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Development of Discriminating Dissolution Method for an Insoluble Drug: Nisoldipine

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Abstract: Nisoldipine is poorly soluble drug. There is no official dissolution method available in the literature or recommended by regulatory agencies. In present study dissolution method was developed. the media selection was done by solubility study of drug in different pH as well as in different surfactant solution. Volume of media was found by calculating sink condition. Sodium lauryl suphate, 1.0% was found to be most suitable surfactant. Further method selection at different rotation speed and volume of media and their discriminating power was evaluated using simple model independent approach. We observed that higher paddle speeds result to flattering drug release profiles and losses its discriminating power while at low paddle speed method was found to be more discriminating. Discriminating dissolution method for Nisoldipine is paddle at 60 rpm, 500 mL of 1.0% sodiul lauryl sulphate solution.
Keywords: Dissolution, similarity factor, dissimilarity factor.

Introduction

Development of the dissolution method for poorly soluble or insoluble drug has been a challenge for scientists. The objectives of challenge vary during the life cycle of a dosage form. The primary focus of objective during Phases 0 and I is to develop a method to establish the mechanism of in vitro drug release and solubilization. During Phases II and III, the objective includes identification of method providing IVIVC. At filling and during Phase IV, the goal is to identify a quality control (QC) dissolution test method to verify process and process parameter. Developed method should be able to satisfy all objectives makes dissolution method development challenging. Physicochemical information e.g. solubility, logP value, pKa serves as guidelines for the method development (1). The solubility of the active ingredient(s) the most important aspects in the screening of possible dissolution media. USP favors media related to physiological conditions, for example buffer solutions or diluted HCl (0.01 N) (2). Importance of solubility study is to find suitable dissolution method, providing sink condition. The term sink conditions is defined as the volume of medium at least greater than three times that required to form a saturated solution of a drug substance.

For the same purpose solubility characteristics of the formulation are to be done over the physiologic pH range of 1.2 to 7.5 (3). For water-insoluble and sparingly water soluble drug products, use of a surfactant such as Sodium lauryl sulfate, Cetyl triammonium bromide and Tween 80 etc are recommended (4) in justified concentration. A maximum of 3.0% of SLS has been allowed for dissolution test of insoluble drugs like Acetracin & Orlistate (5).

Nisoldipine is a antihypertensive drug with poor solubility, high permeability & high hepatic metabolism (6) and belongs to Class II of Bio pharmaceutical system (BCS) and Biopharmaceutical drug disposition system (BDDCS). Since drug and its formulation is not official in any pharmacopoeia and also dissolution method recommendation is not made by Food Drug Administration, it becomes important to develop a discriminating dissolution method to support

product development and quality control for Nisoldipine Extended Release Tablets.

Experimental

Materials

Nisoldipine was procured from Shandong Boyuan Chemical Co.,Ltd, China. Carbopol and Polycarbophil were a gift samples from Lubrizol Advanced Material India Pvt Ltd, Mumbai, Hypromellose was gift sample from Colorcon Asia Pvt Limited Pvt., Goa, Soldium lauryl sulfate (SLS), Tween 80, Cetyl Triammonium Bromide (CTAB), potassium dihydrogen orthophosphate, sodium dihydrogen orthophosphate (Qualigens,Mumbai), sodium hydroxide (S.D.Fine chemicals, Mumbai), methanol (AR grade), and hydrochloric acid (Merck, Darmstadt, Germany) were used. Double-distilled water was used throughout the solubility and dissolution study.

