ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 2, 2024

Online - 2455-3891
Print - 0974-2441

Research Article

DEVELOPMENT OF A DISCRIMINATORY METHOD FOR DETERMINATION OF *IN VITRO* DISSOLUTION OF CILNIDIPINE

VANITA SOMASEKHAR*, TEJASHWINI H, MURALI KRISHNA PV

Department of Pharmaceutical Analysis, KLE College of Pharmacy, Bengaluru, A Constituent Unit of KLE Academy of Higher Education and Research, Karnataka, India.
***Corresponding author: Dr. Vanita Somasekhar; Email: vanitasom@gmail.com**

Received: 15 August 2023, Revised and Accepted: 29 September 2023

ABSTRACT

Objectives: This study involves the development of a discriminatory method to differentiate the *in vitro* dissolution of cilnidipine's mouth-dispersing film from that of a commercial tablet.

Methods: The mouth-dispersing film was initially developed using a reported established method. A discriminatory dissolution method was developed to assess the *in vitro* dissolution of the mouth-dispersing film and compare the same with that of the commercial tablet.

Results: The study findings indicated the method employed was able to differentiate the dissolution of the fast-dissolving film from the commercial tablet. About 98.52±0.60% of the drug was found to be released from the oral film in 40 min whereas the tablet took nearly 5 h for 92.06±0.49% of the drug to get released.

Conclusion: These results demonstrate that the dissolution media identified was able to create the necessary sink condition that would be able to differentiate the dissolution profile of the mouth-dispersing film from the conventional tablet. The ultrasound spectrophotometric method employed was found to be simple rapid and sensitive enough to estimate the drug release from diverse pharmaceutical dosage forms.

Keywords: Cilnidipine, *In-vitro* dissolution method, Fast-dissolving film

 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i2.49160. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Cilnidipine is a calcium channel blocker that relaxes the heart by inhibiting the entry of calcium ions across the heart and widens the heart smooth muscles for better blood flow. In Korea, Japan, India, China, and Nepal, it has been recommended to relieve hypertension [1]. It is a calcium agonist that can occupy calcium receptors of either the L- or N-types. At present, cilnidipine was reclaimed for intended use by those suffering from Raynaud's syndrome and systematic sclerosis [2,3].

The biopharmaceutical classification scheme classifies cilnidipine as a class II medication, as it exhibits low solubility in physiological fluids, which leads to poor oral bioavailability and delayed onset of action. Hence, there is a strong need to improve the drug solubility and, subsequently, its dissolution and absorption [4].

It can be challenging for many elderly and young individuals to take solid dosage forms like pills or capsules [5,6]. Therefore, the simplicity of dosage forms is crucial, especially in emesis-like circumstances where patients struggle to swallow pills or whole capsules. To address these problems, orally disintegrating medication delivery systems have come into existence recently [7].

An example of this kind of drug delivery method is the oral disintegrating tablet, which is a solid dosage form that is placed in the oral cavity and allowed to dissolve before being swallowed. Even though the orally dispersing films are brittle and friable they can solve these issues and enhance patient compliance (Table 1). This new kind of dosage form is a thin polymer film that dissolves quickly when placed on the tongue, which eventually improves patient compliance [8].

METHODS

Cilnidipine was a gift sample from Micro Labs Limited, Bengaluru. HPMC K4M was obtained from Yarrow Chem Products, Mumbai. PVA and PEG 400 were purchased from S. D. Fine-Chem Limited in Mumbai. Other reagents and chemicals used in the study were of analytical grade.

Methodology

Preparation of oral fast-dissolving film

Solvent casting method was used to prepare the oral fast-dissolving film [9-11]. In this method, firstly the water-soluble polymers were dissolved in water that was heated to 60°C and stirred at 1000 rpm. All other excipients such as flavoring agents, colors, sweetening agents, were dissolved separately. Both the solutions were then mixed thoroughly with stirring maintained at 1000 rpm. Cilnidipine dissolved in alcohol was added to the resultant solution. The entrapped air was removed by application of vacuum using a vacuum pump. The resulting clear solution was cast as a film. It was allowed to dry and then cut into smaller pieces of the desired size based on the therapeutic dose.

