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Research Article

Development and Validation of a Discriminating *In Vitro* Dissolution Method for Oral Formulations Containing Satranidazole

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The development of a meaningful dissolution procedure for drug products with limited water solubility has been a challenge to the pharmaceutical industry. Satranidazole (BCS Class II drug) is a new nitroimidazole derivative with potent antiamoebic action. There is no official dissolution medium available in the literature. In the present study, parameters such as saturation solubility in different pH medium, dissolution behavior of formulations, influence of sink conditions, stability, and discriminatory effect of dissolution testing were studied for the selection of a proper dissolution medium. Results of solubility data revealed that solubility of Satranidazole decreases with an increase in pH. Satranidazole showed better sink condition in 0.1 N HCl as compared to other media. The drug and marketed formulations were stable in the dissolution media used. An agitation speed of 75 rpm showed a more discriminating drug release profile than 50 rpm. Using optimized dissolution parameters (paddle at 75 rpm, 900 mL 0.1 N HCl) greater than 80% of the label amount is released over 60 minutes. UV-spectroscopic method used was validated for the specificity, linearity, precision, robustness, and solution stability. The method was successfully applied to granular formulations and also to marketed tablets containing 300 mg Satranidazole.

1. Introduction

Satranidazole (STZ) is a new nitroimidazole derivative with potent antiamoebic action. It is used in the treatment of intestinal and hepatic amoebiasis, giardiasis, trichomoniasis, and anaerobic infections. Its dose is 300 mg twice daily for 3–5 days in the treatment of amoebiasis and 600 mg as a single dose in the treatment of giardiasis and trichomoniasis. It is reported that Satranidazole exhibits significantly higher plasma concentrations than metronidazole and has a plasma elimination half-life of 1.01 h which is significantly shorter than the corresponding metronidazole half-life of 3.62 h [1]. Also Satranidazole is having better tolerability, absence of neurological and disulfiram like reactions, and it can be preferred in patients with susceptible neurological symptoms [2].

Dissolution study is particularly important for insoluble or low solubility drugs where absorption is dissolution rate limited. The incorporation of adjuvants (e.g., diluents, lubricants, and surfactants) into the formulation of a solid oral dosage form can cause significant effects on the dissolution rate of drugs, especially those that are hydrophobic and poorly soluble [3]. In the case of Class 2 drugs in the Biopharmaceutics Classification System (BCS), dissolution may be the rate-limiting step for drug absorption, so suitable dissolution tests can be used to predict differences in bioavailability among different formulations [4]. The choice of formulation is often of critical importance in establishing a successful product for oral administration of this class of drugs [5]. In this context, the purpose of the present study was to evaluate and compare the dissolution profiles of a compounded formulation to that of a marketed product using Satranidazole as a model drug. This drug is poorly soluble in water and has high *in vitro* permeability; it is therefore classified as BCS Class II [6]. To date, there is no published dissolution test for the evaluation of *in vitro* release profiles

of this drug from immediate-release solid oral dosage forms. The objective of the present study was to develop a validated *in vitro* dissolution method for oral granular formulation containing Satranidazole.

2. Materials and Methods

2.1. Materials. Satranidazole was obtained as a gift sample from Alkem Laboratories, Mumbai. Eudragit E100 was obtained from Evonik Degussa, Mumbai. Satrogyl tablets (strength: 300 mg) were purchased from market. All the chemicals and reagents used were of analytical grade.

2.2. Formulation Development of Taste Masked STZ Granules. Two different batches of taste masked granules of STZ were formed by melt granulation technique using stearic acid and Eudragit EPO using different ratio of drug to stearic acid. The composition of the compounded formulation is mentioned below.

Product A. It is labeled to contain 300 mg of the drug and the following excipients: stearic acid, Eudragit EPO, starch 1500, magnesium oxide, mannitol, xylitol, sodium carboxymethyl cellulose, hydroxypropyl cellulose, vanilla, aspartame, and magnesium stearate with drug to stearic acid ratio (1 : 2).

Product B. It islabeled to contain 300 mg of the drug and the same above mentioned excipients with different drug to stearic acid ratio (1 : 1.5).

The assay of the above two products was performed using previously developed and validated HPLC method, and the contents results were used to calculate the percentage release on each time of dissolution profile. These two products were used to study the discriminatory power of developed method.

2.3. Instrumentation. Dissolution test was performed in an Electrolab dissolution test system (TDT-08L), in accordance with USP Pharmacopoeia general method. A double-beam UV-Vis spectrophotometer (Shimadzu 1800, Japan) with 1.0 cm quartz cells was used for all absorbance measurements. All the absorbances were carried out at a UV wavelength of 320 nm.

