. The distinction in release profiles between the core tablet and the pre-coated tablet emanates from the release of a charged dose in pre-coated tablets before expansion, inducing the protective tablet to fragment into particles, thereby augmenting FS dissolution, giving the impression that pre-coated tablets release more FS.

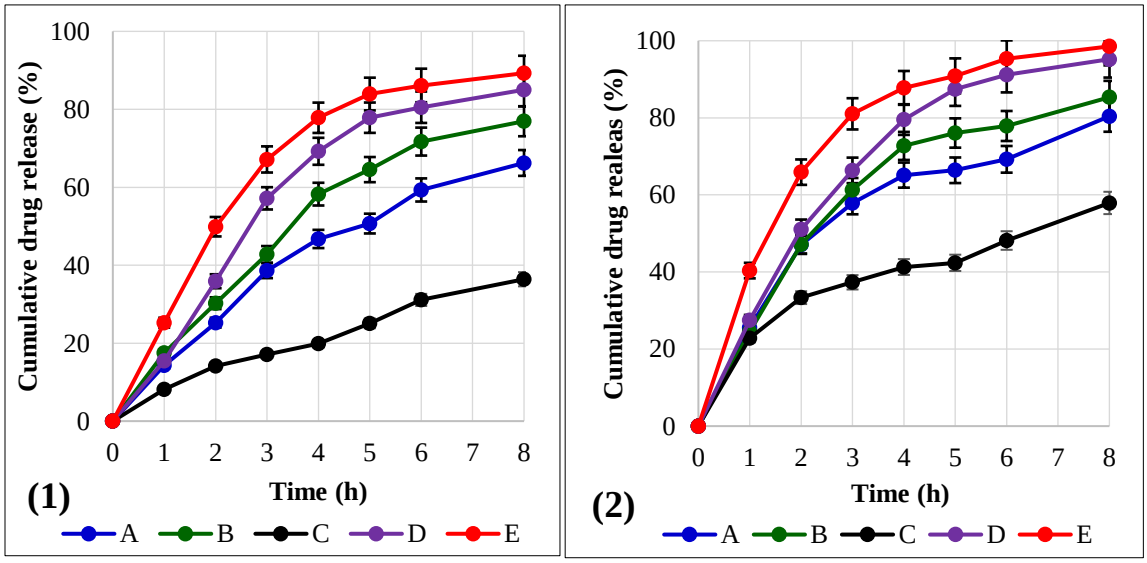

Figure 4. FS release of core tablet (1) and press-coated (2) in medium pH 7.4

Figure 4 (1) and Figure 4 (2) illustrate the FS release profile from the CH matrix at pH 7.4. These figures explicate that an augmented CH concentration expedites FS release due to heightened swelling power, leading to rapid tablet disintegration into particles and FS dissolution in the dissolution medium. Previous studies have emphasized CH's role as a disintegrant (Anisa et al., 2022; Shiyan et al., 2021), signifying its contribution to tablet disintegration into particles poised for FS release into the dissolution medium.

Effect of medium pH on drug release

The drug release profile consisted of commercial press-coated tablet, coated tablet, and core tablet film coated with HPMCP in the pH of medium simultaneous pH 1,2; 5,8 and 7,4 was depicted in Figure 5.

The observed trend indicates that the release of FS at pH 5.8 and 7.4 surpasses the release at pH 1.2. This behavior was attributed to FS being a weak acid (with a pKa of 3.9), resulting in limited solubility in an acidic medium like pH 1.2. Conversely, FS demonstrates enhanced solubility in a slightly acidic medium (pH 5.8), facilitating its release as the HPMCP expands without hindering FS dissolution. At pH 7.4, FS displays significantly high solubility, yet the expansion of HPMCP marginally restrains the dissolution process. These findings are consistent with previous research utilizing CH as a matrix, where

the release of the drug at pH 1.2 was slower compared to pH 6.8 (Shiyan et al., 2021; Suprianto, 2016). Figure 5 illustrates the minimal release of FS in C-coated HPMCP when subjected to simultaneous dissolution in an acidic medium. The coating aims to safeguard the core tablet from degradation within the intestine.