Methods

Saturation Solubility Study

The saturation solubility of Nisoldipine (NS) was determined in double-distilled water, anionic surfactant solution: SLS (0.25, 0.5, 0.75, 1.0, 2.0 and 3.0% W/V), Cationic surfactant solution: CTAB (0.25, 0.5, 0.75, 1.0, 2.0 and 3.0% W/V), Non-inoninc surfactant solution: Tween 20 (0.25, 0.5, 0.75, 1.0, 2.0 and 3.0% W/V), Hydrochloric Acid solution (pH 1.2) & Phosphate buffer (pH 2.0, 4.0, 6.0. 6.4, 6.8, 7.2, 7.6 and 8.0) at 37°C. To find saturated solubility, excess of NS was added to 50 mL of above mentioned solutions/ buffer in a conical flask and agitated continuously at room temperature for 24h using an orbital shaker Orbitek (Scigeneics Biotech). The solutions were kept aside for 6 h for equilibrium. The solutions were then filtered through Whatman filter paper No. 41 followed by filtration through whattman fiters (0.45micron) and filtrates were suitably diluted and analyzed spectrophotometrically at 238 nm (UV–vis spectrophotometer, Perkin-Elmer).

Formulation design

A total of six formulation were prepared using single polymer (E1, E3) and Progressive hydration technology (E5) along with sligh change in each technology (E2, E4 and E6) to challenge dissolution method for their discrimination power. Compositions of formulations are given in Table-1.

Tablets were prepared by compression using twelve station compression machines (Karnavati- Minipress) using 8.0 mm Flat face punches to hardness of 40-55 kp.

In Vitro Drug Release Study

Prepared batches of NS were taken for in vitro drug release study. The dissolution experiments were conducted in eight station bath dissolution apparatus (Electrolab, TOD-08L). Four dissolution methods were designed in USP Apparatus II (paddles) as mentioned below:

Method 1: Volume: 1000ml, 100± 2 rpm, $37^0 \pm 0.5^0$C
Method 2: Volume: 500ml, 100± 2 rpm, $37^0 \pm 0.5^0$C
Method 3: Volume: 1000ml, 60± 2 rpm, $37^0 \pm 0.5^0$C
Method 4: Volume: 500ml, 60± 2 rpm, $37^0 \pm 0.5^0$C

A 5-mL sample was withdrawn using sampling cannula fitted with cannula filter (35 micron) at different time intervals and withdrawn samples were filtered through No. 41 Whatman filter paper. The same volume of fresh medium was replaced. The sample was directly analyzed without dilution using a UV–vis spectrophotometer at 238 nm.

Stability Study

Standard solutions of pure NS and sample solutions from dissolution study of formulation containing high polymer amount i.e. E2, E4 & E6 in 1%w/v SLS were stored in the dark at ambient temperature and at 2–8 °C for up to seven days. Sample aliquots of 5 mL were withdrawn and analyzed spectrophotometrically after every 24-h period. Each day the concentrations of drug found in the standard and sample were compared. The absolute differences between the results at time zero and the time indicated for stability were determined by analysis.

Comparison of Dissolution Profiles by Model-Independent Method

A simple model independent approach using a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles was used (2, 7). The difference factor (f_1) calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/[\sum_{t=1}^{n} R_t]\} \bullet 100$$

where n is the number of time points, Rt is the dissolution value of the reference (prechange) batch at time t, and Tt is the dissolution value of the test (postchange) batch at time t.

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum 2 of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test (postchange) and reference (prechange) products (2).

Results

Solubility study and Medium Selection

The results of the solubility study and the influence on sink conditions for lowest strength and highest strength are summarized in Table 2. NS solubility is 1.1394 mcg/mL. pH-Solubility profile shows solubility does not changes significantly in pH range 1-9 and solubility was found to be pH-independent (Figure -1) to provide sink condition having Cs/Cd (S value) less than 0.20 in 500mL of same media. Significant increases in solubility was found when surfactants were added in media. Selection of surfactant was based on critical micelle concentration (CMC) of each of surfactant. A linear relation was observed between surfactant concentration and solubility enhancement (Figure-2). Similar relation was obtained for Aceclofenac also (8). Non-inoinc surfactant: Tween 20 increased solubility around 150 times in concentration of 3.0% w/v. Ionic surfactant provided great enhancement in solubility than that of by non ionic one and increase in solubility was 314 folds and 165 folds for SLS and CTAB. Maximum effect on solubility was found by SLS indicating minimum amount required to bring sink condition in limited volume of dissolution media. Also being most popular surfactant suggested by FDA to use in dissolution media, SLS was selected as suitable surfactant for dissolution method development. Further amongst various concentrations of SLS, 1.0% w/v gave sink condition to lowest strength of NS (S value 13.79, Table-2) and highest strength (S value 3.45) of NS tablet. Hence 1.0% SLS was selected as satisfactory dissolution media.

