VOL. 17 NO. 9 PAGES 76 www.expresspharma.in

EXPRESS PHARMA

INDIA'S FOREMOST PHARMA & BIOTECH MAGAZINE AUGUST 2022, ₹ 40

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A step towards biopredictive dissolution: Development of biphasic dissolution model for vaginal tablets containing BCS class-II drug

Safina Shaikh, B Pharm student and **Balaji Yadav**, B Pharm student, Vivekanand Education Society's College of Pharmacy; **Archana Pokkalath**, Research Associate, Electrolab India and **Aditya Marfatia**, Director, Electrolab India, explain the role of biphasic dissolution for improving the drug release from extended release tablets of poorly soluble drug

Introduction

In-vitro dissolution study is an official test for evaluating drug release from tablet and capsule dosage forms. It is an important quality control test that determines release characteristics of the product over time. Dissolution tests have also been applied as a tool to predict drug product performance in vivo as a result to minimise costly in-vivo bioequivalence studies required to approve a new drug product. The routinely used dissolution tests are performed in aqueous buffered solutions. Such tests are well suited for a quality control role. However, for understanding the in-vivo performance, conditions which are more relevant in the human body are needed to be evaluated.

Biphasic dissolution system simulates drug dissolution and absorption by the implementation of an immiscible organic phase acting as an absorptive sink over the aqueous solution. In such a system, a drug is dissolved into the aqueous phase and then partitions to the organic layer depending on its distribution coefficient. The movement of the dissolved drug into the organic layer allows dissolution in the aqueous phase to continue by preventing the drug from accumulating in the aqueous phase thus creating sink condition. Biphasic dissolution system is particularly suitable to study the in-vitro dissolution of BCS class-II drugs like Clotrimazole, Ibuprofen and Nifedipine in which dissolution rate limited absorption is observed. It can also be a valuable tool for determining the partition and distribution coefficient of the drugs. Additionally, many studies have reported IVIVC correlation of the results obtained from the biphasic dissolution and the AUC values of the in-vivo studies.

Clotrimazole (CTZ), a BCS class II drug, is widely employed in the treatment of vaginal candidiasis. In the presented study, a biphasic dissolution test was developed for the poorly soluble drug – Clotrimazole using USP apparatus II with a mini-paddle (Electrolab, India) for sufficient stirring of the organic phase along with the conventional paddle blade. The objective of the study was to develop a method that mimics the in-vivo drug behaviour and also aids in improving the sink conditions for Clotrimazole release from the formulation. The experimental parameters associated with dissolution were optimised to discriminate dissolution of extended release Clotrimazole tablets in monophasic and biphasic mediums.

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In-vitro monophasic dissolution study for Clotrimazole ER tablets

Monophasic dissolution with 700 ml pH 4.5 acetate buffer: The dissolution test was performed on Candid V6 extended release (Clotrimazole 100 mg) tablets manufactured by Glenmark. The dissolution studies were performed in the pH 4.5 acetate buffer in order to mimic the in-vivo pH conditions for drug absorption via the vaginal route. The monophasic dissolution studies were performed using 700 ml pH 4.5 acetate buffer. The

samples were collected at predetermined time intervals and the dissolution media was replenished post each collection in order to maintain the sink conditions. The drug concentrations were analysed spectrophotometrically.

Biphasic dissolution strategy for Clotrimazole ER tablets

The biphasic dissolution medium, consisting of 200 mL of n-octanol as an organic phase and 700 mL of acetate buffer pH 4.5 as an aqueous phase, was placed in a dissolution vessel. An additional modification to the conventional paddle was done by attaching a mini-paddle for the uniform mixing of the organic phase. The paddle was rotated at a speed of 50 rpm. 5 ml sample was withdrawn from both the phases at pre-determined intervals and Clotrimazole concentrations were analysed spectrophotometrically.

Figure 1: Biphasic dissolution set-up with the mini-paddle attachment to the conventional paddle blade

Results

Monophasic dissolution

Acetate buffer pH 4.5 was selected as an aqueous phase for biphasic dissolution test since it mimics the pH of the vaginal conditions. However, due to the poor solubility of the API in the dissolution media, this media was not successful in providing sink conditions for drug release from the formulation with about 36.49 per cent drug releasing at the end of 24 hours.