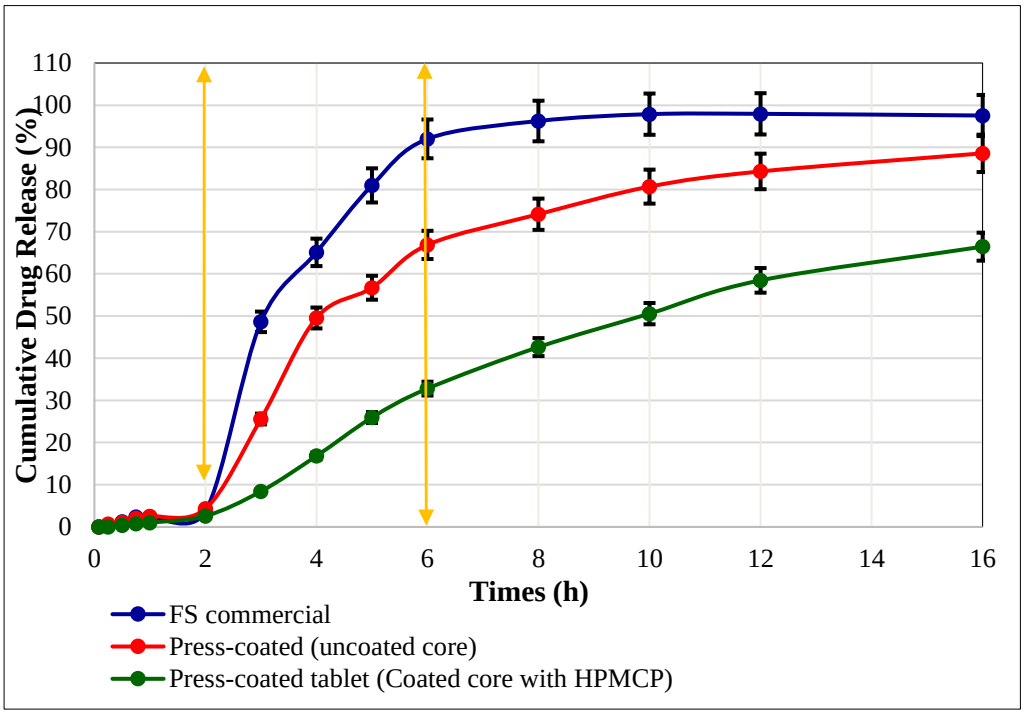

Figure 5. FS release of Furosemide commercial, Press-coated tablet with uncoated core tablet and Press-coated tablet with film coated core tablet in simultaneous medium pH 1.2, 5.8, and 7.4

Drug release kinetics in three mediums

The comprehensive analysis of FS release kinetics from the CH matrix across three different mediums is presented in Table 3, encompassing zero, first, and Higuchi order models alongside Korsmeyer-Peppas models. FS release kinetics was determined at intervals of 0-2, 2-6, and 6-16 h. The correlation coefficients of each model serve as pivotal indicators for determining the FS release kinetics model from the CH Matrix (Arafat et al., 2021; Damodharan, 2020; Suprianto, 2016). Furthermore, Formula C, constituting a core tablet coated with HPMCP, exhibits an unpredictable kinetic model across acidic (pH 1.2), slightly acidic (pH 5.8), and basic (pH 7.4) mediums, conforming to first-order models, Higuchi, and Higuchi, respectively. The coating process does not guarantee mastery over the kinetic model's consistency across various dissolution mediums, as it remains contingent upon the physicochemical properties of the adjuvant utilized within the tablet matrix (Qu & Luo, 2020; Yadav et al., 2021). Notably, except for formula D, the kinetic model governing FS release from the CH matrix in a pH 7.4 medium predominantly adheres to Higuchi's order.

Release kinetics on simultaneous medium

The kinetic model governing the release of FS from the CH matrix in the simultaneous medium is detailed in Table 4. This determination of the kinetic model stems from a comprehensive assessment of correlation coefficients associated with each model, as established in prior studies (Damodharan, 2020;

Moroney & Vynnycky, 2021; Suprianto, 2016). Additionally, this determination is based on the time span analysis, which correlates with the transit time within the gastrointestinal tract (Kali et al., 2022).

During the initial 0-2 hour period, the release of FS from both CH and commercially available matrix tablets at pH 1.2 exhibited no discernible difference. This lack of differentiation arises due to the significantly low solubility of FS at pH 1.2, which is attributed to its nature as a weak acid (pKa = 3.9) (Soni et al., 2021). Consequently, the FS dissolution assay conducted at pH 1.2 was extended for 2 hours, aligning with an approximate transit time of 2 hours within the stomach (Kali et al., 2022). The findings in Table 4 illustrate that the kinetics governing drug release within the 0-2 hour window adhere to the Higuchi, Korsmeyer-Peppas, and zero-order models for each respective product.