Dissolution Method selection and In Vitro Drug Release Study

Results of dissolution study of all six formulation in method I, method II, method III and method IV are given in Figure 3, 4, 5 and 6. Comparison of obtained dissolution curves for method discrimination is done by Model-Independent analysis using F1 and F2 value. F1 value more than 15 indicates significant dissimilarity and F2 value more than 50 indicates significant similarity in results (2).

A comparison of similarity and disimmilarity for all formulation in different dissolution method are mention in table 3 and 4.

Dissolution Method I in 1000mL of 1.0% SLS, paddle speed 100rpm is not able to distinguish between any of the formulation and F1 values are found in the range of 2-5.3. Also F2 shows significant similarity since all values are more than 50.

Dissolution Method II in 500mL of 1.0% SLS, paddle speed 100rpm could differentiate between formulations with single polymer with F1 value 16.8 and 21.3 for E1-E2 and E3-E4 respectively. Also F2 value found to be less than 50 confirming discriminating power of method for these formulations but for formulation E5-E6, progreressive hydration technique, F1 and F2 values are not able to discriminate between formulations.

Dissolution Method III in 1000mL of 1.0% SLS, paddle speed 60rpm also gave same statistical result as that of method II representing unsatisfactory discriminating power for formulation E5-E6 showing F1 14.4 and 65.8.

Dissolution Method IV in 500mL of 1.0% SLS paddle speed 60rpm found to be most satisfactory in terms of discrimination since method discriminated between formulation E1 and E2, E3 and E4 also E5 and E6 with F1 value 34.8, 45.5 and 21.3 and F2 value 27.8, 22.4 and 43.2 respectively.

Another statistical tool of student's t-test was used to find maximum significant difference in dissolution profile. The minimum P value represents maximums significant difference in the drug release in formulations at varying speeds of rotation. Minimum P values i.e 0.132, 0.292 and 0.159 were found in method IV for formulations E1-E2, E3-E4 and E5-E6 indicating maximum significant difference.

Stability Study

Results from stability study are mentioned in Table 5. The absolute difference between the concentrations of drug stored at 2–8 °C were found to be less than 1.75% and the same solution at room temperature over the period of 7 days was found to be less than 3.0% to that of reference solution in 1%w/v SLS.

Discussion

Reference compendia and guidelines of Food drug administration, United States Pharmacopeia, Federation International Pharmaceutique, World Health Organization, European Pharmacopoeia and Japanese Pharmacopoeia recommend use of rotating paddle between 50 to 100rpm with volume of 500 to 1000ml along with surfactant to provide sink condition for insoluble drug products (9).

Surfactants can be used as either a wetting agent below its CMC or beyond CMC to solubilize the drug substance(9) and further their selection should satisfy two factors i.e cost and concentration. (10). Three surfactants approved by regulatory agencies for dissolution media were selected. Suitable concentration required for sink condition were found by solubility study and sink condition. Because of the nature of the NS and micelle interaction, there is typically a linear dependence between solubility and surfactant concentration above the CMC as it seen in Figure-2. The ratio of solubility to drug concentration (dose), expressed as S value which is calculated from Cs/Cd, represents the closeness to sink conditions (9). A sink condition occurs when the amount of drug that can be dissolved in the dissolution medium is at least three times greater than the amount of drug to be

dissolved. A low Cs/Cd ratio shows non-sink condition. The rate of drug dissolution will be slowed by the limited solubility of the drug in the medium. Proper sink condition was maintained in current study using 1% w/v SLS since concentration required was least amongst other surfactant to provide sink condition.

