RESEARCH ARTICLE

inventi Spreading Knowledge

Overcoming Limitations in Dissolution Testing of Poorly Water Soluble Racecadotril

Garala K[1]*, Patel J[1], Dhingani A[1], Raval M[2], Dharamsi A[3]

Abstracts: The conventional dissolution test, particularly the USP apparatus I and II, remains an important tool in the field of the pharmaceutical product development. For accurate dissolution characterization, sink conditions, where saturation solubility of a drug in the dissolution medium is at least three times more than the drug concentration, are significant. These conditions can be difficult to maintain with formulations containing poorly soluble active pharmaceutical ingredients. This research summarizes the role of the excipients to enhance dissolution of racecadotril and facilitate the achievement of sink. The dissolution model utilizes various media (0.1N HCl, Acetate buffer pH 4.5 and Phosphate buffer pH 6.8) with surfactant to improve the dissolution limitation of racecadotril. Crucially, the acetate buffer pH 4.5 with 0.75% SLS does allow sink conditions to be maintained and hence the experiment will yield complete dissolution.

INTRODUCTION

The US Food and Drug Administration (FDA) have defined that 'bioavailability testing in which humans are used as test subjects should be minimized by development and implementation of *in vitro* dissolution standards that reflect *in vivo* drug performance'. [1] Clearly this places significant importance on the dissolution test in the drug development process, particularly in dosage development where it can be used to (i) assist with formulation development and comparison [2-3] and (ii) relate *in-vitro* and *in-vivo* correlation. [4]

Dissolution testing is a method for evaluating physiological availability that is contingent upon having the drug in a dissolved state. [5] The earliest reference to dissolution phenomena was made by Noyes and Whitney in 1897. They proposed the rate at which a solid materials dissolves in its own solution to be proportional to the difference between the concentrations of that solution and the saturated solution. [6] In 1900, Brunner and Tolloczko demonstrated that dissolution rate of solid substance is dependent on the rate of stirring, temperature, medium and arrangement of the dissolution apparatus. [7] In 1970, the basket-stirred-flask test (USP, apparatus I) was accepted as an official dissolution test in six monographs of the USP and National Formulary (NF). [8] Subsequent developments led to the USP adopting other apparatus fit for the analysis of different kind of dosage forms (Table 1). [9] A simplified dissolution mechanism, as understood today (Figure 1), comprises of two stages: (a) initial disintegration of the formulation matrix and (b) subsequent dissolution of drug in the liquid medium. The overall dissolution rate of drug is limited by the slower of these two steps. [10] If the first step is rate-limiting, then the overall dissolution rate is said to be disintegration controlled and the cohesive properties of the dosage forms are important. It should also be documented that disintegration proceeds to yield drug particles directly and/or via a granular intermediate. If the second step is rate-limiting, the mechanism is dissolution controlled and the physical/chemical forms, together with the physicochemical properties of drug, are important. [11]

Conventional dissolution testing remains critical in dosage form development. For compounds with poor aqueous solubility, maintaining sink conditions can be problematic rendering complete dissolution characterization a challenging task to pharmaceutical scientists. To afford sink conditions, several solubility modifiers, such as surfactants, inorganic salts and organic co-solvents, are normally added to aqueous dissolution media. Moreover, innovative dissolution apparatus such as the flow through apparatus (United States Pharmacopeia, USP, IV) can be employed.

When the dissolution method was not identified in literature, therefore, it was necessary to develop the same. At early stages of development, *in vitro* dissolution testing guides the optimization of drug release from formulations. Review of API properties (BCS-classification, pKa, stability, solubility as a function of pH/surfactant concentration and particle size) that are likely to affect the *in vitro* dissolution behavior should be evaluated as part of method development. [12] The development of a dissolution procedure involves selecting the dissolution media, apparatus type and hydrodynamics (agitation rate) appropriate for the product. [13] This research aims to highlight the role of the traditional 'dissolution' test for poorly water-soluble drug, racecadotril, and the problems posed to and overcome for these methodologies.

MATERIALS AND METHODS

Materials

Racecadotril was procured from Ogene Systems (I) Pvt. Ltd., Hyderabad, India. Sodium lauryl sulfate was purchased from Hi Media Labs, Mumbai, India. High performance liquid chromatography (HPLC) grade acetonitrile and water were purchased from Merck Pvt. Ltd., Mumbai, India. All other solvents and chemicals used were of analytical grade (Merck Pvt. Ltd., Mumbai, India).

