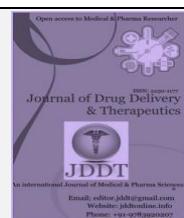


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Research Article

Dissolution Method Development and Validation for Estimation of Noscapine Tablets

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ABSTRACT

A dissolution method was developed and UV spectrophotometry was developed for the evaluation of the dissolution of tablets containing 15 mg Noscapine. The dissolution medium 0.1 N HCl was found suitable to ensure sink conditions. USP Apparatus 2, 900 mL dissolution medium 45 minutes and 100 RPM were fixed. Dissolution profiles were generated at 10, 15, 20, 30; 45 min. Dissolution samples were analyzed with UV spectrophotometer at 213 nm. The UV method for determination of tablet was developed and validated. The method presented linearity ($R^2 = 0.999$) in the concentration range of 1-9 μ g/mL. The recoveries were good, ranging from 97.18% to 101.45%. The intraday and Interday precision results were 0.54% and 0.78% RSD, respectively. The developed dissolution test is adequate for its purpose and can be applied for the quality control of tablets.

Keywords: Dissolution test; Noscapine; Tablets; UV Spectrophotometry method

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INTRODUCTION

Dissolution is defined as the rate and extent in which the amount of drug substance dissolved over a period of time. It is expressed as percentage release of drug substances present dosage forms like Tablets, Capsules, ointments and oral suspensions.^[1] In the present study dissolution method was developed for immediate release tablet(15 mg Noscapine).

The dissolution method developed for tablets is to evaluate the release pattern. ^[2]

In vitro dissolution tests for immediate release solid oral dosage forms are used: (a) to assess the lot-to-lot quality of a drug product;

(b) To assess the stability of the drug product;

(c) To ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process; and

(d) To develop new formulations. In formulation development, dissolution testing can aid in the selection of excipients, help optimize the manufacturing process, and enable formulation of the test product to match the release of the reference product^[3]

For immediate release products the basket (apparatus 1, usually at 100 rpm) and paddle (Apparatus 2, usually at 50 to 75 rpm) are conventional. Immediate release means 75% of the API is dissolved within 45 minutes, while the term rapidly dissolving means 85% API dissolved in 30 minutes and very rapidly dissolving 85% API in dissolved 15 minutes are important in dissolution testing.

Different Medias should be considered for immediate release products during development studies which are following:

- PH 1.2 buffer or 0.1 M Hydrochloric acid.
- pH 4.5 buffer
- pH 6.8 buffer
- Water may be considered as an additional medium

For development purposes the generation of dissolution patterns at short intervals such as 10, 15, 20, 30 and 45 minutes in the above media are recommended. ^[2]

The validation of the dissolution test can be divided into two parts.

- Equipment validation; equipment has to be calibrated taking into consideration the specifications for geometry and alignment of the dissolution apparatus.

- Test validation and requires the study of the performance parameters like accuracy, precision, robustness

It is true that a more discriminating dissolution method is preferred, but it is also true that a reliable dissolution test is of utmost importance.

A dissolution test with good precision makes it possible to efficiently compare several alternative formulation candidates to select the dosage form with the most suitable and reproducible drug release profile.^[4]

Following are the parameters that are usually considered during method development for Dissolution.

- Selection of dissolution medium

Selection of dissolution medium depends upon following parameters.

- Type of formulation (Immediate release or modified release).
- Solubility characteristics of active component.
- Type formulation design, (Tablets, Oily suspension, Soft gel capsule, hard gel capsule, etc.)

- Selection of RPM

Apparatus, Type of formulation and solubility characteristics of active substances are parameters which are used for selection of RPM

Any change in apparatus and use of higher RPM other than recommended parameters should be justified.

- Selection of dissolution time interval

Dissolution time is defined as the time in minutes at which maximum amount (+80% of label claim) of drug is dissolved. For immediate release dosage forms, 30min. to 60min. is recommended as dissolution time.