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 (2,9,11–14). Discriminating power can be statistically analyze by model independent mathematic approach as recommended by FDA for development of Solid oral dosage Forms and guidelines on Scale-up post approval changes (2,15) and bioavailability and bioequivalence (14), This approach is widely accepted in method developments(7, 16–20). In present study, change in formulation by changing type of polymers and their concentrations were taken into account to validate the discriminating power of dissolution method. Most commonly mild agitation condition and lesser volume of dissolution media is considered as more discriminating and dissolution method tends less discriminating if operated at faster speed which shows flatter release profile. Conducted experiment shows the similar observation in which Method IV (Volume: 500ml, 60± 2 rpm) could show the maximum discrimination observed using F1 and F2 factor.

Stability of drug substance in dissolution media alone and with formulation components are important factor to assure accuracy of observed dissolved amount and thus a minimum of 24hr stability of drug is recommended in dissolution media (21,22). NS was found to be stable in 1%w/v SLS solution in solution form and along with excipients.

Conclusion

Discrimination of dissolution is a very important in vitro test for evaluating drug products to encounter change in formulation or process. Since there is no dissolution method specified for NS ER Tablets in the literature, an attempt was made to develop a discriminating dissolution method. The use of 500 mL of 1.0% w/v SLS at 37 ± 2 °C, paddle speed of 60 ± 2 rpm found to be satisfactory.

Table 1. Composition of Formulation to Challenge Dissolution for Discriminating Power.

Composition	E1	E2	E3	E4	E5	E6
Nisoldipine	10.1	10.1	10.1	10.1	10.1	10.1
HPMC 15K	10	30	0	0	25	25
Corn Starch	0	0	0	0	5	15
DCL 11	75.9	55.9	75.9	55.9	30.9	20.9
Aerosil	2	2	2	2	2	2
Carbopol 974P	0	0	10	30	25	25
Talc	1	1	1	1	1	1
Mg stearate	1	1	1	1	1	1

Table 2. Saturation Solubility of NS and Sink Conditions in Different Dissolution Media for lower and higher strengths (n=3).

Medium		Solubility (mcg/mL)	Solubility enhancement	Sink Cs*/Cd#	
				10mg	40mg
DD water		1.1394±0.562	1	0.11	0.03
Acid solution	0.1	1.4684±0.852	1.3	0.15	0.04
	1.2	1.3597±0.698	1.2	0.14	0.03
Phosphate buffer, pH	2	1.2500±0.590	1.1	0.13	0.03
	4	1.2175±0.743	1.1	0.12	0.03
	6	1.2983±1.0432	1.1	0.13	0.03
	6.4	1.1599±0.747	1	0.12	0.03
	6.8	1.0400±0.572	0.9	0.1	0.03

	7.2	0.8913±0.491	0.8	0.09	0.02
	7.6	0.8559±0.563	0.8	0.09	0.02
	8	0.7463±0.509	0.7	0.07	0.02
	0.25	27.6580±1.698	24.3	2.77	0.69
	0.5	55.0929±5.121	48.4	5.51	1.38
	0.75	93.7175±15.012	82.3	9.37	2.34
	1	137.9182±16.923	121	13.79	3.45
	2	263.7546±20.623	231.5	26.38	6.59
SLS	3	357.9368±16.239	314.1	35.79	8.95
	0.25	12.125±1.698	10.62214	1.211	0.27
	0.5	20.7751±3.045	18.2	2.075	0.52
	0.75	26.7751±7.682	23.5	2.68	0.67
	1	85.9108±10.098	75.4	8.59	2.15
	2	133.2528±15.176	116.9	13.33	3.33
CTAB	3	188.5595±18.935	165.5	18.86	4.71
	0.25	19.8699±0.964	17.4	1.99	0.5
	0.5	40.1487±2.006	35.2	4.01	1
	0.75	49.4981±5.967	43.4	4.95	1.24
	1	58.9591±11.970	51.7	5.9	1.47
	2	110.6320±13.672	97.1	11.06	2.77
Tween 20	3	172.5836±16.050	151.5	17.26	4.31

