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RESEARCH ARTICLE

Development and validation of dissolution testing of Flunarizine dihydrochloride in tablet dosage form

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Abstract

Background: Flunarizine dihydrochloride is an antivertigo, antimigraine, and adjunctive therapy for epilepsy, available in Indonesia as tablets. However, the dissolution test for the tablet dosage forms is not yet available in the Pharmacopoeia. **Objectives**: To develop and validate the dissolution method of flunarizine dihydrochloride in tablets. **Methods**: The dissolution profiles of three products were determined using three media (HCl 0.1N, acetate buffer pH 4.5, and 0.2% Tween 80 solution); two apparatus (basket and paddle); at three agitation speeds (50, 75, and 100rpm). The amount of drug released per unit time was measured by a validated High Performance Liquid Chromatography system. **Results**: The method using a paddle apparatus at 50rpm in 900mL of 0.1N HCl medium was better hyperdiscriminating with a Q30 value ≥ 75% ($p < 0.05$). The selected method met the acceptance criteria in terms of precision, accuracy, and specificity.

Introduction

Flunarizine HCl (1- [bis (4-fluorophenyl) methyl] -4 - [(2E) -3-phenylprop-2-en-1-yl] piperazine dihydrochloride) is a difluorinated piperazine derivative (Holmes *et al.*, 1984). It is used in migraine prophylaxis, occlusive peripheral vascular disease, dizziness/vertigo of central or peripheral origin, and as adjunctive therapy in the management of epilepsy (AA Pharma Inc., 2010).

There are 17 brands of flunarizine dihydrochloride (FDC) products available in Indonesia, and all of them are in tablet dosage forms (Badan Pengawas Obat dan Makanan, 2020). The official method for dissolution testing of FDC tablets is not available in the Indonesian Pharmacopoeia 2014 or in other pharmacopoeias. The monograph of the FDC capsule is available in the Pharmacopeia of The People's Republic of China 2010. The dissolution test uses a basket method at 100rpm; the dissolved substance is determined using the same method as in the assay. However, the dissolution method for capsules cannot simply be used for tablet dosage form, considering that capsules require a time lag before they are dissolved. In addition, tablets contain excipients such as binders and disintegrants, which affect drug release. The aims of this study were to develop and validate a discriminatory dissolution method for FDC tablets.

Materials and methods

Materials

The Indonesian Food and Drug Authority provided the FDC reference standard (Indonesian Pharmacopoeia reference standard), and two commercial FDC 10mg tablets were purchased, one generic (G) and the other branded (F and S). Other materials included Talc, Starch, and Lactose (Brataco, Indonesia), methanol for liquid chromatography (Merck, Germany), distilled water (Brataco, Indonesia), ortho-phosphoric acid

(Merck, Germany), sodium acetate anhydrous (Merck, Germany)acetic acid (glacial) 100 per cent anhydrous (Merck, Germany), hydrochloric acid fuming 37 per cent (Merck, Germany), tween 80 (Merck, Germany), sterile water for injection (Ika Pharmindo, Indonesia), regenerated cellulose 0.45 mm membrane filter (Sartorius, Germany), and PVDF 0.45 mm syringe filter (Whatman, USA). Everything was pro analytical or High-performance liquid chromatography (HPLC) grade.

Dissolution procedure development

HPLC analysis

The development and validation of the HPLC assay have been reported previously (Yelli *et al.*, 2020).

Solubility test

The solubility test of FDC was carried out in 10ml of 0.1N HCl, acetate buffer pH 4.5 or 0.2% (w/v) tween 80 solutions using a water bath shaker (Labtech, Korea) set at 37°C and 100rpm. Samples (1.0mL) were withdrawn after 1, 2, 3, 4, 5, 24, and 48 hours, diluted with the same medium and analysed using a validated HPLC method (Yelli *et al.*, 2020). This procedure was performed with three replications in each medium.

Disintegration test

Disintegration test was conducted using a PTZ AUTO EZ Disintegration Tester (Pharma Test AG, Germany) in 700mL of the same medium as the solubility test. Each sample was tested with six replications

Dissolution studies

The 10mg FDC tablets are products G, F, and S. G, F, and S dissolution profiles were tested in 0.1N HCl. G and F had profiles in acetate buffer pH 4.5 and 0.2% (w/v) tween 80 solutions. The uniformity of the contents of all sample tablets was acceptable (Yelli *et al.,* 2020). We tested six tablets in a PTWS D620 Dissolution Tester (Pharma Test AG, Germany) with 900 mL medium at 37°C. The apparatus 1 (basket) and 2 (paddle) rotated at 50, 75, and 100rpm, respectively. After 5, 10, 15, 20, 30, 45, and 60minutes, samples (10mL) were withdrawn and replaced with fresh medium, except 0.1N HCl media. Each sample was then injected into the validated HPLC system using a 0.45m PVDF syringe filter.

