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Validation of spectrophotometric method to quantify cabotegravir in simulated vaginal fluid and porcine vaginal tissue in *ex vivo* permeation and retention studies from thermosensitive and mucoadhesive gels

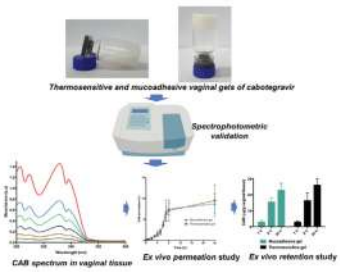
Sulistiawati [a], Cindy Kristina Enggi [a], Hansel Tridatmojo Isa [a], Stevens Wijaya [b], Komang Agus Rai Ardika [a], Rangga Meidianto Asri [a], Ryan F. Donnelly [c], Andi Dian Permana [a,*]

[a] Faculty of Pharmacy, Hasanuddin University, Makassar 90245, Indonesia
[b] Faculty of Medicine, Hasanuddin University, Makassar 90245, Indonesia
[c] School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, United Kingdom

HIGHLIGHTS

- Spectrophotometric method to quantify cabotegravir was developed.
- The analytical method was validated according to ICH guidelines.
- The validated method was applied in *in vitro* study and *ex vivo* vaginal delivery.

GRAPHICAL ABSTRACT



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ABSTRACT

Cabotegravir (CAB) is an antiretroviral therapy (ARV) used for Human Immunodeficiency Virus (HIV) treatment. CAB has low solubility, which affects its bioavailability in oral therapy. Moreover, the injection form of CAB has difficulty in the administration process. Therefore, it is essential to develop a new drug delivery system for CAB. Vaginal drug delivery system offers many advantages such as a large surface area, increased drug bioavailability, and improved drug delivery. CAB was developed in thermosensitive and mucoadhesive vaginal gel preparations that provided optimal distribution in the vaginal mucosa. To support the process of formulation development, in this study, UV–visible spectrophotometry method was validated in methanol, simulated vaginal fluid (SVF) and vaginal tissue to quantify the amount of CAB in the gel preparations, *in vitro*, and *ex vivo* studies, respectively. The developed analytical method was subsequently validated according to ICH guidelines. The calibration curves in these matrices were found to be linear with correlation coefficient values (R^2) ≥ 0.998. The LLOQ values in methanol, SVF and vaginal tissue were 2.15 μg/mL, 2.22 μg/mL, and 5.13 μg/mL, respectively. The developed method was found to be accurate and precise without being affected by dilution integrity. These methods were successfully applied to quantify the amount of CAB in gel preparations, *in vitro*, and *ex vivo* studies, showing uniformity of drug content and controlled release manner in the permeation profile for 24 h for both thermosensitive and mucoadhesive vaginal gels. Further analytical method is required to be developed for the quantification of CAB in *in vivo* studies.

* Corresponding author at: Faculty of Pharmacy, Hasanuddin University, Indonesia.
E-mail address: andi.dian.permana@farmasi.unhas.ac.id (A.D. Permana).

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1. Introduction

botegravir (CAB) is known as an HIV-1 integrase inhibitor, f the antiretroviral medications for HIV patients. It is catego- as Biopharmaceutics Drug Disposition Classification System S) II, which has low solubility and high permeability, affect- e absorption of the drug [1,2]. It has been reported that the lity of CAB in the aqueous solution is limited to 4.8 μg/mL urthermore, the log P value of CAB is 1.04 [4]. Currently, available in tablet and injection forms. However, following dministration, many HIV patients were found to develop oral diasis, causing difficulty in swallowing. [5]. On the other the long-acting injectable form of CAB also possesses several tions. Despite having less frequency of administration, CAB ion needs to be administered by healthcare professionals. onally, the injection form is not comfortable and painful, could lead to a decrease in the patient compliance to the ations [6].

order to increase patient compliance and obtain sustained delivery, in this study, CAB was separately developed in the of thermosensitive and mucoadhesive vaginal gels. Ther- nsitive dosage forms would enable easy administration due liquid form of the formulation, which would transform to olid form in the vaginal temperature [7]. Furthermore, the adhesive preparations offer the advantage, mainly due to bility to prolong the contact of the drugs in the vaginal tissue e delivery of CAB through vaginal delivery can be an alterna- herapy as it provides various advantages, including large sur- area and rich blood supply, resulting in higher drug ailability. Importantly, due to the presence of receptors and eptors of HIV, such as CD4+ T cells and CCR5, vagina is the route of HIV infection [9]. Therefore, vaginal administration B could be an alternative delivery approach for the treatment revention of HIV.