Selection of Dissolution Medium

Racecadotril was found to be less soluble at almost all

[1]Atmiya Institute of Pharmacy, Kalawad Road, Rajkot-360005, Gujarat, India.
Email: kevincgarala@gmail.com
*Corresponding author

[2]Saurashtra University, Rajkot, Gujarat, India.

[3]Maliba Pharmacy College, Surat, Gujarat, India.

Table 1: USP Dissolution Apparatus and its Applications

USP Apparatus	Applications
I: Rotating basket	Solid oral DFs
II: Paddle assembly	Solid oral DFs
III: Reciprocating cylinder	Bead-type modified-release DFs
IV: Flow-through cell	Modified-release DFs (poorly soluble actives); soft gelatin capsules
V: Paddle over disk	Transdermal DFs
VI: Cylinder	Transdermal DFs
VII: Reciprocating holder	Transdermal and non-disintegrating oral modified-release DFs

Table 2: Dissolution Profile of Racecadotril in Different Media

Time (min)	Cumulative Percentage Release (CPR) *		
	0.1 N HCl	Acetate Buffer pH 4.5	Phosphate Buffer pH 6.8
0	0	0	0
5	0.65 ± 0.11	28.51 ± 0.97	0.18 ± 0.03
10	1.87 ± 0.31	45.35 ± 1.02	0.59 ± 0.42
15	4.27 ± 0.54	47.96 ± 1.13	3.23 ± 0.35
20	7.35 ± 0.42	49.85 ± 1.27	6.54 ± 0.54
30	11.64 ± 0.53	52.97 ± 1.54	13.97 ± 0.67
45	20.29 ± 0.64	53.12 ± 2.18	18.38 ± 0.63
60	25.32 ± 0.89	53.34 ± 2.15	22.35 ± 1.24

*Results are of mean of three observations ± SD

Table 3 Optimization of SLS Concentration

Time (min)	CPR in Acetate Buffer pH 4.5*				
	0% SLS	0.25% SLS	0.5% SLS	0.75% SLS	1% SLS
0	0	0	0	0	0
5	28.51 ± 0.97	33.65 ± 1.26	37.21 ± 1.89	69.35 ± 2.65	72.06 ± 2.34
10	45.35 ± 1.02	44.60 ± 1.17	50.23 ± 2.15	75.39 ± 2.18	77.67 ± 1.86
15	47.96 ± 1.13	74.95 ± 1.62	53.65 ± 2.39	79.17 ± 1.96	80.14 ± 2.72
20	49.85 ± 1.27	50.42 ± 2.06	57.37 ± 2.64	80.91 ± 2.93	81.32 ± 2.21
30	52.97 ± 1.54	53.28 ± 2.38	61.23 ± 3.17	81.28 ± 2.31	82.13 ± 2.97
45	53.12 ± 2.18	57.01 ± 2.19	64.96 ± 2.35	81.81 ± 2.17	82.51 ± 2.32
60	53.34 ± 2.15	57.56 ± 2.24	65.51 ± 2.18	82.26 ± 2.32	83.03 ± 2.85

*Results are of mean of three observations ± SD

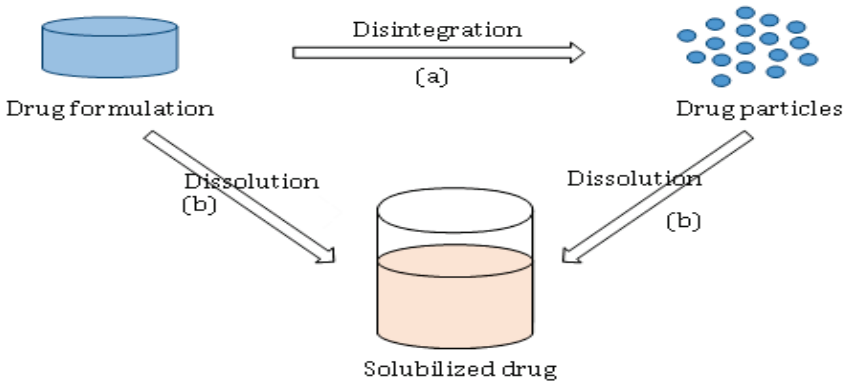

Figure 1: Accepted dissolution mechanism for dosage forms. The overall dissolution rate of drug is said to be either disintegration or dissolution controlled depending on whether (a) or (b) is the slowest step, respectively

physiological pH and therefore, it was necessary to select a suitable dissolution media so as to obtain a good release profile. Solubility of racecadotril was evaluated in various buffers. Media such as 0.1 N HCl and buffers (pH 4.5 and 6.8) were evaluated for racecadotril much in the same way as conventional tablets. [14]