Evaluation of the films

Determination of weight uniformity

The films obtained were weighed on a digital electronic balance (Shimadzu BL-220H, Japan) to determine the weight of the films. The results were expressed as mean and standard deviation of three determinations.

Determination of thickness

The thickness of the films was determined using digital calipers (Mitutoyo digimatic caliper, Mitutoyo Corporation, Japan). Similarly, the results were expressed as mean and standard deviation of three determinations.

Determination of content uniformity

To assess the homogeneity of the medication in the films, 1 cm^2 films were cut from three distinct places. Each film cut out was taken into a

100-ml volumetric flask filled with a phosphate buffer that had a pH of 6.8. Around 1 ml of the resultant solution was diluted to 10 mL of pH 6.8 phosphate buffer. An ultrasound (UV)-visible spectrophotometer (Shimadzu UV-Visible spectrophotometer 1900i) was used to record the absorbance at 240 nm [12]. The standard curve constructed in pH 6.8 buffer was used to assay and arrive at the drug content of the oral film.

In vitro disintegration studies
The *in vitro* disintegration of the film was determined by dropping the film in a Petri plate containing water. The time taken for the film to completely disintegrate was determined in triplicate.

Determination of *in vitro* dissolution
The *in vitro* dissolution of the film was performed in a USP paddle apparatus. The film was placed in the apparatus. About 900 mL of phosphate buffer (pH 6.8) was used for the dissolution with 50 revolutions/min at 37°C. Samples measuring 5 mL were withdrawn at 5, 10, 15, 20, 25, 30, 35, and 40 min and diluted suitably to assess the drug release from the film. Similarly, the same method was used to determine the dissolution of conventional marketed tablets. However, the sample volume of the media was withdrawn at 1, 2, 3, 4, 5, and 6 h to determine the amount of drug release from the tablet. All the samples were measured for their absorbance using a UV spectrophotometer at 240 nm [13].

Table 1: Comparison between orally fast-dissolving films and tablet

Orally dissolving films	Oral disintegrating tablet
It is a film	It is a tablet
A bigger surface area causes more disintegration	A lesser surface area causes less disintegration
More durable than tablets that dissolve in the mouth	Less robust than oral films in terms of durability
Improved patient compliance	Patient compliance is lower than with films
It is possible to use a low dose	It is possible to use a high dose
Choking is not a possibility	There are chances of choking

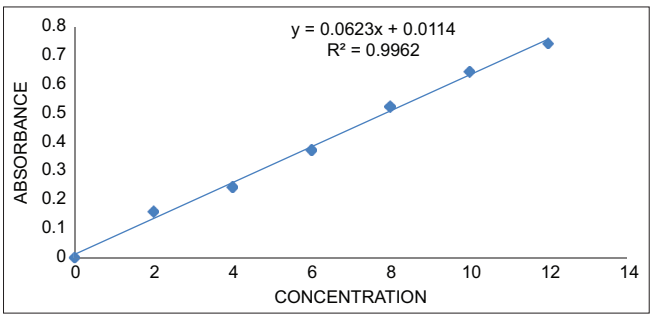

Fig. 1: Calibration curve for cilnidipine

RESULTS AND DISCUSSION

Thickness, uniformity of weight

It is crucial to assess the uniformity of the film's thickness because it directly affects the precision of the dose in the film. This was done using micrometer Vernier calipers at several important sites (at least 3 locations) [14]. The thickness of the film was measured using Vernier calipers with a minimum count of 0.01 mm and was found to be 0.56±0.03 mm on average. The uniformity of thickness would also ensure the uniformity of weights of the films casted.

The weight of the film was determined by a digital balance [15] and the average weight was found to be 0.082±0.002 mg. The uniformity of weight would directly influence the content uniformity of the films.