The dissolution test conducted on FS in a simultaneous medium at pH 5.8 for 4 hours corresponds to the anticipated drug transit time within the intestine, estimated between 2 to 6 hours. Analysis of the release profile revealed that the C-coated formulation exhibited a notably slower release rate than other variants, indicating that HPMCP coating impeded FS release from the CH matrix (Kali et al., 2022). Conversely, the non-coated C formulation showed a faster release, solely relying on the ability of CH to expand and diffuse FS into the dissolution medium, albeit still slower than the release rate of commercial FS. HPMCP C-coated tablets exhibit insolubility in the pH 5.8 medium; however, FS release occurs due to the formation of pores by HPMCP, allowing liquid penetration into the tablet's core and subsequent dissolution of FS. The FS release kinetics primarily followed first-order kinetics, except for the C-coated tablets, which exhibited zero-order kinetics, indicating a constant release rate of FS at pH 5.8 from these specific tablets, as detailed in Table 4. During 6 to 16 hours, the release of FS from CS matrix tablets was observed in a simultaneous medium at pH 7.4. Figure 5 highlights the absence of FS release from commercial tablets, while uncoated and HPMCP-coated CH matrix tablets exhibited FS release in the study. Notably, the dissolution rate of coated C was slower than that of non-coated C, underscoring the substantial role played by HPMCP coating in facilitating FS release from the tablets. Further insights into release kinetics are provided in Table 4. Moreover, at pH 7.4 in the simulated medium, both types of tablets exhibited first-order release kinetics. It emphasizes that the release of FS depends not only on the matrix components and HPMCP coating employed in the preparation of controlled formulations but also on the concentration of FS within the tablet a critical factor influencing release behavior (Shiyan et al., 2021; Soni et al., 2021).

Table 3. Model of drug release kinetics in three medium

pH	Formula	Correlation coefficient (R)				Kinetic Model
		N	S	H	K	
1.2	A	0.9862	0.9919	0.9512	0.9959	K
	B	0.9946	0.9874	0.8911	0.9942	N
	C	0.9668	0.9722	0.9427	0.9485	S
	D	0.9946	0.9879	0.8995	0.9924	N
	E	0.9785	0.9906	0.9560	0.9884	S
5.8	A	0.6793	0.8920	0.9769	0.9707	H
	B	0.7788	0.8920	0.9728	0.9807	K
	C	0.7016	0.9003	0.9797	0.9468	H
	D	0.8073	0.9817	0.9926	0.9793	
	E	0.8344	0.9765	0.9522	0.8849	S
7.4	A	0.8295	0.9519	0.9726	0.9313	
	B	0.8367	0.9638	0.9667	0.9296	H
	C	0.8533	0.9289	0.9835	0.9753	
	D	0.8534	0.9638	0.9711	0.9474	
	E	0.7511	0.9955	0.9473	0.9164	S

Notes: Zero order (N); First Order (S); Order of Higuchi (H); Order of Korsmeyer-Peppas (K)

Table 4. Release kinetics model of chitosan matrix tablet FS on simultaneous medium

pH	Formula	Correlation coefficient (R)				Kinetic Model
		N	S	H	K	
1.2	A	0.9862	0.9919	0.9512	0.9959	K
	B	0.9946	0.9874	0.8911	0.9942	N
	C	0.9668	0.9722	0.9427	0.9485	S
	D	0.9946	0.9879	0.8995	0.9924	N
	E	0.9785	0.9906	0.9560	0.9884	S
5.8	A	0.6793	0.8920	0.9769	0.9707	H
	B	0.7788	0.8920	0.9728	0.9807	K
	C	0.7016	0.9003	0.9797	0.9468	H
	D	0.8073	0.9817	0.9926	0.9793	
	E	0.8344	0.9765	0.9522	0.8849	S
7.4	A	0.8295	0.9519	0.9726	0.9313	
	B	0.8367	0.9638	0.9667	0.9296	H
	C	0.8533	0.9289	0.9835	0.9753	
	D	0.8534	0.9638	0.9711	0.9474	
	E	0.7511	0.9955	0.9473	0.9164	S

Notes: Zero order (N); First Order (S); Order of Higuchi (H); Order of Korsmeyer-Peppas (K)

CONCLUSION

The HPMCP-coated and non-coated CH matrix core tablets exhibit promising potential as controlled preparations with planned release. Release kinetics analysis indicates that the non-coated CH matrix core tablets follow a first-order release pattern at pH 5.8 and pH 7.4 within the periods of 2-6 hours and 6-16 hours, while at pH 1.2 within the initial 0-2 hours, the release switches to zero order. On the other hand, the HPMCP-coated CH matrix core tablets demonstrate more complex release kinetics, following the Korsmeyer-Peppas order pattern at pH 1.2 in the initial 0-2 hours, then transitioning to zero order and first order within the periods of 2-6 hours and 6-16 hours. At pH 5.8 and 7.4, the release follows zero order and first order sequentially across various periods. These findings depict the potential application of these tablets in controlled drug delivery with tailored release profiles adaptable to different environmental conditions and time requirements.

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