ug detection and quantification are essential parts of the opment of novel drug delivery systems. Accordingly, an priate analytical method is crucial to be developed for this se. In this study, calculation of drug content in the formula- and measurement of drug concentration in *in vitro* and *ex vivo* s were critical evaluations during the development of CAB osensitive and mucoadhesive vaginal gels. *In vitro* studies initial step to evaluate drug release behavior using a suitable e medium. Besides, *ex vivo* studies are performed using tis- from organisms by mimicking natural conditions. *Ex vivo* s are advantageous for evaluating the drug behavior in speci- ans/tissues as they can eliminate other physiological factors, ing in more controlled conditions compared to living organ- This indicates the importance of *ex vivo* experiments before eding to *in vivo* studies [10]. As the gel was intended for vagi- plication, the concentration of CAB was measured both in the ated vaginal fluid (SVF) and vaginal mucosa. To the best of nowledge, analytical methods to quantify CAB in both of these have not been reported previously. Various analytical meth- ave been developed to quantify CAB in various matrices, ling HPLC-UV [11] and HPLC-MS/MS [3]. However, the ed methods are expensive, time-consuming and require sticated equipment and, thus, are difficult to apply in the e- and low-income countries/laboratories. On the other hand, sible spectrophotometer for CAB detection and quantifica- n *in vitro* and *in vitro* studies would be promising due to its city, cost-effectiveness and high adaptability in small labora- Therefore, in the present study, for the first time, CAB quan- ion methods were developed in SVF and vaginal mucosa a UV–visible spectrophotometer. Several previous studies reported the ability of UV–visible spectrophotometer in quantifying numerous types of drugs in both *in vitro* and *ex vivo* studies [12,13]. Following the development of analytical proce- dures, method validation must be carried out to ensure reliability, traceability, and comparability of the results.

This study aimed to develop and validate analytical methods of CAB in thermosensitive and mucoadhesive vaginal gels using a UV–Visible spectrophotometer. The developed analytical method was subsequently validated according to the International Conference Harmonization (ICH) guidelines. Linearity, accuracy, precision, limit of detection (LOD), limit of quantification (LOQ) were established. The validated method was finally applied to determine the drug content in vaginal preparations, as well as the *in vitro* and *ex vivo* permeation profiles.

2. Materials and methods

2.1. Materials

Cabotegravir (CAB) was kindly provided by ViiV Healthcare Ltd. (Research Triangle Park, NC, USA). Pluronic® F127 and F68 were kindly gifted by BASF Indonesia, Jakarta. Other materials were analytical grade.

2.2. Preparation of simulated vaginal fluid

Simulated vaginal fluid (SVF) was prepared by weighing 5 g of glucose, 0.4 g of urea, 3.51 g of NaCl, 2 g of lactic acid, 1.4 g of KOH, 1 g of acetic acid, 0.22 g of $Ca(OH)_2$, and 0.016 g glycerin. Deionized water (800 mL) was added to dissolve the mixture, and the pH was adjusted to 4.2 [14]. Deionized water was then added to obtain 1 L of SVF. In this study, as SVF was used in the *in vitro* and *ex vivo* permeation studies, 20% v/v of methanol was added into SVF to achieve the sink condition during the experiment.

2.3. Preparation of CAB stock solution

An amount of 10 mg of CAB was carefully weighed and placed into a 10 mL volumetric flask. Afterwards, methanol was added to dissolve CAB, obtaining the concentration of 1000 μg/mL.

2.4. Determination of maximum UV light absorption wavelength, preparation of calibration standards and quality control samples

The maximum UV light absorption wavelength was determined using a UV–Visible spectrophotometer (Dynamica, HALO XB-10). CAB solutions, with the concentration of 50 μg/mL, in methanol (CAB-MeOH) and SVF (CAB-SVF) were scanned between 200 and 400 nm at room temperature. Furthermore, the calibration solutions were prepared in six different concentrations in triplicate in the range concentration between 0.5 μg/mL and 16 μg/mL by spiking the stock solution with methanol and SVF. In addition, quality control (QC) samples were prepared using each solvent in four different levels, namely lower limit of quantification (LLOQ), low quality control (LQC), medium quality control (MQC), and high quality control (HQC). For CAB-MeOH, the QC samples included LLOQ – 2.15 μg/mL, LQC – 4 μg/mL, MQC – 7.5 μg/mL, and HQC – 12 g/mL. For CAB-SVF, the QC samples were LLOQ – 2.2 μg/mL, LQC – 4 μg/mL, MQC – 7.5 μg/mL, and HQC – 12 μg/mL. All samples were prepared and measured in triplicate.