2.4. Saturation Solubility Study. The saturation solubility of Satranidazole was determined in pH 1.2 (0.1 N HCl), 2.1 (0.01 N HCl), 4.5 (acetate buffer), 6.8 (phosphate buffer), 7.4 (phosphate buffer), and distilled water at 37°C. Excess STZ was added to 100 mL of dissolution medium in a conical flask and agitated continuously at room temperature for 8 h on a shaker. The solutions were kept aside for 1 h until equilibrium was achieved. The solutions were then filtered through no. 41 Whatman filter paper, and the filtrate was suitably diluted and analyzed spectrophotometrically at 320 nm.

2.5. Determination of Sink Conditions and Dissolution Conditions. For poorly soluble drugs, medium selection for dissolution tests is an important step in method validation due to the difficulty to achieve *sink* condition [7], which is defined as the volume of medium at least three times greater than that required to dissolve the dose of the drug being tested [8].

Sink condition was determined using following equation:

$$\text{Maximum Dissolvable Dose} = V \times \frac{C_S}{\text{Sink}}, \quad (1)$$

where

V = Dissolution medium volume,

C_S = Saturated solubility of the compound in the medium,

Sink = Sink condition factor.

From preselected, 0.1 N HCl media, dissolution testing was performed on granules ($n = 6$) in compliance with USP <1092> using paddle (USP-II). The discriminatory power of the dissolution method was assessed by analyzing two in-house developed granular formulations of STZ (coded as products A and B) of 300 mg strength prepared by using different composition of excipients. Product A contains 600 mg stearic acid as a disintegrant whereas product B contains 450 mg stearic acid. Other excipients in both products were the same.

The dissolution rate of STZ from granules of product A was assessed at 50 and 75 rpm, the recommended speeds for USP apparatus II. At 75 rpm, product A exhibited a very rapid dissolution without coning.

A calibrated dissolution apparatus (USP II) was used with paddle at 75 rpm and bath temperature maintained at 37 ± 0.5°C. Nine hundred millilitre freshly prepared 0.1 N HCl solution was used as the dissolution medium. Dissolution samples were collected at 10, 15, 30, 45, and 60 min for immediate-release granules (products A and B) and replaced with an equal volume of the fresh medium to maintain a constant total volume. After the end of each test time, samples aliquots were filtered, diluted in dissolution medium, when necessary, and were analyzed by UV at 320 nm. At each time point, a 5 mL sample was removed from each vessel and filtered into labeled glass tubes, diluted and analyzed by UV at 320 nm. The dissolution of marketed formulation was also carried out in same conditions. The % cumulative release of drug was calculated using standard calibration curve of STZ prepared in 0.1 N HCl.

2.6. Comparison of Dissolution Profiles by a Model-Independent Method. The *in vitro* dissolution data of products A and B was compared by two-tailed Student's t-test. Moore and Flanner proposed a model-independent mathematical approach to compare the dissolution profile using two factors, f_1 and f_2 [9]:

$$f_1 = \left\{ \frac{\left[\sum_{t=1}^{n} |R_t - T_t|\right]}{\left[\sum_{t=1}^{n} R_t\right]} \right\} \times 100,$$
$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n}\right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}, \quad (2)$$

where R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the reference and

test product, respectively. The factor f_1 is proportional to the average difference between the two profiles, whereas factor f_2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time points. The factor f_2 measures the closeness between the two profiles. Because of the nature of measurement, f_1 was described as difference factor and f_2 as similarity factor [10]. FDA has set a public standard of f_2 value between 50 and 100 to indicate similarity between two dissolution profiles.

2.7. Analytical Method Validation. UV-spectroscopic method used for estimation of Satranidazole in dissolution samples was validated by determining the specificity, linearity, precision, robustness, and solution stability according to USP and ICH guidelines [11–13]. The standard solution containing 25 μg/mL of Satranidazole in 0.1 N HCl was scanned between 200 and 400 nm to determine the λ max using 0.1 N HCl as blank in UV spectrophotometer (Shimadzu 1800).

2.7.1. Specificity. Placebo batch of the granules was prepared in its usual concentration. Dissolution was performed similarly as that of the STZ granules in 900 mL of 0.1 N HCL as dissolution medium using USP apparatus II at 37 ± 0.5°C at 75 rpm for 1 hr. Aliquots of this solution were filtered, diluted appropriately, and analyzed by UV spectrophotometric method.