**Cs* indicates saturation solubility of NS in 500 mL dissolution medium;
[#]*Cd* dose of NS in tablet formulation;
D.D indicates double-distilled;
SLS is sodium lauryl sulfate.
CTAB is cetyl triammonium bromide

Table 3. Comparison of Tablet Dissolution Profiles using dissimilarity Factor (f1) at Different dissolution methods.

Dissolution methods	**E1-E2**	**E3-E4**	**E4-E6**
Method I	2.0	5.3	4.5
Method II	16.8	21.3	3.9
Method III	33.3	55.8	14.4
Method IV	34.8	45.5	21.3

Table 4. Comparison of Tablet Dissolution Profiles using similarity Factor (f2) at Different dissolution methods.

Dissolution methods	**E1-E2**	**E3-E4**	**E4-E6**
Method I	82.5	64.6	75.0
Method II	42.6	38.3	76.4
Method III	28.4	26.0	65.8
Method IV	27.8	22.4	43.2

Table-5 Stability Study Data (percentage of absolute difference) of NS Standard Solutions and NS Formulations in method 4 on Day 7.

Formulation	Samples	
	Test	Reference
E2	97.20	99.15
E4	98.54	98.98
E6	97.04	98.25

Figure 1. pH-Solubility profile of NS. Each point refers to mean ± SD

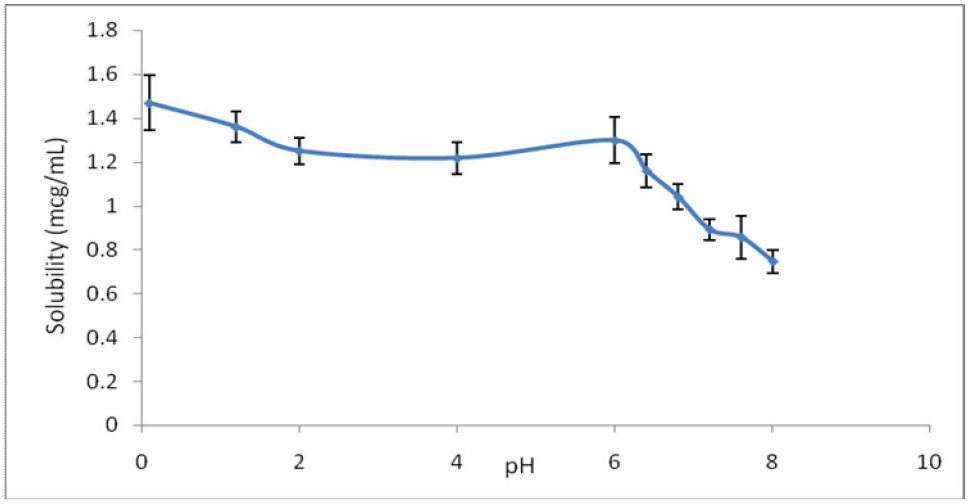


Figure 2. Solubility profile of NS in presence of different surfactants. Each point refers to mean ± SD

