Original Article

Unsuitability of pharmacopoeial dissolution conditions for entacapone: Effects of various dissolution parameters on dissolution profile

S. K. Pallewar, T. A. Premchandani, A. M. Pethe

Department of Pharmaceutics, SVKM'S, NMIMS University, School of Pharmacy and Technology Management, Dhule, Maharashtra, India

Abstract

Purpose: Entacapone, a catechol-O-methyltransferase inhibitor, is poorly water soluble (BCS class IV). The dissolution profile of pure Entacapone is improved in the presence of an alkaline buffer and after addition of a surfactant by facilitating the drug release process at the solid/liquid interface. **Rationale:** According to USP the best dissolution medium for Entacapone is phosphate buffer 5.8 in type II paddle-type apparatus with a paddle speed of 50 rpm. **Materials and Methods:** In this article an effect of various parameters (buffer, surfactant, and RPM) on the dissolution profile of Entacapone is studied by applying factorial design 33 (phosphate buffer- 5.3, 5.8, and 6.8; sodium lauryl sulfate- 0.5%, 1.0%, and 1.5%; rotation speed of paddle- 50, 75, and 100). Pure Entacapone pellets were formed using a hydraulic press. **Conclusion:** The release profile data revealed that the dissolution profile of Entacapone is remarkably improved in the alkaline medium (6.8), addition of surfactant does not affect the release profile, whereas increasing RPM of the paddle reduces the dissolution profile; hence it can be stated that Entacapone dissolution is pH dependent, showing maximum dissolution and pH 6.8 which is contradictory to the conditions specified in USP 2010.

Key words: Dissolution rate, entacapone, sodium lauryl sulfate, solubility

INTRODUCTION

United States Pharmacopeia (USP) for the first time introduces dissolution tests in USP XVIII in 1969, with an objective that, so as to get absorbed, drug should be dissolved appropriately in gastrointestinal tract. Hence dissolution tests become most important to determine product quality and drug release behavior. In general, drug dissolution is defined as the rate and extent of dissolution and this involves two steps, drug release from the dosage form by the liberation process and drug transport within the dissolution medium by the convection process.[1-6]

Access this article online	
Quick Response Code:	Website: www.pnrjournal.com
	DOI: 10.4103/0976-9234.99667

Several factors influence drug dissolution including:

1. Physicochemical properties of drug (e.g., solubility, crystalline forms, and particle size).
2. Formulation characteristics (e.g., additives, manufacturing parameters).
3. Dissolution method (e.g., apparatus type; volume, surface tension, viscosity, and pH of the medium).[2-4]

Entacapone is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs with the highest activities in the liver and kidney. COMT also occurs in the heart, lung, smooth and skeletal muscles, intestinal tract, reproductive organs, various glands, adipose tissue, skin, blood cells, and neuronal

Address for correspondence:
Mr. Tushar A. Premchandani, Department of Pharmaceutics, School of Pharmacy and Technology Management, SVKM'S NMIMS University, Shirpur, District Dhule, Maharashtra State, 425 405, India. E-mail: tusharpremin@gmail.com

tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, and epinephrine), and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major metabolizing enzyme for levodopa, catalyzing the metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the brain and periphery.[6]

The dissolution study is particularly important for insoluble or low-solubility drugs, where absorption is dissolution rate limited (class II and class IV drugs in respect to Biopharmaceutics Classification System [BCS]). At the same time, development of a dissolution method for this group of drugs is very challenging. The dissolution medium must provide sink conditions (i.e., saturation solubility is at least three times more than the drug concentration in the dissolution medium). The absence of sink conditions may result in unpredictable release kinetics and suppression of release profiles. Generation of dissolution data under the nonsink condition can easily overweigh the role of formulation changes in the selection of formulation.[7-11]

This study describes dissolution quality assessments, in the evaluation of the rate of dissolution for Entacapone, a poorly soluble class IV drug. It was noted that their dissolution depends on many variables. The influence of surfactant concentration, paddle speed, and varied buffer medium pH on their dissolution behavior was investigated.