Validation of the dissolution method

The precision test was performed on a homogeneous powder equivalent to one tablet, using the selected dissolution method (six replicates). Each sample was filtered with a 0.45m PVDF filter syringe and injected into the HPLC system. A precision of 2% RSD was required. In order to obtain the accuracy, standard FDC was added to 200mg of excipient (a mixture of 1% (w/w) magnesium stearate, 2% (w/w) talc, 10% (w/w) starch and lactose) to 100% recovery (three replicates). The aliquot went into the HPLC. The specificity test used the same method as the solubility test but with a PDA detector at 210-400nm instead of a UV detector.

Statistical analysis

Data are shown as mean $\pm$ standard deviation, analysed by one-way or two-way ANOVA ($\alpha = 0.05$) to establish the significant differences between means.

Results

Solubility test

FDC was slightly soluble in 0.1 N HCl (3.30mg/mL) and in 0.2% w/v tween 80 (3.50 mg/mL) solutions but practically insoluble in acetate buffer pH 4.5 (0.05 mg/mL).

Disintegration test

Product S was the fastest (1.48 $\pm$ 0.10 minutes) in 0.2% w/v tween 80 solutions, the slowest was product G (31.49 $\pm$ 18.74 minutes) in 0.1 N HCl (Table I).

Table I: Disintegration time of FDC tablets in various medium

Medium	Disintegration time (minute)		
	Product G	Product F	Product S
0.1 N HCl	31.49 ±18.74	14.68± 8.80	5.25 ± 3.36
Acetate buffer pH 4.5	8.51 ± 2.07	2.64 ± 0.57	3.16 ± 0.29
0.2% (w/v) Tween 80	7.58 ± 2.73	2.42 ± 0.50	1.48 ± 0.10

The fastest tablet disintegration time in 0.2% w/v tween 80 solutions was well correlated with the highest solubility of FDC in the medium.

Dissolution studies

The amount of FDC dissolved from generic tablet samples rises gradually; it starts from (1.36$\pm$0.46) % at the fifth minute in the acetate buffer pH 4.5 (50 rpm; basket method). This is well correlated with the slowest disintegration time of G tablets among other tablets in 0.1N HCl, acetate buffer pH 4.5, and 0.2% (w/v) tween 80 solutions, respectively. On the other hand, the dissolution of F (a branded tablet) started from (15.4 $\pm$

8.3%) at the fifth minute in acetate buffer pH 4.5 (50rpm; paddle method), samples of S (a branded tablet) have dissolved (57.7 ± 2.8%) at the fifth minute in 0.1N HCl medium (50rpm; basket method). Dissolution process occurs more efficiently in 0.1N HCl medium for all samples tested (Figure 1).

The Q_{30} value (Table II) of all test samples in HCl 0.1N medium met the acceptance criteria (≥ 75%) except for product G with basket method at 50rpm agitation. Most of the data obtained from the other mediums showed the Q_{30} values < 75%. Therefore, 0.1N HCl was chosen as the dissolution medium for FDC in the tablet dosage form. The dissolution profiles in 0.1N HCl using the basket method at 50rpm failed to meet the acceptance criteria because there was one Q_{30} value of less than 75%. Therefore, the 50rpm basket method was excluded from the candidate.