To prepare the calibration standards of CAB in vaginal tissue (CAB-VT) for *ex vivo* studies, fresh vaginal tissue of porcine was used. Vaginal mucosa matrices were initially prepared by mixing vaginal tissue with deionized water (9:1) using UltraTurrax

homogenizer for 10 min. The calibration standard solutions were made by mixing 200 mL of drug stock solutions into 1.8 g of blank vaginal matrices to obtain the concentrations in the range of 1 μg/mL – 32 μg/mL. In addition, Quality Control (QC) samples in vaginal tissue include LLOQ – 5.13 μg/mL, LQC – 7.5 μg/mL, MQC – 15 μg/mL, and HQC 24 μg/mL were prepared.

2.5. Sample preparation and CAB extraction from vagina samples

The preparation of the vaginal mucosa sample was carried out to precipitate proteins and other molecules in the organ to avoid any interferences during the measurement. The CAB extraction method was performed using methanol and acetonitrile. The volumes of methanol and acetonitrile used to extract the drug were varied, as shown in Table 1. Initially, 1 g of the matrices-spiked CAB were mixed with the extraction solvent. The mixture was then homogenized for 10 min using a vortex mixer and centrifuged for 15 min, 14000 × g. The supernatant obtained was then placed at room temperature to allow the evaporation of the organic solvent. Finally, 1 mL of methanol was added to reconstitute the dry extract, homogenized, and centrifuged as previously mentioned. The supernatant obtained was then measured using spectrophotometry UV–visible.

2.6. Preparation of thermosensitive and mucoadhesive vaginal gels

CAB thermosensitive gel was prepared by dissolving 16% w/w of Pluronic® F127 and 4% w/w of Pluronic® F68 in cold water using a magnetic stirrer to produce a gel base. Then, 1% w/w of CAB was dispersed in 5% w/w of (poly(ethylene glycol) (PEG) 400 before being added into the gel base. Finally, after all mixtures were homogenous, 0.1% w/w of DMDM hydantoin was added into the mixture and homogenized for 15 min at 1000 rpm.

CAB mucoadhesive gel was prepared by hydrating 0.5% w/w of Carbopol 940 in distilled water for 24 h. Afterwards, 2% w/w of triethanolamine (TEA) was added into Carbopol 940, and the mixture was homogenized for 15 min, 1000 rpm to obtain a gel base. The 1% w/w of CAB was first dispersed in 5% w/w of PEG 400 before being added into the gel base. After all mixtures were homogenous, 0.1% w/w of DMDM hydantoin was added into the mixture and homogenized for 15 min at 1000 rpm.

2.7. Validation of analytical method

2.7.1. Specificity

Specificity was determined by comparing the UV spectra of blank thermosensitive gel, mucoadhesive gel and vaginal tissue with appropriate CAB standard solution after scanning between 200 and 400 nm. This parameter was assessed to identify any possible interferences between the responses of the analyte and other compounds at the relevant wavelength.

Table 1
Volume of organic solvent for CAB extraction from vaginal samples.

Organic Solvent	Methods	Volume (mL)
Methanol	A	1
	B	3
	C	5
	D	7
Acetonitrile	A	1
	B	3
	C	5
	D	7

2.7.2. Linearity

Linearity was evaluated using six different concentrations of each CAB-MeOH, CAB-SVF and CAB-VT. The sample solutions were analyzed in triplicate using UV–Vis spectrophotometry at 276 nm for CAB-MeOH, 278 nm for CAB-SVF and 305 nm for CAB-VT. The calibration curve, which consisted of six different concentrations versus absorbance was analyzed to obtain the value of correlation coefficient (r^2), slope, and y-intercept [15].