MATERIALS AND METHODS

Materials

Entacapone was obtained as a gift sample from Ajanta Pharmaceuticals Ltd., Mumbai, India. Sodium lauryl sulfate, sodium hydroxide, orthophosphoric acid, and other chemicals were procured from SD Fine chemicals Mumbai. Deionized water was used in preparation of all test media.

Methods

Preparation of the standard curve

As Entacapone is poorly soluble in an aqueous medium, pure Entacapone 10 mg was dissolved in 10 ml methanol, and from the resultant solution 0.2 ml is dissolved in 10 ml methanol. From this solution, 0.5--3 ml of solution was again dissolved in 10 ml methanol to get a 01--06 ppm standard Entacapone solution respectively. These solutions were then scanned spectrophotometrically at 300--500 nm wavelength. The following calibration curve along with readings was obtained [Graph 1].

Entacapone pellet preparation

Entacapone was obtained as a gift sample from Ajanta pharmaceuticals Ltd., Mumbai. To study the intrinsic dissolution profile of Entacapone, pure form of 200 mg drug without excipients was compressed using a hydraulic press. Prepared pellets were stored in a closed container, and used for dissolution studies.

Preparation of buffer solutions

Dissolution studies were to be carried out using 5.3, 5.5, and 6.8 phosphate buffers as dissolution media; thus buffer preparation was carried out as per USP 30th edition.

Dissolution studies

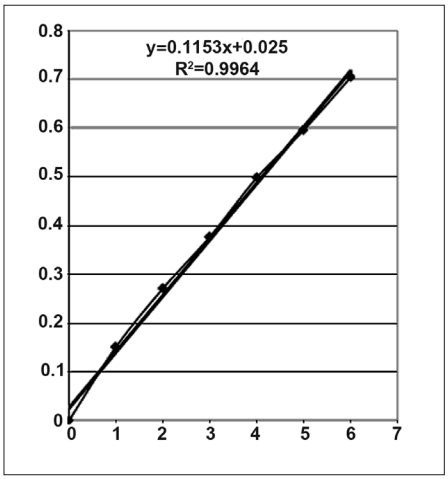
Dissolution studies were carried out using a dissolution tester type II (Electrolab TDT-08L). The test material was placed in 900 ml of dissolution media at 37 ± 0.5°C using a USP dissolution apparatus II (paddle method). Following variables were studied in this study.

1. Paddle speed of 50, 75, and 100 RPM.
2. Phosphate buffer of 5.3, 5.5, and 6.8 pH.
3. Sodium lauryl sulfate concentration of 0.5%, 1.0%, and 1.5%.

At regular intervals [1, 2, 3, 4, 5, 6, 7, and 8 hours], 5 ml of an aliquot of medium were withdrawn and sink conditions

Table 1: Calibration curve absorbance values

Concentration	Absorbance
1	0.151
2	0.271
3	0.377
4	0.498
5	0.596
6	0.704



Graph 1: Calibration curve for Entacapone

were maintained by replacing with an equivalent amount of fresh medium. The samples are analyzed at 370 nm using a Perkin Elmer UV-vis spectrophotometer, using the respective phosphate buffer as reagent blank.

Following trials were thus generated by Minitab software and thus carried out. For each pH 10 trials were carried out. At each pH, a single trial having a paddle speed 50 RPM, with no SLS concentration, was carried out so as to find out the effect of surfactants.

RESULTS

The % release for different sets of pH was as described in following Tables 1-5.

DISCUSSION

Since Entacapone is poorly water soluble, dissolution studies were carried out in three different media as 5.3, 5.5, 6.8 phosphate buffers. The comparative release profile is being shown in Tables 2,3 and 4. All the calculations were performed in triplicate.

As the pH of the media was increased the dissolution of Entacapone was found to be increased, which gives an idea about the pH-dependent solubility of Entacapone.

Among the three different pHs, the maximum % release was observed at 6.8 pH at which it is independent of SLS concentrations.