Drug content uniformity

A calibration curve was constructed which indicated a linearity range from 2 to 12 µg/mL with an R^2 value of 0.9962 indicating a good linearity of the method developed (Fig. 1).

The film had 98.53±0.31% of documented drug content. The distribution of medications throughout the film was found to be consistent, as indicated by a relatively low standard deviation.

In vitro disintegration studies

When an oral film encounters saliva or water, disintegration time begins to occur. The time of disintegration should be between 5 and 30 s for a quickly disintegrating film [16]. The prepared films were observed to disintegrate in 8±2 s.

Comparison of mouth-dissolving film against the marketed tablet

Cilnidipine is known to exhibit low crystalline solubility (0.03–0.06 µg/mL) and amorphous solubility (0.3–2.3 µg/mL) at physiological pH conditions [17]. In such a case, it has to be noted that even though the drug would be released from the formulations, the method may not be able to quantify the same due to the poor aqueous solubility in buffers. Therefore, as the drug release fails to exceed the saturation solubility of the drug in the buffers, the method fails to discriminate the release profiles of two different formulations. In such cases, there is a need to develop a method that would ensure the sink condition for the drug (that would be released) to completely dissolve in the dissolution media. Such a media would also be able to discriminate the dissolution profiles of two different formulations that are known to exhibit two diverse dissolution profiles. Commonly, 0.1% tween 80 would be used to ensure the necessary sink condition for the dissolution of poorly soluble drugs. Normally, most of the pharmacopoeias would allow an addition of 0.1% of tween 80 to ensure sink conditions to the media [17]. On comparing the release properties of cilnidipine fast-dissolving film and cilnidipine oral tablet (Fig. 2) a notable difference in their release rates was revealed. The findings indicate that the fast-dissolving oral film formulation displayed rapid drug release, with 98.52±0.60% of the medication being released within 40 min. On the contrary, the tablets were found to display 92.06±0.49% of drug release after 5 h.

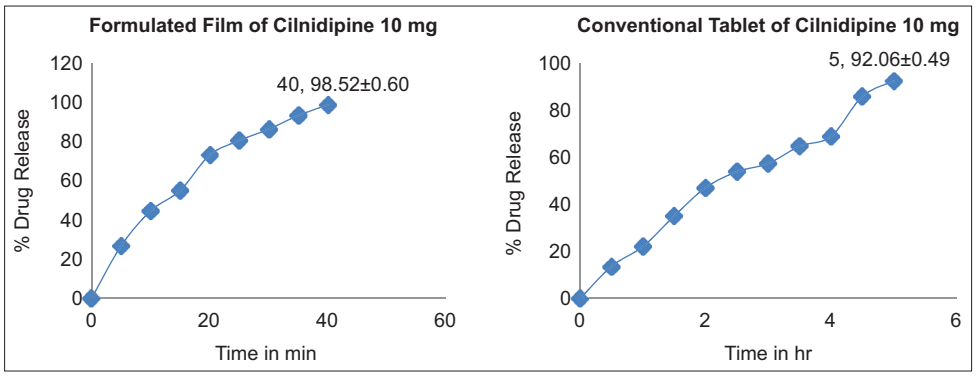

Fig. 2: Comparison of the release properties of cilnidipine fast-dissolving film and cilnidipine oral tablet

CONCLUSION

The samples were analyzed at 240 nm as cilnidipine was found to exhibit an absorption maximum of 240 nm. The linearity was observed in the concentration range of 2 and 12 µg/mL with a slope of 0.0623. The results indicated that the extinction coefficient of the drug was high enough to estimate the drug during dissolution. The dissolution media selected was found to maintain the sink condition that would be necessary to assess the complete dissolution of cilnidipine from the two different dosage forms. Overall, the studies revealed that the method used was able to discriminate the dissolution from two different types of dosage form that is known to display diverse dissolution profiles.