2.7.3. Limit of detection (LOD)

LOD expresses the smallest concentration of analyte which can be identified in a sample [16]. LOD was determined by using Eq. (1), where sy is the standard deviation of the blank (without analyte) and b is the slope obtained from the regression equation of the calibration curve

$$\mathrm{LOD} = \frac{3.3\mathrm{sy}}{\mathrm{b}} \quad (1)$$

2.7.4. Lower limit of quantification (LOQ)

LLOQ is expressed as the smallest concentration of samples which can be determined accurately with satisfactory accuracy and precision [15]. LLOQ was determined by using eq. (2), where b is the slope obtained from the regression equation of calibration curve and sy is the standard deviation of the blank (without analyte) [17].

$$\mathrm{LLOQ} = \frac{10\mathrm{sy}}{\mathrm{b}} \quad (2)$$

2.7.5. Accuracy and precision

Accuracy and precision demonstrate the closeness to the reference value and degree of scattering between a series of measurements attained from numerous testing in an analytical method. These parameters were evaluated by intra-day and inter-day measurements of QC samples (HQC, MQC, LQC, and LLOQ). Percentage of relative error (%RE) and relative standard deviation (%RSD) were calculated to represent the values of accuracy and precision, respectively [18].

2.7.6. Dilution integrity

Dilution integrity was evaluated by preparing 75 μg/mL for both CAB-MeOH and CAB -SVF and 150 μg/mL for CAB-VT. Each of the solutions was diluted 5 and 10 times with appropriate solvents. The experiment was in triplicate and the absorbance of the analyte was observed [16].

2.7.7. Extraction recovery

The extraction recovery determination was conducted by comparing the values obtained from all samples at LLOQ, LQC, MQC, and HQC extracted from vaginal tissue with the measured values of the concentrations of the same samples (LLOQ, LQC, MQC, and HQC) [19].

2.8. Application of the analytical method

2.8.1. Drug content measurement

A total of 0.1 g of gel was dissolved in methanol up to 10 mL in a volumetric flask, obtaining a CAB concentration of 100 μg/mL. The solution was then diluted by taking 1 mL of the gel solution and diluted with methanol up to 10 mL. The absorbance of the final solution was determined using UV–Vis spectrophotometry at 276 nm. Measurements were performed in triplicate.

2.8.2. In vitro permeation, ex vivo permeation and ex vivo retention studies of CAB from thermosensitive and mucoadhesive gels

The permeation behavior of CAB from thermosensitive and

2.9. Statistical analysis

All data were expressed as means ± stan

3.3. Linearity, LOD, and LLOQ

In an attempt to assess the linearity and determine LOD and

erated by measuring a set concentration of the standard solutions of CAB in methanol, SVF and vaginal tissue, respectively, using the optimized UV–Vis spe

Table 3
Properties of the calibration curve for analysis of CAB with LOD and LLOQ values.

Matrices	Concentration range (μg/mL)	r^2	LOD (μg/mL)	LLOQ (μg/mL)
MeOH	0.5–16	0.9990	0.71	2.15
SVF	0.5–16	0.9989	0.74	2.22
Vaginal Tissue	1–32	0.9985	1.69	5.13