Dissolution Method

In-vitro release study of agglomerates and prepared dosage form of racecadotril was carried out in USP type II (paddle type) dissolution apparatus with appropriate dissolution medium (US FDA guidelines). The dissolution medium was equilibrated to 37 ± 0.5°C. Aliquots of 5 mL were withdrawn at specified time interval and replaced with fresh media. The samples were analyzed using previously developed HPLC method for the dissolved drug. [15] All

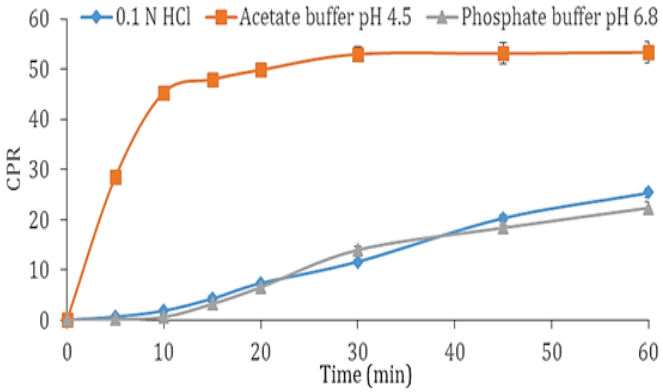

Figure 2: Drug release in different dissolution media

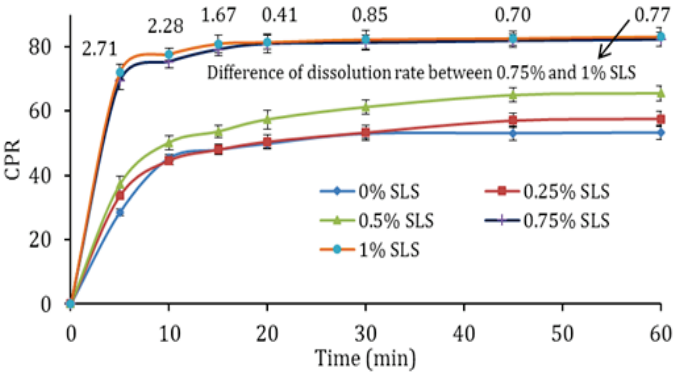

Figure 3: Effect of SLS on drug release

determinations were performed in triplicate.

RESULTS AND DISCUSSION

Intended for most dosage forms to be efficacious, the active pharmaceutical ingredient (API) must be absorbed into the systemic circulation so that it can be transported to its site of activity. This process contributes to the bioavailability of the drug substance and involves two steps: dissolution and absorption (or permeability). Understanding the multi-step dissolution process is essential to develop proper *in vitro* dissolution method. Dissolution is the process of extracting the drug out of the dosage form solid-state matrix into solution within the gastrointestinal tract. The dissolution test as defined in the United States Pharmacopoeia 32 [16] is used in judging the essential quality attributes of pharmaceutical products. Absorption is the process of transporting the dissolved drug from the gastrointestinal lumen into the systemic circulation. Dissolution testing is an *in vitro* method that characterizes how a drug is extracted out of a solid dosage form. It can indicate the efficiency of *in vivo* dissolution but does not provide any information on drug absorption.

Racecadotril is highly insoluble drug at almost all physiological pH and therefore, it was necessary to select a suitable dissolution media so as to obtain a good release profile. The 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 were taken for the selection of dissolution media. [14] Results of dissolution method were depicted in Table 2 and Figure 2.

Perusal to Table 2 and Figure 2, it was observed that very less amount racecadotril was released in 0.1 N HCl and in phosphate buffer 6.8, while in acetate buffer pH 4.5 more amount of drug was released. So, acetate buffer pH 4.5 was selected as the dissolution media for racecadotril. But drug release was found only 53.34 % in 60 min which was not satisfactory. For APIs that exhibit low solubility in aqueous media throughout the pH range, the addition of surfactants is recommended. [17] A medium resulting in a gradual increase of released drug near to 100% was preferred because it is more likely to detect differences in formulation or processing parameters. Therefore, the dissolution media was changed with addition of surfactant such as sodium lauryl sulfate (SLS) to improve the dissolution profile. Further, dissolution profile of racecadotril was obtained in acetate buffer of pH 4.5 with different concentration of SLS (0.25% w/v, 0.5 % w/v, 0.75% w/v and 1.0% w/v) and form that minimum optimal concentration of SLS was selected. Further, SLS could not influenced the peak retention time of RCD during determination of drug released by HPLC method. Effect of SLS on dissolution observed in Table 3 and Figure 3.