In some cases dissolution time may be higher i. e. up to 90min to 120min.

In such cases suitable justification should be provided. For modified release formulations (delayed release, enteric coated and sustained release), time depends upon design of formulation, site of action and therapeutic use.

Time for such formulations may be from about 6 hrs to 24 hrs or may be higher.

- Selection of other parameters

Media volume:

The volume of dissolution media is ideally 900ml, however if label claim is less than 5mg and if active substances has less absorbance at selected wavelength, then in that case dissolution volume can be reduced to 500ml.

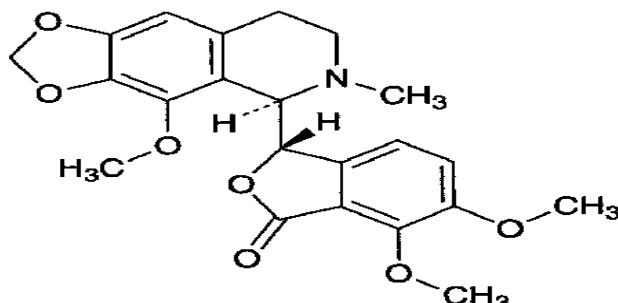
Media temperature:

The dissolution media temperature is fixed (i. e. 37.0 °C)^[4]

Introduction to drug

Noscapine is (3S)-6,7-Dimethoxy-3-[(5R)-4-methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinolin-5-yl]isobenzofuran-1(3H)-one (Figure 1). It is practically insoluble in water but soluble in organic solvents like in acetic acid (100), Ethanol (95) and in diethyl ether. It is centrally acting Antitussive.^[5-8] Noscapine inhibit bradykinin as the mode by which it functions. Noscapine's effect in treating strokes has been attributed to its

Bradykinin suppressive effect and its anti-cancer effect has been primarily attributed to its Microtubuleinterfering effect.^[9]



[MW=413.42 g/mol, chemical structure: C 22H23N07]

MATERIALS AND METHODS

Noscapine reference standard (99.947%) and noscapine tablets (containing 15 mg Noscapine) were kindly given by Bharat Parenterals Pvt. Ltd, Haripura, and Savli.

Analytical reagent grade, Hydrochloric acid, anhydrous potassium hydrogen phosphate, sodium hydroxide were used. Freshly distilled water was used throughout the study. Phosphate buffer pH 6.8, Phosphate buffer pH 4.0, 0.1 N HCl was prepared according to USP 27.

Apparatus

The dissolution test was performed in a six-station Electrolab dissolution tester in accordance with USP 27 general methods. A Shimadzu UV-vis spectrophotometer (model UV-1800) using 1.0-cm quartz cells and UV probe software were used for all absorbance measurements. A digital pH meter was used to determine the pH of all solutions. The ultrasonic bath used for deaeration.

Selection of Dissolution Media

Solubility data were used as the basis for the selection of a dissolution medium for Noscapine.

Quality Control Testing of 15-mg Noscapine Tablets

Noscapine tablets containing 15 mg of Noscapine were evaluated for color, shape, size, weight, variation, friability, disintegration time, hardness, drug content, and content uniformity.

Optimization of Dissolution method

The dissolution experiments were conducted in a six-station bath dissolution apparatus by adding Noscapine tablet (n=6) in bowl of 900 mL of each dissolution medium, a paddle dissolution apparatus, and stirring speeds of 50, 75, and 100 RPM. The temperature was stabilized at 37 ± 0.5 ° C. Aliquots of 10 mL were withdrawn manually at 45 min. The same volume of medium at 37 ± 0.5 ° C was replaced for constant volume. The sample was filtered through Whatman No. 41 filter paper and analyzed spectrophotometrically at 213 nm. The standard solution used in all dissolution tests was prepared using Noscapine equivalent to 15 mg. The UV spectrophotometric method was developed and validated.