2.7.2. Linearity. Stock solution of 1000 ppm was prepared by dissolving 50 mg drug in 50 mL methanol. From this 2nd stock solution of 100 ppm was prepared in 0.1 N HCL. Further dilutions were carried out to give solutions of 2, 4, 6, 8, 10, 15, 25, and 30 μg/mL. 0.1 N HCL was used as blank and absorbances of prepared solutions were noted at 320 nm and calibration curve was constructed. Each solution was prepared in triplicate.

2.7.3. Recovery/Accuracy. A recovery study was carried out by adding granules equivalent to 80, 100, and 120% of drug in the dissolution vessel. The dissolution test was done for 60 min using 900 mL of dissolution 0.1 N HCL, apparatus 2 rotating at 75 rpm. Aliquots of 5 mL were filtered with quantitative filter and analyzed by UV spectrophotometric method at the final concentrations 13.3, 16.6, and 20 μg/mL, respectively. Each concentration was prepared in duplicate and each one was analyzed in triplicate [14].

2.7.4. Method Precision/Repeatability. It was performed on 6 doses of granules from same batch and samples were analyzed according to the test method and aliquots were taken at the end of 60 minutes [15].

Intermediate precision was evaluated to determine the effects of random events on the precision of the analytical procedure. This was done by performing the dissolution on same batch of granules on different day by changing the analyst.

Table 1: pH dependent solubility of Satranidazole in different buffer solutions.

pH	Solubility (mg/mL)*	Sink condition
1.2 (0.1 N HCl)	1.5125	4.5375
2.1 (0.01 N HCl)	1.1985	3.5955
4.5 (acetate buffer)	0.9813	2.9439
6.8 (phosphate buffer)	0.8251	2.4753
7.4 (phosphate buffer)	0.9825	2.9475
Distilled water	0.8133	2.4399

*Mean of 3 determinations.

2.7.5. Robustness. Robustness was studied by changing the wavelength of UV spectrophotometer at 320 ± 2 nm and also by changing agitation rate of dissolution apparatus at 75 ± 2 rpm.

2.7.6. Solutions Stability. To evaluate solution stability, the sample solution was stored at room temperature and was analyzed by UV spectrophotometer for 24 hrs at various time intervals.

3. Results and Discussions

For immediate-release formulations, apparatus 1 (baskets) at 100 rpm or apparatus 2 (paddles) at 50 or 75 rpm is most commonly used. Other agitation speeds and apparatus are acceptable with appropriate justification. For dosage forms that exhibit coning (mounding) under the paddle at 50 rpm, the coning can be reduced by increasing the paddle speed to 75 rpm, thus reducing the artifact and improving the data.

Reference compendia and guidelines of Food Drug Administration, United States Pharmacopeia, Federation International Pharmaceutique, World Health Organization, European Pharmacopoeia, and Japanese Pharmacopoeia recommend the use of rotating paddle between 50 and 100 rpm with volume of 500 to 1000 mL along with surfactant to provide sink condition for insoluble drug products [16].

The most common way to check the discriminatory power of the method is to test formulations with differences resulting forms, changes in the characteristics of the API, drug product composition, product manufacturing process, and stability conditions [10, 17–19].

Drug solubility and solution stability are important properties to be considered when selecting the dissolution medium. From the saturation solubility data and established sink conditions (Table 1), it was found that pH 1.2 (0.1 N HCL) was better dissolution medium for Satranidazole.

The solution stability data is represented in Table 2. The solution of drug was found to be stable in 0.1 N HCL for 24 hours. The cumulative % RSD obtained was less than 2 at the end of 24 hrs.

The stirring speeds of 50 rpm and 75 rpm for product A were tested. The statistical Student t-test was applied to compare the percent drug release, using 50 or 75 rpm for granules (Table 3). The P value for granules was smaller than the delineated significance level, indicating that there is statistically significant difference between the drug release

Table 2: Stability data in 0.1 N HCL.

Time	Absorbance	Mean	SD	% RSD
30 minutes	0.757	—	—	—
1 hr	0.758	0.7575	0.00071	0.093
2 hrs	0.752	0.75567	0.00321	0.425
4 hrs	0.759	0.7565	0.00311	0.411
8 hrs	0.745	0.7542	0.00581	0.770
16 hrs	0.734	0.75083	0.00975	1.298
24 hrs	0.745	0.75	0.00917	1.222

Table 3: Product A dissolution tests results ($n = 12$), using different stirring speeds and HCl 0.1 N as dissolution medium.