From the above results it was revealed that dissolution

Table 2: Trials generated by Minitab

Trial no.	Buffer	Concentration of SLS (%)	Rotation speed of the paddle (RPM)
1	6.8	1	100
2	5.5	1	100
3	5.3	1.5	50
4	6.8	0.5	75
5	6.8	1.5	75
6	5.3	0.5	50
7	5.5	1.5	75
8	5.5	0.5	75
9	5.3	1	50
10	5.3	1.5	75
11	5.5	1	75
12	6.8	1	50
13	5.3	0.5	75
14	5.5	0.5	50
15	5.3	1	75
16	5.3	1.5	100
17	6.8	1	75
18	5.5	1.5	100
19	5.3	0.5	100
20	5.5	0.5	100
21	6.8	1.5	50
22	6.8	0.5	100
23	6.8	0.5	50
24	5.5	1.5	50
25	6.8	1.5	100
25	5.3	1	100
27	5.5	1	50
28	5.3	–	50
29	5.5	–	50
30	6.8	–	50

Table 3: % release at pH 5.3 at the end of 8 hours

pH	SLS	RPM	% release
5.3	1.5	50	4.5 + 0.98
5.3	0.5	50	7.6 + 1.98
5.3	1.0	50	12.6 + 3.5
5.3	1.5	75	5.4 + 2.38
5.3	0.5	75	7.0 + 2.43
5.3	1.0	75	13.5 + 1.52
5.3	1.5	100	3.3 + 1.54
5.3	0.5	100	5.0 + 1.65
5.3	1.0	100	4.9 + 2.74
5.3	–	50	1.6 + 2.38

Table 4: % release at pH 5.5 at the end of 8 hours

pH	SLS	RPM	% release
5.5	1.0	100	6.3 + 1.96
5.5	1.5	75	52.3 + 2.18
5.5	0.5	75	17.6 + 0.59
5.5	1.0	75	3.1 + 1.75
5.5	0.5	50	18.1 + 0.54
5.5	1.5	100	5.30 + 1.97
5.5	0.5	100	2.5 + 1.34
5.5	1.5	50	2.0 + 1.97
5.5	1.0	50	21.1 + 3.51
5.5	–	50	14.6 + 1.99

Table 5: % release at pH 6.8 at the end of 8 hours

pH	SLS	RPM	% release
6.8	1.0	100	43.2 + 2.62
6.8	0.5	75	85.5 + 1.30
6.8	1.5	75	34.8 + 4.02
6.8	1.0	50	75.5 + 2.49
6.8	1.0	75	48.7 + 2.18
6.8	1.5	50	80.3 + 0.64
6.8	0.5	100	37.7 + 1.40
6.8	0.5	50	68.3 + 2.87
6.8	1.5	100	34.8+ 4.02
6.8	–	50	23.0 + 1.82

of Entacapone was dependent on pH, and favorable in alkaline pH.

As per USP 30, official conditions for Entacapone dissolution are using a pH 5.5 phosphate buffer as the dissolution medium (900 ml) at a 50 RPM paddle speed. But the above data revealed that the dissolution of Entacapone was least in 5.3 pH and was maximum in 6.8 pH phosphate buffer at paddle speed of 75 RPM containing 0.5 % w/v of SLS. The main effect plot confirms that by changing pH from 5.3 to 6.8 marked improvement of % drug release was seen, addition of surfactant to the dissolution medium hardly affects release profile, whereas increasing rotation speed of paddle decreases the release profile of Entacapone.

From above different trials it was also observed that % release of Entacapone was independent on SLS concentration, and there was a negative impact of the paddle speed.

CONCLUSION

The effect of pH of dissolution media on % release of Entacapone suggests that least % release was observed at 5.3 pH and maximum at 6.8 pH.