Validation of Dissolution Method

The method was validated by the analysis of specificity, linearity and range, accuracy, precision (intermediate precision and repeatability) and robustness (change in analyst, laboratory, instrument).

Specificity

A placebo sample of the reference formulation of tablets in the usual concentration of excipients was prepared to demonstrate reliability and reproducibility of the method. The placebo sample was transferred to vessels containing 900 mL of dissolution medium and stirred at 37 °C for 45 minute at 100 RPM using a paddle apparatus. Aliquots of the solutions were filtered through filter paper (Whatman No. 41) and analyzed by UV spectrophotometric method. [10]

Linearity: Aliquots of Noscapine stock solution (100 µg/mL) were diluted with 0.1 N HCl to give concentrations of 1–9 µg/mL (n=5). [11-14]

Accuracy:

The recovery study was performed using Noscapine tablets. Noscapine reference substance was added to the dissolution vessels in known amounts at the 80%, 100%, and 120% levels. 12, 15, and 18 mg of Noscapine reference standard respectively was added along with each 15-mg Noscapine tablet. The dissolution test was performed on Noscapine tablets for 45 min using 900 mL of 0.1 N HCl as medium in a paddle apparatus at 100RPM. Aliquots of 10 mL were filtered through filter paper (Whatman No. 41) and analyzed by developed UV spectrophotometric method at the spiked concentration levels of 80%, 100%, and 120%, respectively. Each concentration was analyzed in triplicate. [11-14]

Table 1: Accuracy data for dissolution method

Tablet amount	Level of addition (%)	Amount added (mg)	Absorbance	Total amount	Amount recovered (mg)	% Recovery	Average % recovery
-	0	-	0.254	1.49	-	-	-
-	0	-	0.257	1.51	-	-	-
-	0	-	0.255	1.50	-	-	-
15 mg		12	0.423	2.69	11.89	99.09	99.48779
15 mg	80	12	0.427	2.72	12.17	101.45	
15 mg		12	0.421	2.68	11.75	97.91	
15 mg		15	0.467	3.01	15.01	100.07	
15 mg	100	15	0.463	2.97	14.73	98.18	98.50276
15 mg		15	0.461	2.96	14.58	97.24	
15 mg		18	0.507	3.29	17.85	99.15	
15 mg	120	18	0.506	3.28	17.78	98.76	
15 mg		18	0.502	3.25	17.49	97.18	98.37142

Precision

Repeatability was determined by analyzing six samples of Noscapine tablets with the optimized dissolution test. Aliquots were collected and evaluated by the UV method at 213 nm. Thus, repeatability was evaluated with the relative standard deviation (RSD) of the data at the 100% level.

The evaluation of intermediate precision was performed using Noscapine tablets. The intermediate precision was

determined on different time on same day (intraday) and different days (Interday) and the RSD values were calculated. The dissolution test was performed on six Noscapine tablets for 45 min using 900 mL of 0.1 N HCl as dissolution medium in Apparatus 2 at 100 RPM. Aliquots of 10 mL were filtered with quantitative filter and analyzed by the UV spectrophotometric method. Each concentration was analyzed in triplicate. [11-14]

Table 2: Dissolution Release Rate of Noscapine Tablets in 0.1 N HCl, Paddle Apparatus, 100 rpm

Sr No.	10 minute	% drug dissolved	15 minute	% drug dissolved	20 minute	% drug dissolved	30 minute	% drug dissolved	45 minute	% drug dissolved
1	0.097	33.10	0.189	64.50	0.258	88.05	0.299	102.04	0.301	102.73
2	0.098	33.44	0.197	67.23	0.201	68.60	0.275	93.85	0.278	94.88
3	0.115	39.24	0.177	60.40	0.238	81.22	0.302	103.07	0.306	104.43
4	0.109	37.20	0.199	67.91	0.255	87.03	0.287	97.95	0.291	99.31
5	0.112	38.22	0.184	62.79	0.221	75.42	0.296	101.02	0.298	101.70
6	0.118	40.27	0.173	59.04	0.234	79.86	0.273	93.17	0.278	94.88