Time in minutes	% Cumulative release		t-test	P
	50 rpm	75 rpm		
0	0	0		
5	5.91	8.65		
10	17.57	33.15		
15	39.62	45.29	4.4858	0.0065
30	45.88	66.67		
45	60.43	76.48		
60	71.38	87.59		

Table 4: Comparison of dissolution profile of two products (A and B) with different ratio of drug : stearic acid.

Time (minutes)	Product A Drug: stearic acid (1 : 2)	Product B Drug: stearic acid (1 : 1.5)
0	0	0
5	8.71 ± 0.426	8.02 ± 0.512
10	33.9 ± 0.299	52.99 ± 0.69
15	46.05 ± 0.343	62.68 ± 0.489
30	65.83 ± 0.378	73.40 ± 0.397
45	78.57 ± 0.418	81.66 ± 0.434
60	87.65 ± 0.404	90.01 ± 0.546
Similarity factor f_2	46	
Difference factor f_1	17	

Table 5: Linearity data.

Concentration (in mcg/mL)	Absorbance
2	0.0822
4	0.1433
6	0.2175
8	0.2793
10	0.3398
15	0.5057
20	0.6301
25	0.7518
30	0.9204

percent, and suggested that the stirring speed of 75 rpm is better than 50 rpm.

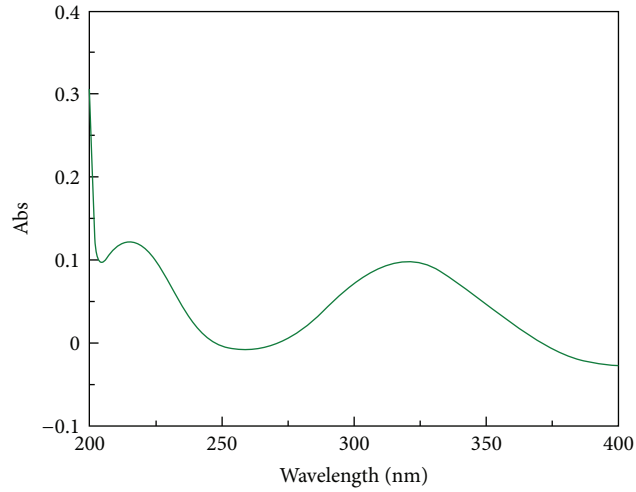

Figure 1: UV spectrum of STZ in 0.1 N HCl.

Table 6: Results of accuracy.

Added amount (μg)	Recovered amount (μg)	Recovery* (%)	Mean (%)	% RSD
13.3 (80%)	12.93	97.21 ± 1.2430	99.1133	1.90
16.6 (100%)	16.46	99.15 ± 1.3256		
20 (120%)	20.196	100.98 ± 1.5234		

*Each value is the mean of 3 determinations.

On comparison of dissolution of products A and B the f_1 value was found to be 46 and f_2 value was found to be 17 as shown in Table 4, indicating dissimilarity between products A and B. It can be concluded that the drug release profile at 75 rpm detected small changes in drug product composition.

The λ max was found to be 320 nm in dissolution medium and hence it was taken as the analytical wavelength. The UV spectrum of STZ in 0.1 N HCl is shown in Figure 1.

3.1. Specificity. It was found that dissolution of placebo was having no effect on dissolution of Satranidazole granules. Also the excipients used for the formulation of granules were not showing interference with the maximum absorption of drug.

3.2. Linearity. The calibration curve of STZ in 0.1 N HCL was plotted as shown in Figure 2. The correlation coefficient was found to be 0.997. These data indicated good linearity of STZ in the range of 2–30 μg/mL as shown in Table 5.

Limit of quantitation (LOQ) is the lowest amount of analyte in a sample that can be determined with acceptable precision and accuracy under stated experimental conditions. The quantitation limit is expressed as the concentration of analyte in the sample. The standard deviation and related standard deviation for the limit of quantitation were well within the desirable limit of no more than 2.0%. The lowest quantifiable concentration was 5.22 mcg/mL and this parameter can be used for predicting the drug release in low dose formulation.

Table 7: Method precision/repeatability.

Sample number	% cumulative release at 60 min		
	Day 1 Analyst 1		Day 2 Analyst 2
1	87.09		88.34
2	86.23		89.23
3	87.24		87.89
4	88.78		86.21
5	87.65		87.47
6	88.94		87.01
Mean	87.655		87.691
Standard deviation (SD)	1.042		1.052
Relative standard deviation (% RSD)	1.189		1.199
Mean		87.673	
Standard deviation (SD)		0.999	
Relative standard deviation (% RSD)		1.139	

Table 8: Change in wavelength.