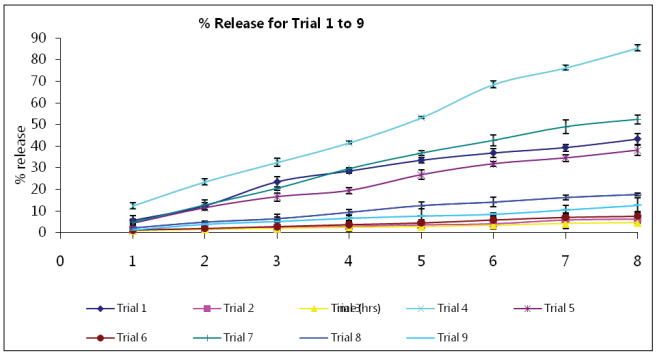


Figure 1: % Release for trials 1-9

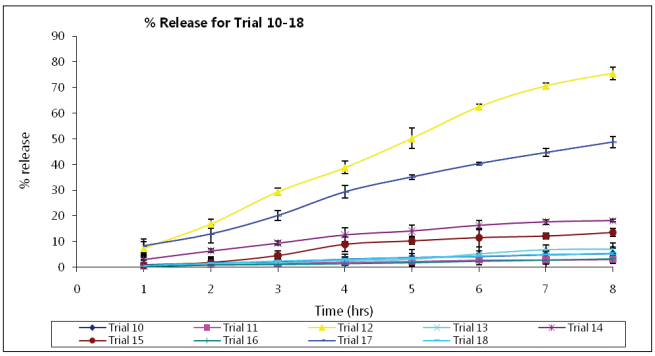


Figure 2: % Release for trials 10-18

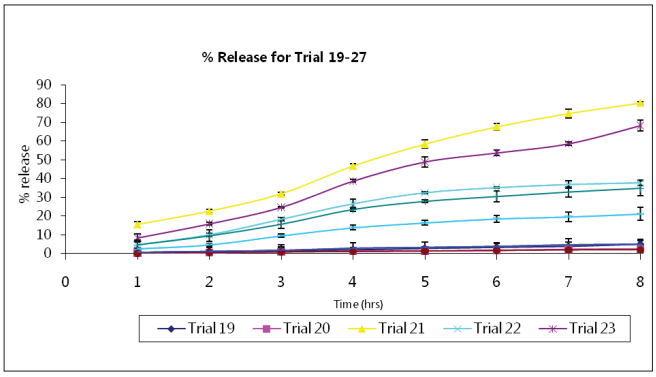


Figure 3: % Release for trials 19--27

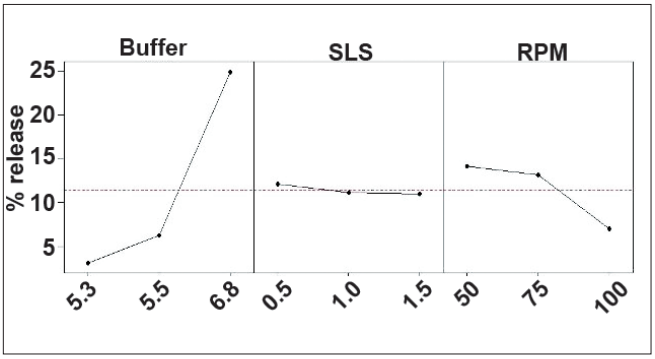


Figure 4: Main effects plot-data means for % release

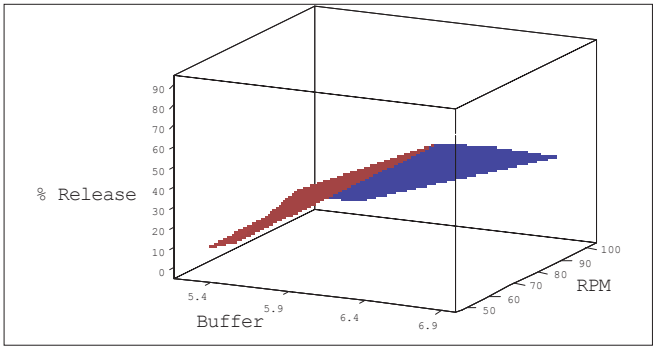


Figure 5: Three-dimensional graphical representation of % release, buffer, and RPM

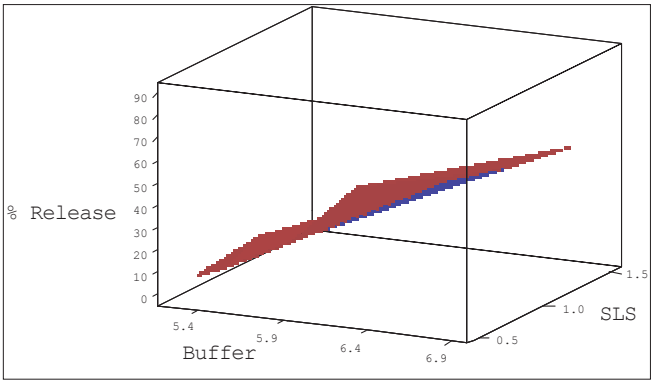


Figure 6: Three-dimensional graphical representation of % release, buffer, and SLS