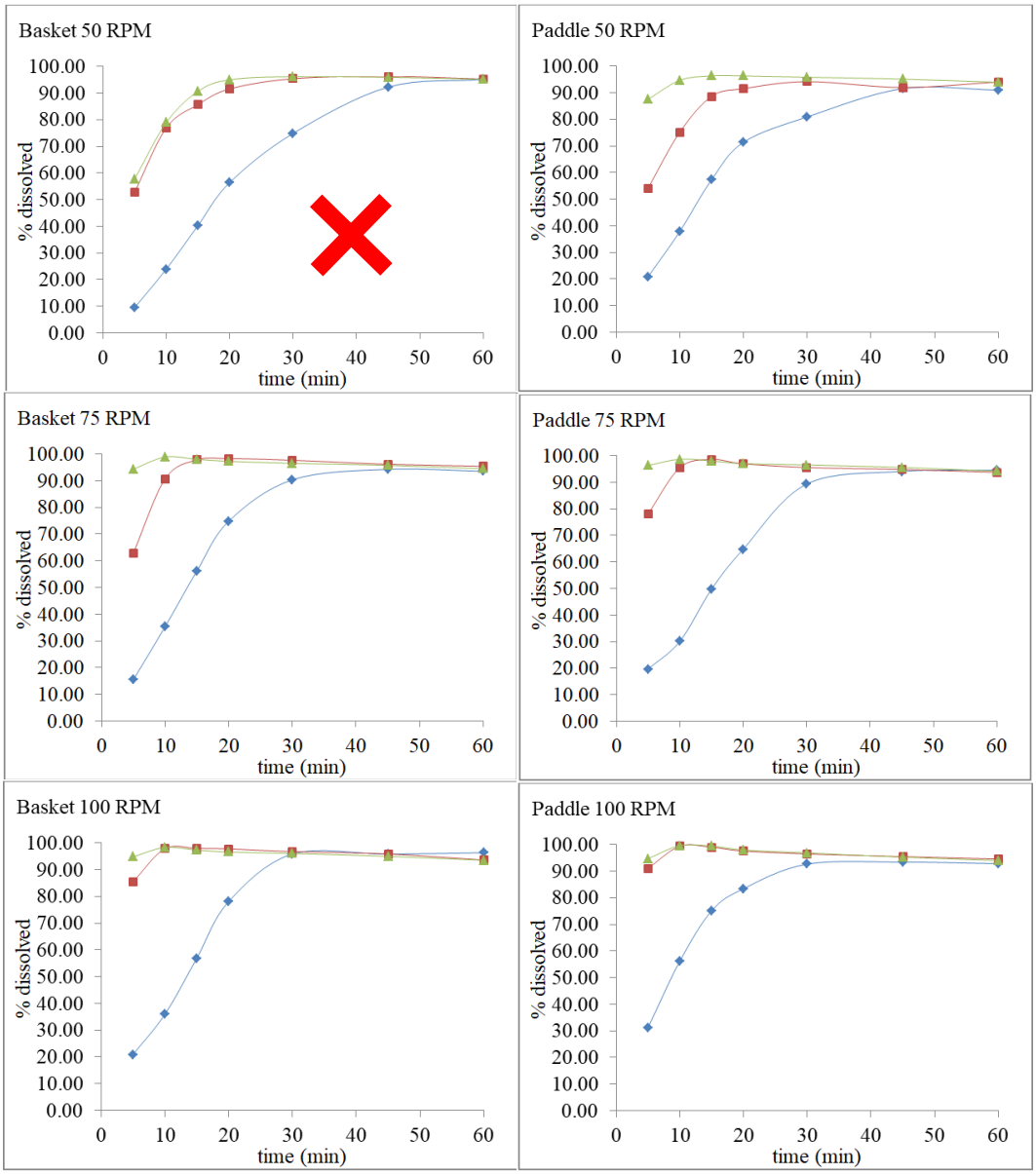
Table II: The Q_{30} values of FDC tablets in various medium and methods

Medium	Product	Percentage dissolved in 30 minutes (Q_{30}) (%)					
		Basket apparatus			Paddle apparatus		
		50 RPM	75 RPM	100 RPM	50 RPM	75 RPM	100 RPM
0.1 N HCl	G	74.84±4.81	90.37±4.15	95.90±2.42	80.91±3.65	89.37±3.09	92.68±0.79
	F	95.38±1.82	97.67±0.48	96.80±0.52	94.18±3.18	95.59±0.23	96.51±1.27
	S	96.16±0.61	96.53±0.95	96.06±1.26	95.84±1.99	96.56±0.43	96.89±1.14
Acetate buffer pH	G	22.58±1.48	35.24±5.71	51.40±3.53	24.58±5.08	45.37±5.28	54.33±6.09
4.5	F	54.37±8.06	87.34±6.64	82.44±4.92	71.25±1.82	85.33±1.86	87.07±7.19
0.2% (w/v) Tween	G	54.13±2.93	66.39±4.87	76.91±3.78	63.45±10.84	76.52±4.68	85.33±2.51
80	F	82.09±3.64	84.78±2.38	88.91±1.86	90.32±1.70	94.96±0.96	95.64±1.85

In contrast, the paddle method at 50rpm showed better discriminatory nature at a sampling time of 30 minutes. Statistical analysis by one-way ANOVA confirmed this argument. Validation of dissolution method. The selected method met the acceptance criteria (Table III) on the linearity (R2 0.9998), precision (95.74 ± 0.881% with RSD 0.920%), accuracy (95.09 - 103.76%) and specificity (USP 39, 2016).