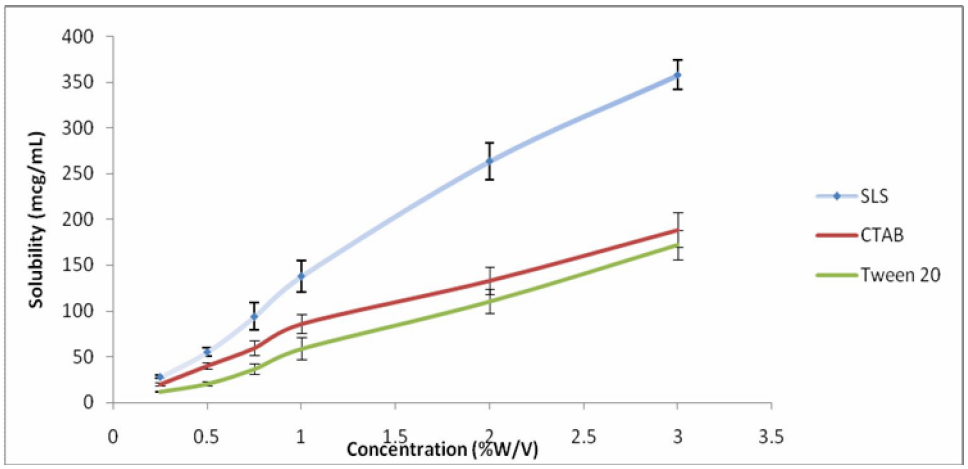


Figure 3. Dissolution profile of formulations using method 1. Each point refers to mean ± SD (n=6).

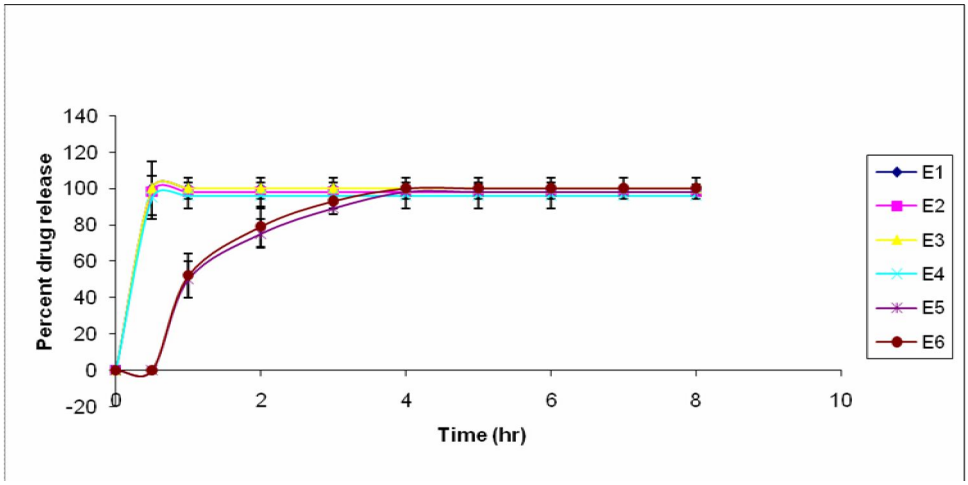


Figure 4. Dissolution profile of formulations using method 2. Each point refers to mean ± SD (n=6).