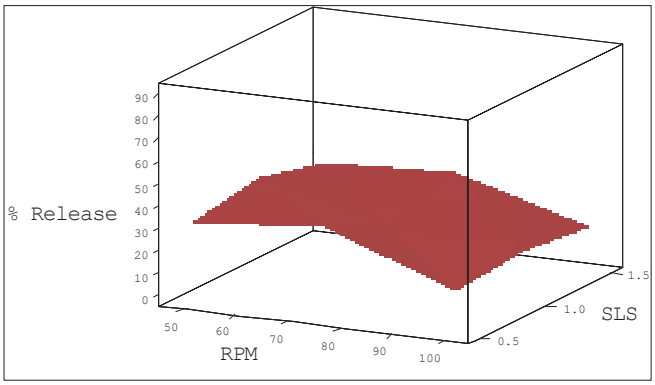


Figure 7: Three-dimensional graphical representation of % release, RPM, and SLS

The effect of paddle speed on % release of Entacapone was maximum at 50 RPM, and decreased with higher paddle speed.

Similarly for SLS concentration it was observed that media containing 0.5% SLS showed optimum % release whereas least release was observed in media containing 1.5% SLS concentration, and moreover the % release seems to be unaffected by SLS concentration.

The comparative release profiles for various trails is shown in Figures 1-4. The 3D surface plot also suggests that alkaline media favors the release of Entacapone at intermediate rotation speed of paddle.

Among the three variables studied, the effect of pH on the dissolution profile of Entacapone was found to be more prominent and order of release is 6.8 > 5.5 > 5.3. The 3D graphical representation shown in Figures 5-7 also confirms the major effect of pH on the release profile of Entacapone. Thus from the above results it was concluded that 0.5 % w/v SLS in a 6.8 phosphate buffer at a 75 RPM paddle speed gives a better release profile amongst all the trials.

REFERENCES

1. Jamzad S, Fassihi R. Role of Surfactant and pH on Dissolution Properties of Fenofibrate and Glipizide—A Technical Note. AAPS PharmSciTech 2006;7:E33.
2. Dressman JB, Reppas C. *In vitro–in vivo* correlations for lipophilic, poorly water-soluble drugs. Eur J Pharm Sci 2000;11 Suppl 2:73-80.
3. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc 1897;19:930-4.
4. Horter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv Drug Del Rev 1997;25:3-14.
5. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms. Pharm Res 1998;15:11-22.
6. United State of Pharmacopeia 30- National Formulary- 25. Vol. 1. USA: The United states Pharmacopoeial Convention Inc.; 2007. p. 277-87.
7. Horter D, Dressman JB. Influence of Physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv Drug Delivery Rev 2001;46:75-87.
8. Dressman JB, Vertzoni M, Goumas K, Reppas C. Estimating drug solubility in the gastrointestinal tract. Adv Drug Del Rev 2007; 59:591-602.
9. Gupta VR, Patil PB, Udupi RH. Development of dissolution medium for poorly soluble mefenamic acid. Res J Pharma Biol Chem Sci 2010;1:544-8.
10. Shah VP, Konecny JJ, Everett RL, McCullough B, Noorizadeh AC, Skelly JP. *In vitro* Dissolution Profile of Water Soluble Dosage Forms in Presence of Surfactants. Pharm Res 1989;6:612-8.
11. Park SH, Choi HK. The Effects of Surfactants on Dissolution Profile of Poorly Soluble Acidic Drugs. Int J Pharm 2006; 321:35-41.

How to cite this article: Pallewar SK, Premchandani TA, Pethe AM. Unsuitability of pharmacopoeial dissolution conditions for entacapone: Effects of various dissolution parameters on dissolution profile. J Pharm Negative Results 2012;3:49-53.

Source of Support: Nil. **Conflict of Interest:** None declared.