Biphasic dissolution

Since pH 4.5 acetate buffer couldn't achieve the required sink for driving the drug release from the formulation, an organic solvent – n-octanol was added into the aqueous buffer to develop biphasic media for dissolution. N-octanol was chosen as the organic phase based on the solubility consideration in addition to the fact that it is immiscible with water, doesn't evaporate at 37°C, has relatively low viscosity and has properties that mimic biological membrane. The appearance of Clotrimazole in the organic phase is the result of two consecutive processes, the dissolution of Clotrimazole in the aqueous phase followed by the partitioning of Clotrimazole into the organic phase. The cumulative drug dissolved in the organic phase at the end of 22 hours was found to be 51.36 per cent.

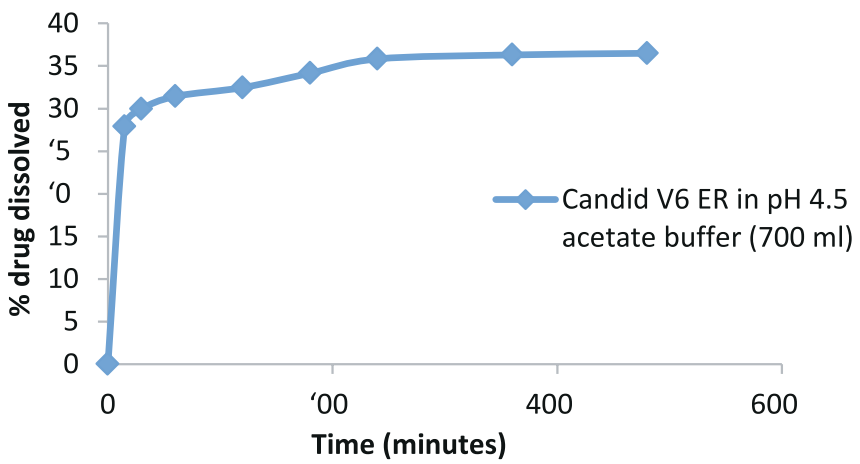

Figure 2: Dissolution profile of Clotrimazole ER tablets in pH 4.5 acetate buffer (700 ml)

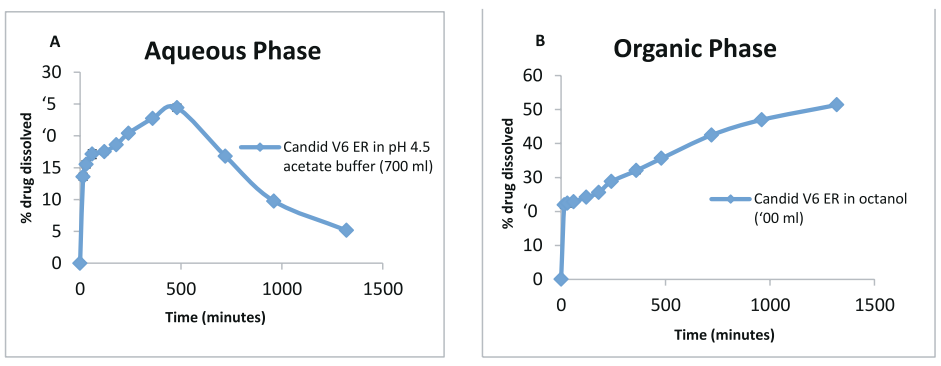

Figure 3: Dissolution profiles of Clotrimazole tablets ER from the (A) aqueous and (B) organic phases in the biphasic dissolution test. Mean values (n = 3) are shown; error bars represent maximum and minimum values

Conclusion

The pH 4.5 acetate buffer failed to provide the sink conditions for the Clotrimazole drug release from the formulation (36.49 per cent drug release at the end of 24 hours). The addition of n-octanol in the dissolution medium was found to be successful in improving the drug release of the poorly water-ssoluble drug with 51.36 per cent drug release in n-octanol at the end of 22 hours. In addition, in the biphasic buffer/octanol system (intended to mimic the fluid/tissue environment in vivo), sink conditions of established since the dissolved drug in aqueous phase partitions to the organic phase which allows more drug to be dissolved in the aqueous phase. Hence, Biphasic dissolution could be effective in improving drug release for poorly water-soluble drug and can be IVIVC tool in early exploratory studies during drug development.