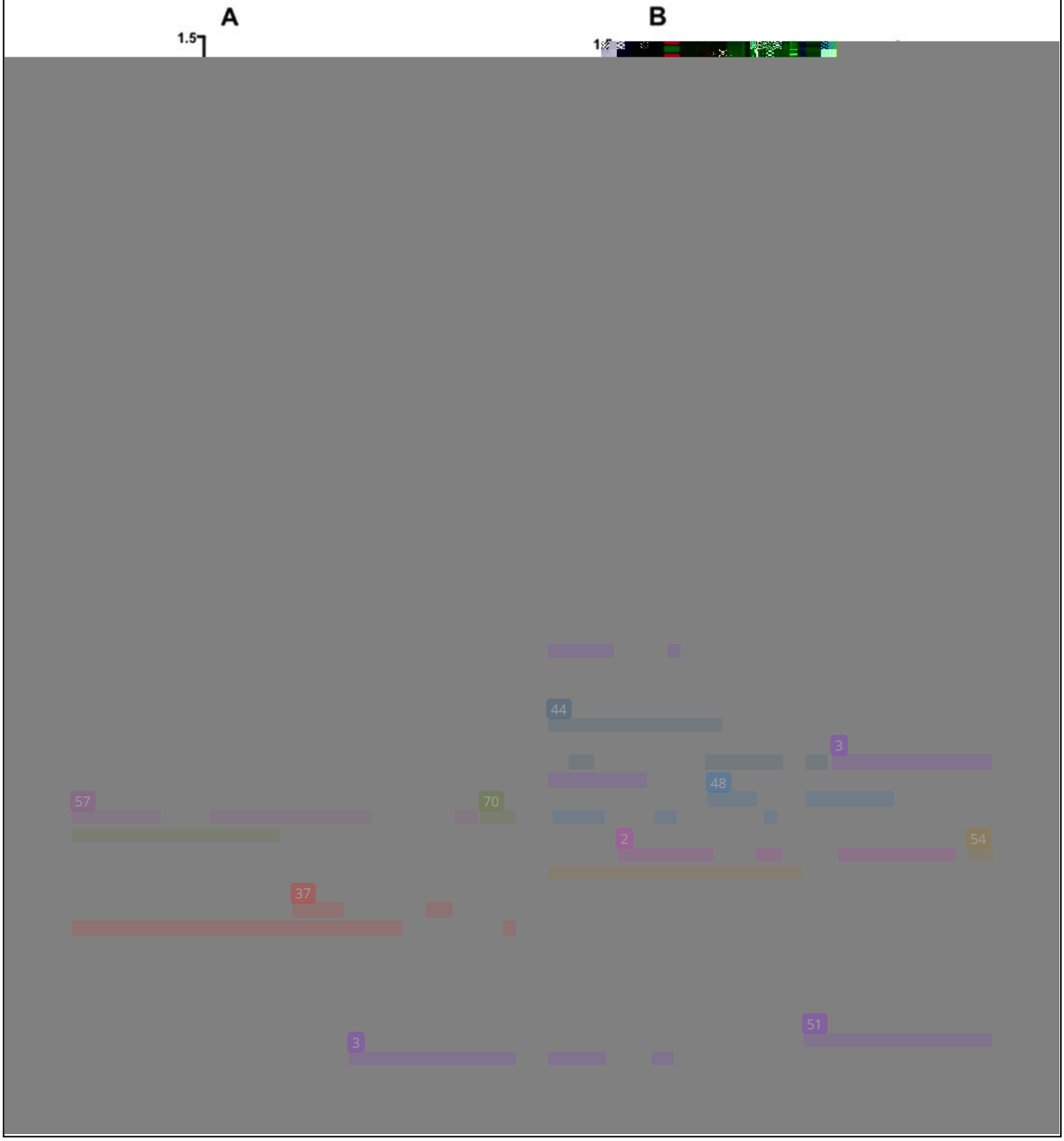

Table 4
The results of precision and accuracy evaluations of the UV–Vis spectrophotometry method for analysis of CAB in MeOH (mean ± SD, n = 3).

Intra-day Precision and Accuracy				
Replication	Concentration added (μg/mL)	Concentration found (μg/ mL) ± SD	Precision (%RSD)	Accuracy (%RE)
1	2.15	2.07 ± 0.10	4.63	−3.50
	4	3.91 ± 0.15	3.94	−2.19
	7.5	7.63 ± 0.11	1.39	1.76
	12	11.54 ± 0.18	1.53	−3.86
2	2.15	2.12 ± 0.12	5.87	−1.23
	4	4.13 ± 0.09	2.28	3.31
	7.5	7.71 ± 0.18	2.32	2.80
	12	12.19 ± 0.18	1.46	1.60
3	2.15	2.18 ± 0.08	3.56	1.28
	4	4.09 ± 0.18	4.51	2.33
	7.5	7.85 ± 0.12	1.52	4.63
	12	12.06 ± 0.48	3.95	0.50

Inter-day Precision and Accuracy				
Day	Concentration added (μg/mL)	Concentration found (μg/ mL) ± SD	Precision (%RSD)	Accu
1	2.15	2.41 ± 0.08	3.35	11.9
	4	4.23 ± 0.26	6.21	5.63
	7.5	7.50 ± 0.17	2.22	−0.0
	12	12.43 ± 0.35	2.81	3.56
2	2.15	2.10 ± 0.15	7.00	−2.3
	4	4.02 ± 0.24	5.86	0.62
	7.5	7.63 ± 0.09	1.15	1.76
	12	11.70 ± 0.39	3.34	−2.4
3	2.15	2.07 ± 0.12	5.78	−3.5
	4	3.99 ± 0.19	4.86	−0.3
	7.5	7.66 ± 0.41	5.32	2.09
	12	11.90 ± 0.38	3.16	−0.8

Table 5
The results of precision and accuracy evaluations of the UV–Vis spectrophotometry method for analysis of CAB in SVF (mean ± SD, n = 3).