ACKNOWLEDGMENT

The authors would like to acknowledge the support and facilities provided by KLE College of Pharmacy for carrying out this research work.

CONTRIBUTION OF AUTHORS

All authors have contributed equally.

CONFLICTS OF INTERESTS

There are no conflicts of interest. We certify that this submission is an original work and is not under review at any other journal.

FUNDING

We have received no financial support for the research, authorship, and publication of this article.

REFERENCES

1. Yoshimoto R, Dohmoto H, Yamada K, Goto A. Prolonged inhibition of vascular contraction and calcium influx by the novel 1, 4-dihydropyridine calcium antagonist cilnidipine (FRC-8653). Jpn J Pharmacol 1991;56:225-9. doi: 10.1254/jjp.56.225, PMID 1881002
2. Proudfoot JR. Drug likeness and analogue-based drug discovery. In: Analogue-based Drug Discovery. New Jersey: John Wiley and Sons; 2006. p. 25-52.
3. Ando K. L-/N-type calcium channel blockers and proteinuria. Curr Hypertens Rev 2013;9:210-8. doi: 10.2174/15734021106661401311 5331, PMID 24479751
4. Harshitha KN, Shruthi BN, Bhagawati S. Design and characterization of fast dissolving films of cilnidipine solid dispersions. Am J Pharm Tech Res 2018;8:2249-3387. doi: 10.46624/ajptr.2018.v8.i4.017
5. Rekha MS, Sultana SK, Mahathi K, Parveen P, Prathima B, Devi AS. Formulation and evaluation of fast dissolving buccal film containing isradipine solid dispersion. Am J Pharmtech Res 2015;5:221-47.
6. Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: Innovations in formulation and technology. Int J Pharm Sci Rev Res 2011;9:50-7.
7. Hanif M, Zaman M, Chaurasiya V. Polymers used in buccal film: A review. Des Monomers Polym 2015;18:105-11. doi: 10.1080/ 15685551.2014.971389
8. Jyoti VJ, Rathore RP, Kapse SN. A comparative *in-vitro* dissolution and *in-vivo* bioavailability study of mouth dissolving film of promethazine hydrochloride against the marketed tablet formulation. Eur J Mol Clin Med 2021;8:2515-8260.
9. Haju SS, Yadav S. Formulation and evaluation of cilnidipine mucoadhesive buccal film by solvent casting technique for the treatment of hypertension. Int J Pharm Pharm Sci 2021;13:34-43.
10. Sheoran R. Fast dissolving oral films: A review with future prospects. Int J Pharm Pharm Res 2018;12:15-32.
11. Garsuch V, Breitkreutz J. Comparative investigations on different polymers for the preparation of fast-dissolving oral films. J Pharm Pharmacol 2010;62:539-45. doi: 10.1211/jpp.62.04.0018, PMID 20604845
12. Saini P, Kumar A, Sharma P, Visht S. Fast disintegrating oral films: A recent trend of drug delivery. Int J Drug Dev Res 2014;4:80-94.
13. Kaur P, Garg R. Oral dissolving film: Present and future aspects. J Drug Deliv Ther 2018;8:373-7. doi: 10.22270/jdt.v8i6.2050
14. Sharma D, Kaur D, Verma S, Singh D. Fast dissolving oral films technology: A recent trend for an innovative oral drug delivery system. Int J Drug Deliv 2015;7:60-75.
15. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: An innovative drug delivery system and dosage form. Int J Chem Tech Res 2010;2:576-83.
16. Rao SV, Bhavya G, Padmalatha K. Mouth dissolving films: An effective oral disintegrating drug delivery system. Eur J Biomed Pharm Sci 2019;6:158-63.
17. Liu Q, Mai Y, Gu X, Zhao Y, Di X, Ma X, *et al*. A wet-milling method for the preparation of cilnidipine nanosuspension with enhanced dissolution and oral bioavailability. J Drug Deliv Sci Technol 2020;55:101371. doi: 10.1016/j.jddst.2019.101371