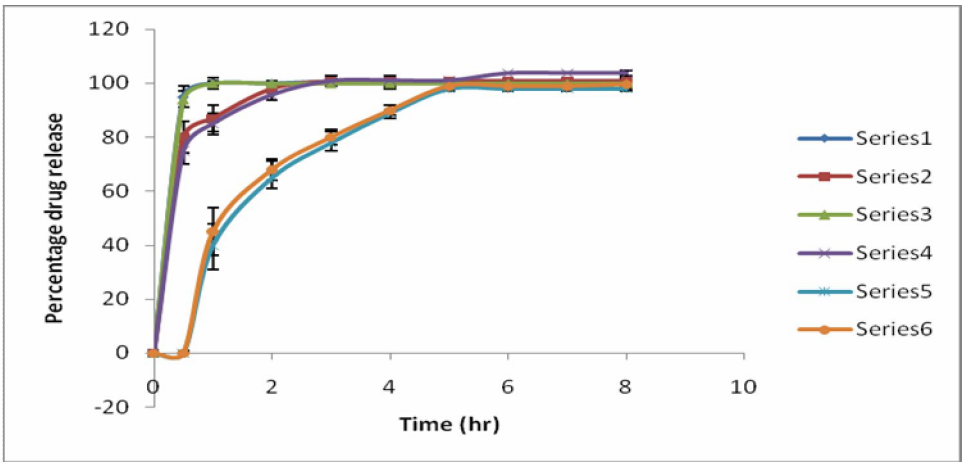


Figure 5. Dissolution profile of formulations using method 3. Each point refers to mean ± SD (n=6).

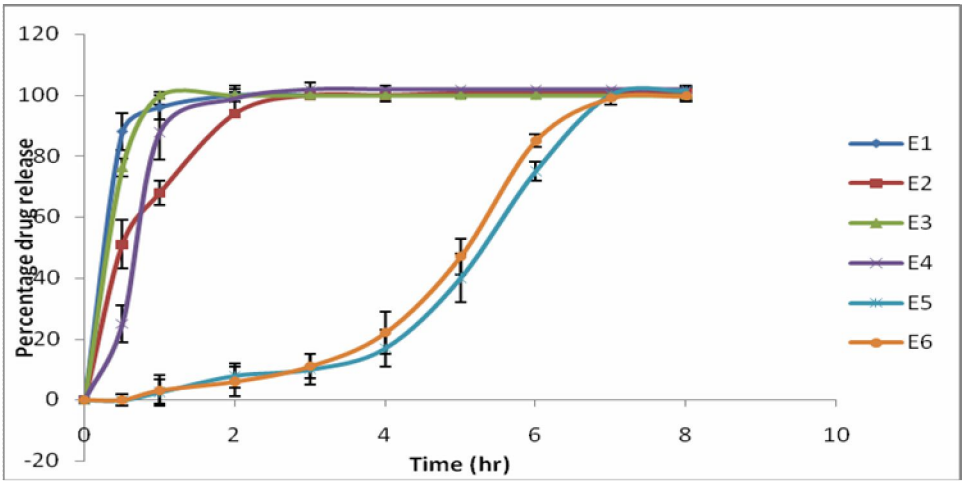
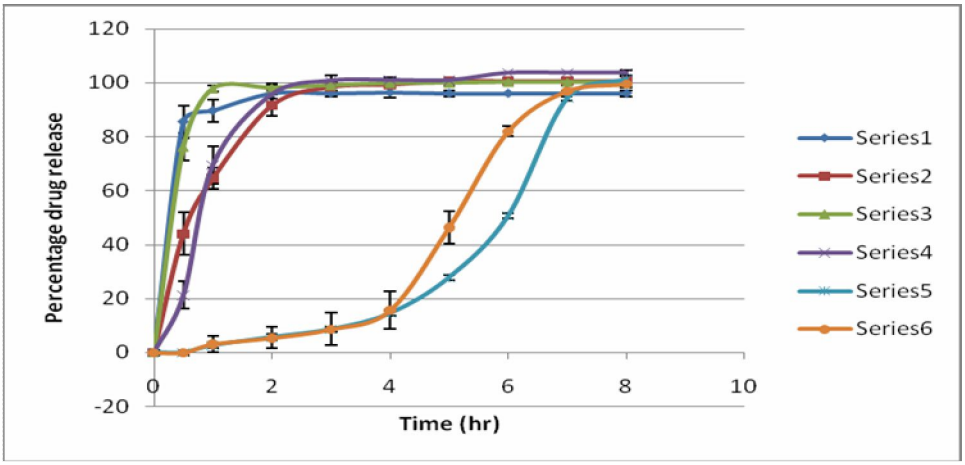


Figure 6. Dissolution profile of formulations using method 4. Each point refers to mean ± SD (n=6).



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