Intra-day Precision and Accuracy				
Replication	Concentration added (μg/mL)	Concentration found (μg/ mL) ± SD	Precision (%RSD)	Accu
1	2.2	1.89 ± 0.14	7.37	−13.
	4	3.97 ± 0.08	2.00	−0.6
	7.5	7.43 ± 0.12	1.66	−0.9
	12	12.20 ± 0.10	0.83	1.64
2	2.2	2.31 ± 0.20	8.46	4.91
	4	4.05 ± 0.09	2.11	1.28
	7.5	7.48 ± 0.12	1.61	−0.2
	12	12.16 ± 0.18	1.45	1.33
3	2.2	2.28 ± 0.25	10.79	3.56
	4	4.15 ± 0.07	1.62	3.79
	7.5	7.68 ± 0.25	3.27	2.38
	12	12.10 ± 0.14	1.17	0.86

Inter-day Precision and Accuracy				
Day	Concentration added (μg/mL)	Concentration found (μg/ mL) ± SD	Precision (%RSD)	Accu
1	2.2	2.11 ± 0.15	6.92	−4.0
	4	3.97 ± 0.08	2.00	−0.6
	7.5	7.66 ± 0.37	4.80	2.18
	12	12.92 ± 0.39	2.98	7.66
2	2.2	2.09 ± 0.20	9.65	−5.0
	4	3.95 ± 0.14	3.49	−1.3
	7.5	7.86 ± 0.08	1.02	4.86
	12	12.65 ± 0.07	0.59	5.45
3	2.2	1.96 ± 0.08	4.04	−10.
	4	4.08 ± 0.08	1.92	1.93
	7.5	7.48 ± 0.10	1.29	−0.3
	12	12.14 ± 0.31	2.52	1.17

Table 6
The results of precision and accuracy evaluations of UV–Vis spectrophotometry method for analysis of CAB in vaginal tissue (mean ± SD, n = 3).

Intra-day Precision and Accuracy				
Replication	Concentration added (μg/mL)	Concentration found (μg/ mL) ± SD	Precision (%RSD)	Accuracy (%RE)
		25.19 ± 0.33		