Time (minutes)	At 318	At 320	At 322
	Average % release ± SD (n = 6)		
0	0	0	
5	8.95 ± 0.5456	85.12 ± 0.7678	83.98 ± 0.6789
10	34.01 ± 0.4345	98.23 ± 0.6678	97.31 ± 0.8012
15	44.25 ± 0.5987	99.81 ± 0.8978	98.12 ± 0.5612
30	66.87 ± 0.6745	101.29 ± 0.7809	99.24 ± 0.6769
45	77.12 ± 0.7568	76.84 ± 0.5982	77.46 ± 0.8145
60	85.93 ± 0.4768	87.09 ± 0.3780	85.76 ± 0.4568
Average at 60 min		86.26 ± 0.6744	
% RSD at 60 min		0.839	

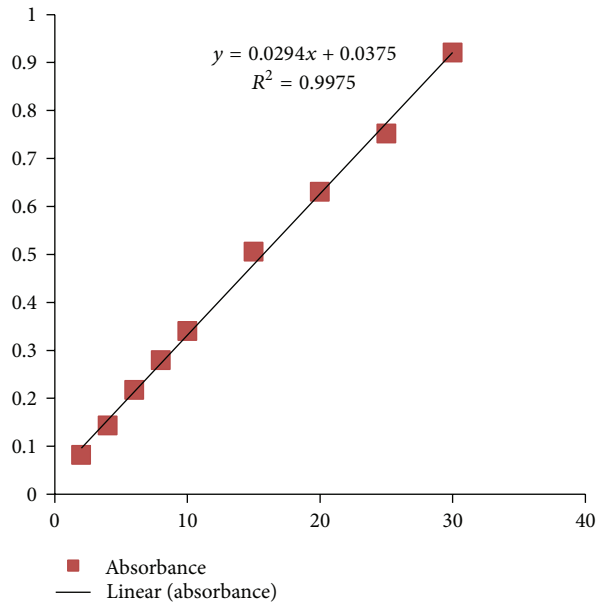

Figure 2: Linearity curve of STZ in 0.1 N HCl.

3.3. Accuracy. According to USP guidelines, the recovery for a dissolution test must be in the range of 95–105%. The percent recovery was from 97.21% to 100.98%. The accuracy of the method is acceptable from the results seen in Table 6.

3.4. Method Precision and Intermediate Precision. The percent RSD did not exceed 2% for the repeatability and intermediate precision, demonstrating suitable precision. The results are represented in Table 7.

3.5. Robustness. The percent RSD values were within the specified limit of 2% indicating the robustness of dissolution method on changing the agitation rate and also of UV method by changing the wavelength. The results are shown in Tables 8 and 9.

3.6. Evaluation of Marketed Formulation. By using above optimized dissolution conditions, the dissolution of marketed STZ film coated tablet was performed. The satisfactory % drug release was obtained at the end of 60 minutes. The results are shown in Table 10.

Table 9: Change in agitation rate.

Time (minutes)	At 73 rpm	At 75 rpm	At 77 rpm
	Average % release ± SD (n = 6)		
0	0	0	0
5	8.98 ± 0.3987	8.17 ± 0.5679	8.21 ± 0.5012
10	35.18 ± 0.5671	36.93 ± 0.5712	33.94 ± 0.6782
15	44.45 ± 0.6745	42.81 ± 0.7986	45.24 ± 0.5867
30	66.23 ± 0.7681	69.81 ± 0.6897	66.87 ± 0.6139
45	76.56 ± 0.8142	74.26 ± 0.5893	78.43 ± 0.7831
60	87.32 ± 0.4587	88.23 ± 0.6897	88.42 ± 0.4879
Average at 60 min		87.99 ± 0.7633	
% RSD at 60 min		0.668	

Table 10: Dissolution of marketed tablet.

Time (minutes)	% cumulative release
0	0
5	9.34 ± 0.432
10	28.87 ± 0.471
15	39.1 ± 0.572
30	65.43 ± 0.503
45	83.66 ± 0.66
60	88.1 ± 0.55

4. Conclusion

The dissolution test developed and validated for STZ granules was considered satisfactory. The conditions that allowed the dissolution determination were USP apparatus II (paddle) with 0.1 N HCl dissolution medium at 37.0 ± 0.5°C rotating at a speed of 75 rpm. STZ was found to be stable for 24 hrs indicating good stability of the drug in dissolution medium. The validated method was found to be specific, linear, precise, and accurate. The stated analytical method can be successfully used for *in vitro* dissolution and routine analysis of samples for STZ granules and also marketed STZ tablets.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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