Robustness

The robustness was tested by changing several parameters of the dissolution method subsequently, equipment, analyst and laboratory. The dissolution test was performed on six Noscapine tablets for 45 min using 900 mL of 0.1 N HCl as

medium in Apparatus 2 at 100 RPM in different laboratories, with two different analysts and with two different analytical instruments in the same laboratory. Aliquots of 10 mL were filtered and analyzed by the UV method. The dissolution data were compared with the initial data. [11-14]

RESULTS AND DISCUSSION

Determination of Solubility: As Noscapine is not soluble in water and phosphate buffer pH6.8, distilled water and phosphate buffer pH6.8 were not selected for media as solubility in 0.1 N HCl so, it was selected for media.

Quality control test results of 15-mg Noscapine tablets containing Noscapine complied with IP specifications. (Results not reported.)

Mechanical Calibration of Dissolution Apparatus

Dissolution apparatus was calibrated as per guidelines. [14, 15]

Optimization of Dissolution method

0.1 N hydrochloric acid is suitable dissolution media. The results of the dissolution study are depicted in Figures.

Dissolution of drug from a dosage form involves two consecutive steps, liberation of the drug from the formulation matrix which is disintegration followed by dissolution of

The drug which is solubilization of the drug particles in the dissolution medium.

The optimum dissolution conditions for the assessment of release were 900 mL of 0.1 N HCl at 37 °C as the dissolution medium, paddle apparatus at a stirring speed of 100

RPM and 45 min as collection time.

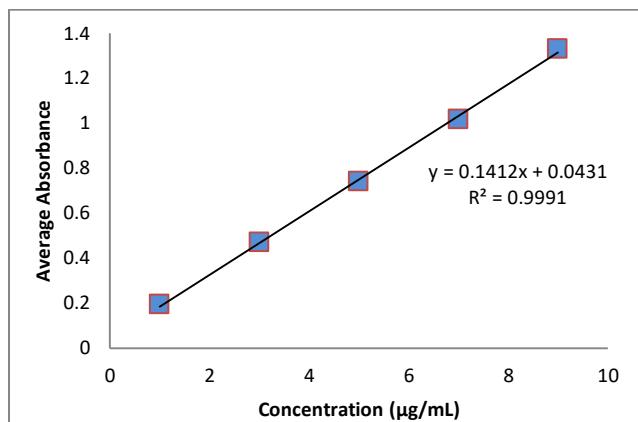
Specificity

When the placebo tablets were subjected to the dissolution test and analyzed, the absorbance was equivalent to 1.71 % of Noscapine tablet concentration. According to ICH guidelines, the dissolution method is specific if the interference is not more than 2%. The dissolution method was specific.

Linearity

For Assessing linearity, a standard curve for Noscapine was constructed by plotting average absorbance versus

concentration. The linearity was evaluated by linear regression analysis. The curves show good linearity in the range of 1–9 µg/mL. The line equation was $y = 0.141x + 0.043$ with a slope of and $R^2 = 0.999$. The RSD for each point was less than 2%. These data indicate that the method is linear for Noscapine within the specification limits.



Sr. No.	Concentration (µg/mL)	Abs (mean ± SD) (n = 5)	% RSD
1	1	0.192 ± 0.0029	1.54
2	3	0.468 ± 0.0029	0.62
3	5	0.738 ± 0.0032	0.44
4	7	1.015 ± 0.0130	1.30
5	9	1.330 ± 0.0053	0.40

Accuracy

The accuracy expresses the agreement between the accepted value and the observed value. The recovery for a dissolution test must be in the range of 95–105%, according to ICH guidelines. The percent recovery was from 96.407% to 100.24%. The accuracy of the method is acceptable.