References

Phillips, D.J., Pygall, S.R., Cooper, V.B., & Mann, J.C. (2012). Toward Biorelevant Dissolution: Application of a Biphasic Dissolution Model as a Discriminating Tool for HPMC Matrices Containing a Model BCS Class II Drug. Dissolution Technologies, 19, 25-34.

Pestieau, A., & Evrard, B. (2017). In vitro biphasic dissolution tests and their suitability for establishing in vitro-in vivo correlations: A historical review. European Journal of Pharmaceutical Sciences, 102, 203–219.

Phillips, D.J., Pygall, S.R., Cooper, V.B., & Mann, J.C. (2012). Overcoming sink limitations in dissolution testing: a review of traditional methods and the potential utility of biphasic systems. Journal of Pharmacy and Pharmacology, 64.

association of Gangwal with Barentz. It was followed by the corporate presentation of Gangwal given by Dr Gaurav Yeola, General Manager, Technical Sales and Marketing, Gangwal.

The first session started with the insights given by Ranjit Gokhle, Director-Business Development, Chemicals NISSO CHEMICAL INDIA on the topic 'Pharma Excipients - Hydroxypropyl Cellulose'. He gave an overview of hydroxypropyl cellulose and its mechanical properties. He also enlightened the audience with HPCs applications in the pharma industry.

The next presentation was given by Dr Bhavesh Patel GM - Technical pharma excipients and nutraceutical ingredients-Asia pacific region, Fuji Chemical. He spoke about 'Troubleshooting of Formulation challenges using specialty excipients'. Dr Patel explained in detail the problem solving applications from Fuji chemical, Japan concerning the products like Neusilin US2/Fujicalin/FujiSil.

Subsequently, Dr Baidyanath Mishra, President-Natural Products, Sarvotham Care Ltd. touched upon 'Natural in Nutraceuticals: Global Opportunity'. He gave a detailed overview of nutraceutical market of India and also highlighted his company's journey in this sector so far. Dr Mishra also stressed the benefits of phytochemicals or phytonutrients and their role in preventing chronic diseases. He also highlighted the formulation challenges of nutrition tablet design along with the need of the hour as far regulations of nutraceuticals are concerned.

Dr Mitesh Phale, Global Pharmaceutical and dermo pharmaceutical marketing manager Seppic, Paris while speaking on the topic 'Optimise your topical drug developments with versatile and performant excipients', touched upon API-centric formulation solutions, building the optimal dosage form and matching texture to the application site & medicine use.

Dr Saurabh Srivastava, Associate Professor & Head, Department of Pharmaceutics, Associate Dean & Chair-Board of Studies and Research, NIPER Hyderabad shared his insights on a very trending topic 'Nanomedicines: Bench-to-Bedside Challenges'. Talking about the major challenges in clinical translation of nanomedicines and products, he highlighted four major points i.e., lack of pilot and large scale production, cost-effective outflows, unclear regulatory guidelines and compliance along with challenges of stability and reproducibility. He also emphasised on the FDA's perspective of nanomaterials and mentioned that academia, industry and regulatory bridging is the need of the hour for the overall growth of this sector.

The last presentation of the event was given by Rajkishor Rajak, Marketing Manager, DuPont on the topic 'DuPontTM LiveoTM healthcare portfolio & launch of pharma TPE tubing for bio-pharmaceutical process'. He shared about the various pharma solutions provided by DuPont with a focus on transdermal and topical. He also explained that DuPont™Liveo™Healthcare is accelerating its investments for the future of the bio-pharma processing industry by expanding its supply capacity of silicone elastomers & tubing, and by enlarging its single-use pharma product lines with new Pharma TPE Tubing. Liveo™Pharma product lines help fulfill customer requirements in terms of purity, performance, quality and reliability.

The event was concluded with a vote of thanks.

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