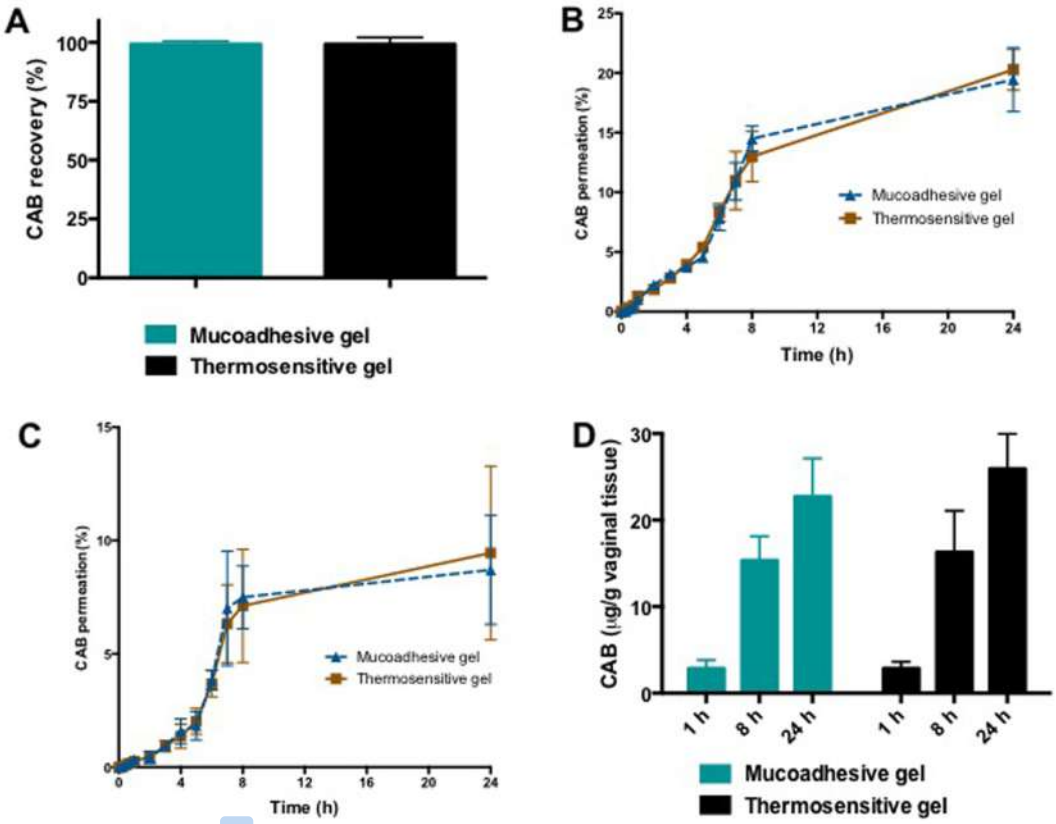

Fig. 4. (A) CAB recovery (%) from gels, (B) *In vitro* permeation profile of CAB from thermosensitive and mucoadhesive gel, (C) *Ex vivo* permeation profile of CAB from thermosensitive and mucoadhesive gel, (D) *Ex vivo* retention of CAB (mean ± SD, n = 3).

to explain CAB release behavior from both thermosensitive and mucoadhesive gels. For the *in vitro* permeation of CAB from the thermosensitive gel, the value of coefficient correlation was 0.8613, 0.8936, 0.8240, 0.9247, 0.8836 for ZO, FO, Higuchi, KP, and HC, respectively. For the *in vitro* permeation of CAB from the mucoadhesive gel, the value of coefficient correlation was 0.8116, 0.8461, 0.7977, 0.8850, 0.8354 for ZO, FO, Higuchi, KP, and HC, respectively. Furthermore, the *ex vivo* permeation study showed coefficient correlation values of 0.7794, 0.7939, 0.7338, 0.8318, 0.7892 for thermosensitive gel and 0.6838, 0.7015, 0.7036, 0.7689, 0.6957 for mucoadhesive gel for Zero order, First order, Higuchi, Korsmeyer Peppas, and Hixson-Crowell, respectively. The result obtained clearly showed that all formulations tested in the *in vitro* and *ex vivo* permeation studies followed Korsmeyer-Peppas kinetic models. This model has been used to describe drug release from the polymeric matrix based on relaxation and diffusion [27].

Based on the results obtained, the validated analytical methods using spectrophotometry UV–visible were successfully applied to determine the amount of CAB in the thermosensitive and mucoadhesive gels. Moreover, the methods were also be able to determine the concentration of CAB following *in vitro* and *ex vivo* permeation tests, as well as *ex vivo* retention tests. Moving forward, *in vivo* studies using suitable animal models for both types of gels are essential to be carried out to obtain pharmacokinetic and pharmacodynamic profiles of CAB.

4. Conclusion

This study was conducted to develop and validate spectrophotometry UV–visible methods for the analysis of CAB. The proposed method was validated in the parameter of selectivity, accuracy and precision, linearity, LOD and LLOQ, and dilution integrity, as well as extraction recovery of CAB and vaginal tissue. Additionally, the suitable extraction method of CAB from vaginal tissue was also determined. The results showed that all validation parameters were well-established and met the requirements of ICH guidelines. Moreover, the validated analytical method was successfully employed to evaluate the percentage recovery, permeation profiles, and retention of CAB following each appropriate study. In conclusion, the validated method was able to be used for various studies of CAB in thermosensitive and mucoadhesive gel formulations.

CRediT authorship contribution statement

A. Sulistiawati: Conceptualization, Methodology, Funding acquisition, Writing – original draft. **Cindy Kristina Enggi:** Methodology, Writing – original draft. **Hansel Tridatmojo Isa:** Methodology, Writing – original draft. **Stevens Wijaya:** Methodology, Data curation. **Komang Agus Rai Ardika:** Data curation, Validation. **Rangga Meidianto Asri:** Validation, Supervision. **Ryan F.**

Donnelly: Writing – review & editing, Project administration. **Andi Dian Permana:** Conceptualization, Writing – review & editing, Project administration, Funding acquisition, Validation, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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