Table 3:

Tablet amount	Level of addition (%)	Amount added (mg)	Absorbance	Total amount	Amount recovered (mg)	% Recovery	Average % recovery
-	0	-	0.254	1.49	-	-	-
-	0	-	0.257	1.51	-	-	-
-	0	-	0.255	1.50	-	-	-
15 mg		12	0.423	2.69	11.89	99.09	99.48779
15 mg	80	12	0.427	2.72	12.17	101.45	
15 mg		12	0.421	2.68	11.75	97.91	
15 mg		15	0.467	3.01	15.01	100.07	
15 mg	100	15	0.463	2.97	14.73	98.18	98.50276
15 mg		15	0.461	2.96	14.58	97.24	
15 mg		18	0.507	3.29	17.85	99.15	
15 mg	120	18	0.506	3.28	17.78	98.76	
15 mg		18	0.502	3.25	17.49	97.18	98.37142

Precision:**6.10.4(a) Repeatability****Table 4: Repeatability data for dissolution method**

Sr. No.	Absorbance	% Drug dissolved
1	0.287	97.95
2	0.288	98.29
3	0.289	98.63
4	0.287	97.95
5	0.287	97.95
6	0.288	98.29
	Average	98.17
	SD	0.278668
	% RSD	0.283834

6.10.4. (b) intermediate precision**Table 5: Intraday precision data for dissolution method**

Sample No.	T ₁	T ₂	T ₃
% drug dissolved (mean \pm SD)	98.46 \pm 1.67	98.00 \pm 1.68	97.49 \pm 1.59
%RSD	1.69	1.71	1.63

Table 6: Interday precision data for dissolution method

Sample No.	Day i	Day ii	Day iii
% drug dissolved (mean \pm SD)	98.63 \pm 1.93	97.66 \pm 1.82	97.32 \pm 1.81
%RSD	1.95	1.86	1.86

The percent RSD did not exceed 5% for the repeatability and intermediate (Interday and intraday) precision, demonstrating suitable precision.

Robustness:**Table 7: Robustness data (Change in analyst)**

Sr. No.	Analyst 1	Analyst 2
% drug dissolved (mean \pm SD)	98.52 \pm 1.74	98.40 \pm 1.73
% RSD	1.77	1.763

Table 8: Robustness data (Change in equipment)

Sr. No.	Equipment 1	Equipment 2
% drug dissolved (mean \pm SD)	98.52 \pm 1.74	98.23 \pm 1.78
% RSD	1.77	1.81

Table 9: Robustness data (Change in laboratory)

Sr. No.	% Recovery	% Recovery
% drug dissolved (mean \pm SD)	98.52 \pm 1.74	98.23 \pm 1.78
% RSD	1.77	1.81

Table 10: Robustness data (Change in rotation speed, changing normality and volume of dissolution medium)

Factor	Change level(n=3)	Average % drug dissolved± SD	% RSD
Rotation speed	98	99.31±2.04	2.06
	100	100.11± 1.38	1.37
	102	100.57±1.19	1.19
Normality of dissolution medium	0.09 N	98.75±2.56	2.59
	0.1 N	99.43±1.38	1.38
	0.11 N	100.11±2.27	2.26
Volume of dissolution medium	890 mL	102.16±0.52	0.51
	900 mL	99.43±0.86	0.86
	910 mL	97.84±0.52	0.52

The robustness of the method was demonstrated by changing the instrument, the analyst and the laboratory (interlaboratory study). The percent RSD values were within the specified limit of 5 % indicating the robustness of dissolution method

CONCLUSION

The dissolution method was developed and validated for Noscapine tablets is satisfactory. The most discriminating conditions for dissolution testing of Noscapine tablets (0.1 N HCl as a dissolution medium paddle apparatus, stirring speed of 100 rpm, and collection time of 45 min) appear to be the best conditions. Validation shows that the dissolution test is appropriate for quantification of Noscapine in tablet pharmaceutical form for in vitro studies, presenting linearity and range, specificity, precision (intermediate and repeatability), accuracy, and robustness. The method is adequate for use in quality control testing of noscapine tablets

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