From the analysis of Table 3 and Figure 3, it was observed that about 82.26% of racecadotril was released in acetate buffer pH 4.5 with 0.75% SLS in 60 minutes which was prerequisite. Percentage drug release of racecadotril in acetate buffer pH 4.5 with 1 % SLS was found similar as compared to acetate buffer pH 4.5 with 0.75% SLS while less amount of drug released in acetate buffer pH 4.5 with 0.5 % SLS. Therefore, it was conclude that acetate buffer pH 4.5 with 0.75% SLS was the suitable media for drug release of racecadotril as it gave desirable dissolution profile.

CONCLUSION

Dissolution method for racecadotril was successfully developed by using acetate buffer pH 4.5 and SLS (0.75%). By adopting these dissolution parameters, the dissolution limitations of poorly water soluble, racecadotril can be resolved successfully.

REFERENCES AND NOTES

1. Banakar U V, Block L H. Beyond bioavailability testing. Pharm Technol, 7: 107–117, 1983.
2. Löbenberg R. Dissolution testing as a prognostic tool for oral drug absorption: dissolution behavior of glibenclamide. Pharm Res, 17: 439–444, 2000.
3. Dyas A M, Shah U U. Dissolution and dissolution testing. In: Swarbrick J, ed. Encyclopedia of Pharmaceutical Technology, Vol. 1, 3rd edn. New York: Informa Healthcare USA, Inc., 908–928, 2007.
4. Dressman J B. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharm Res, 15: 11–22, 1998.
5. Saccone C S, Tessore J, Olivera S A, Meneces N S. Statistical properties of the dissolution test of USP. Dissolution Technologies, 25-28, 2004,
6. Noyes A W, Whitney W R. The rate of solution of solid substances in their own solutions. J Am Chem Soc, 19:930–934. 1897.
7. Brunner L, Tolloczko S. Über dieAuflösungsgeschwindigkeit Fester Körper. Z Phys Chem 35: 282–290, 1900.
8. Dokoumetzidis A, Macheras P. A century of dissolution research: from Noyes andWhitney to the Biopharmaceutics classification system. Int J Pharm, 321: 1–11, 2006.

9. The dissolution procedure. United States Pharmacopeia and National Formulary USP32 – NF27. Rockville, M D: The United States Pharmacopeial Convention, Inc., 601, 2009.
10. Brown C K. Acceptable analytical practices for dissolution testing of poorly soluble compounds. Pharm Technol, 28: 56–65, 2004.
11. Gowthamarajan K, Singh S K. Dissolution testing for poorly soluble drugs: a continuing perspective. Dissolution Technol, 17: 24–33, 2010.
12. Zhang H, Yu L. Dissolution Testing for Solid Oral Drug Products: Theoretical Considerations. American Pharmaceutical Review, 7(5): 26-31, 2004.
13. Tadey T, Carr G. Dissolution Testing for Solid Oral Dosage Forms", Pharmaceutical Formulation and Quality, July/August 11(4): 22-27, 2009.
14. Bandari S, Mittapalli R K, Gannu R, Rao Y M. Orodispersible tablets: An overview. Asian J Pharm., 2: 2–11, 2008.
15. Kevin G, Patel J, Dhingani A, Raval M, Dharamsi A. Development and validation of a rapid and sensitive HPLC method for estimation of racecadotril. Inventi Rapid: Pharm Analysis & Quality Assurance, 2013(1):1-5, 2012.
16. United states pharmacopoeia 32, The United States Pharmacopeial Convention, 2009.
17. In Vitro dissolution testing for solid oral dosage forms. Technical Brief (5): 2010. www.particlesciences.com

Acknowledment

The authors are grateful to the Gujarat Council on Science and Technology (GUJCOST), Gandhinagar, Gujarat for providing financial assistance in this work (MRP-2015538).

Cite this article as: Garala K, Patel J, Dhingani A, Raval M, Dharamsi A. Overcoming Limitations in Dissolution Testing of Poorly Water Soluble Racecadotril. Inventi Rapid: Pharm Tech, 2013(1):1-4, 2012.