Table III: Summary of the validation parameters for the selected dissolution method of FDC in tablet dosage forms

Validation parameters	Results				Acceptance criteria
Linearity	R^2 = 0.9998				R2 ≥ 0.99
Precision	RSD = 0.92 %				RSD ≤ 3.7%
Accuracy	95.09 % to 103.76 %				95.0 % to 105.0%
Specificity	The spectrum profile of the tablet sample solution is the same as the standard solution of flunarizine dihydrochloride				The spectrum profile of the sample solutions is the same as the standard solution
	Injected solution	Retention time (min)	Purity angle	Purity threshold	
	Medium	3.447	8.536	13.193	
	Excipient	3.450	2.282	2.877	Retention time of sample solution = standard solution
	Standard	3.459	0.095	0.234	Purity angle < purity threshold
	Sample	3.461	0.132	0.272	
	Standard spiked sample	3.451	0.095	0.258	
	Percentage of the area of the medium compared to the area of the standard solution = 0.462%				Percentage of the area of the medium compared to the area of the standard solution ≤ 1%
	Percentage of the area of the excipient compared to the area of the standard solution = 1.172%				Percentage of the area of the excipient compared to the area of the standard solution ≤ 2%



(Tablet G; Tablet F and Tablet S) in 0.1N HCl medium with various methods, basket method at 50RPM was removed as a candidate

Figure 1: The dissolution profiles of a various sample

Discussion

As a Biopharmaceutical Classification System (BCS) class II compound, the dissolution profile is a critical quality attribute of an FDC tablet; thus, a discriminatory dissolution method is required (Benet, 2013). A systematic approach was conducted to screen medium pH, solubility enhancers, and testing conditions to propose a valid dissolution test for routine quality control of the tablet dosage form and compare products' performance (Krämer *et al.*, 2005).

The screening of the dissolution medium was performed based on the solubility and disintegration properties of FDC in the test solutions. These data support selecting a medium that dissolves the maximum dose of FDC tablets on the market (10mg) and obtains the sink condition at a volume of 900mL. The results are in accordance with the ICH Guideline (2018) that a drug is classified as having high solubility if the maximum dose available in the market can dissolve in a maximum of 250 mL of the aqueous medium in the range of pH 1.2 - 6.8 temperature 37± 1°C.

The dissolution profile of three sample products showed that the drug release from the generic tablets looks very different from branded tablet samples. The amount of drug released per unit time among products

is strongly influenced by the manufacturing platforms and the type of excipients used in the dosage form. The amount of drug dissolved in the first five minutes is related to those available for absorption and directly proportional to the onset time of therapeutic effect. This phenomenon explains the variation in the onset time of drug effects among products.

FDC tablets showed different dissolution profiles in 0.1N HCl, acetate buffer pH 4.5 or 0.2% (w/v) tween 80 solutions. The acceptance criteria of an immediate-release drug such as FDC tablets are to dissolve 75% within 30 minutes (USP 39, 2016). The amount of drug released in the 0.1 N HCl medium was the highest compared to other mediums. Although the solubility and the disintegration time are better in 0.2% (w/v) tween 80 medium, this does not guarantee the per cent dissolved will also be the highest in this medium. The presence of polymers in tablet formulas may cause an increase in the thickness of the diffusion layer by adsorbing water molecules and causing a decrease in dissolution rate.

The nature of 0.1N HCl as a strong acid can prevent this increase in medium viscosity through its ability to hydrolyse polymers from tablet excipients (Nagarajan, 2001; Chen *et al*., 2003). Suppose using 0.2% (w/v) tween 80 medium, the interaction of the polymer with this surfactant decrease in the size of the micelles, thereby reducing the effectiveness of the surfactant in increasing the amount of drug release. In addition, the increase in the diffusion layer thickness due to the adsorption of surfactant on the surface of the analyte crystal further reduces the drug release from the tablets (Balakrishnan *et al*., 2004). Besides the explanation above, the number of bubbles generated by the 0.2% (w/v) tween 80 medium takes a longer time to deaerate. Technically, the 0.2% (w/v) tween 80% is not recommended as a dissolution medium.

The dissolution test using the paddle method at 50rpm is more discriminatory than other conditions. The Q_{30} values obtained from this method showed a higher calculated F value (F = 44.00) than other methods which means that the method could show a higher variation between sample means relative to the variation within the samples. In contrast, the basket method at 100rpm, which was a compendial procedure in the Pharmacopoeia of The People's Republic of China (2010) for FDC capsules, cannot differentiate the dissolution profiles of the FDC tablets studied ($p > 0.05$).

Validation of the selected method showed that the dissolution test in 0.1N HCl using apparatus 2 (paddle method) at 50rpm was valid and specific for FDC in tablets. The specificity test results indicated that the method is specific for determining the amount of FDC released, which is not significantly affected by the presence of the dissolution medium and tablet excipients.

Conclusions

A dissolution method for FDC tablets has been successfully developed using 0.1N HCl medium volume 900mL maintained at 37°C with paddle apparatus at agitation speed 50 rpm, which resulted in Q_{30} values of ≥ 75%. Validation procedures show that it meets the acceptance requirements as a valid, accurate and specific method for monitoring FDC tablets sold in the Indonesian market.

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