Development and Validation of In-Vitro Discriminatory Dissolution Testing Method for Fast Dispersible Tablets of BCS Class II drug

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ABSTRACT

Objectives: Fast dispersible tablets (FDTs) get dispersed very fast due to which the discrimination of *in-vitro* drug release and their evaluation is difficult. Hence in the present study a new *in-vitro* discriminatory dissolution method was developed and validated for FDTs of domperidone of BCS class II.

Materials and Methods: FDTs of domperidone were prepared by direct compression method. The dissolution studies were performed in an eight- station Electrolab TDT-082 dissolution testing apparatus, analyzed by UV spectrophotometer and evaluated in different dissolution mediums i.e. sodium lauryl sulphate (0.5%, 1.0% and 1.5%) with fresh distilled water, simulated intestinal fluid (SIF) pH 6.8, simulated gastric fluid (SGF) pH 1.2 without enzymes, phosphate buffer solution (PBS) (pH 6.8) and 0.1N hydrochloric acid (HCl) at different agitation speeds.

Results: The developed method was validated in terms of specificity, accuracy, precision, linearity and robustness. Amongst the different mediums, 0.5% SLS with distilled water was found to be optimum with higher rate of discriminatory power. The percentage recovery was found to be 96 to 100.12 % and the % RSD value for precision (intraday and interday) was found to be less than 1%. Also a dissolution profile of prepared FDTs were compared in distilled water containing 0.5% SLS using similarity (f2) & dissimilarity (f1) factor calculation which showed dissimilarity in release profile and confirms the discriminatory nature of developed method.

Conclusion: The discriminatory dissolution method for FDTs was developed and validated. All the obtained results were satisfactory, accurate and in range. The current method could be beneficial for formulation development and for assessment of quality of FDTs.

Key words: Validation, discriminative dissolution method, FDTs, Domperidone.

INTRODUCTION

Fast dispersible tablets (FDTs) are one of the formulations which can be used as a substitute for suspensions and are capable to compensate with the problems associated with the swallowing of solid dosage forms. They disperse in liquid to give a homogenous dispersion before administration and also dispersed immediately in mouth when come in contact with saliva or get rapidly disintegrate in water usually within 3 minutes to form a stabilized suspension. Such formulations provide an opportunity for those who have difficulty with conventional oral dosage forms viz., capsules, tablets, suspensions, solutions or who may not have access to water and have problem in swallowing etc [1, 2]. As the intrinsic solubility of active pharmaceutical ingredient (API) controls dissolution rate and as disintegration of FDTs is very rapid, it become difficult to evaluate the effect of formulation on *in vitro* drug release.

From the discussion above, it can be seen that it is necessary to develop a dissolution strategy specific to FDTs and in particular, to develop a method that has capability to discriminate between *in vitro* release profiles with different nature also to detect possible changes if any in the quality of product before performing *in vivo* to detect changes through an in-vitro dissolution test for a drug with limited solubility is very challenging. The capability of a dissolution method to detect changes in drug product is known as its discriminating power which can be demonstrated by analyzing the dissolution profiles by considering the changes made in method [3].

Dissolution is a quantitative and qualitative technique which provide required necessary information regarding bioavailability of drug to ensure lot-to-lot consistency.

The purpose of dissolution test remains incomplete without performing its validation which ensures the accuracy, consistency and precision with repeatable results. The validation of dissolution can be performed by considering equipment validation which considers the geometrical specifications of dissolution apparatus and its alignment. And another by considering the performance parameters whose evaluation assesses the reliability of dissolution test especially precision [4, 5].

In the reported manuscript a discriminating dissolution test method was developed and validated for FDTs of domperidone of Biopharmaceutics Classification System (BCS)

Class II drug, having poor water solubility and high permeability. It is D_2 antagonist and usually prescribed as antiemetic agent having molecular weight 425.91 g/mol, pk_a value of 7.9 and melting point in range of 244-246°C.

The official dissolution medium prescribed for domperidone 0.1 N HCl is unable to discriminate the dissolution test of FDTs. Hence the goal of prevailing study is to develop and validate discriminatory dissolution method for FDTs of domperidone to support product development efforts [6].

MATERIAL AND METHODS

Materials

Domperidone reference standard was supplied by Metrochem API, Pvt. Ltd**.** Hyderabad, as a gift sample. Vomistop 10 DT tablets (M.L.L/07/436/MNB), Mfd.by Cipla Ltd, 20, Indi Area-1, Baddi (H.P 173205) containing 10 mg of domperidone IP were obtained commercially. Sodium lauryl sulphate, di-sodium hydrogen phosphate, hydrochloric acid were obtained from Nice Chemicals Pvt. Ltd, Kerala. Potassium dihydrogen phosphate, methanol and sodium bi-carbonate were bought from Central Drug House (P) Ltd, New Delhi. Sodium chloride was purchased from Chemigens Research and Fine Chemicals, New Delhi. Sodium hydroxide pellets, citric acid, magnesium stearate, crosscarmellose sodium, micro-crystalline cellulose were purchased from Qualikems Fine Chem; Pvt, Ltd. India. All chemicals were used without any further purification and were of analytical grade. SLS (0.5 %, 1.0%, and 1.5%) with fresh distilled water was used throughout the study. SIF (pH 6.8), SGF (pH 1.2) without enzyme, PBS (pH 6.8), 0.1N HCl, Simulate intestinal fluid (SIF) (pH 6.8), simulated gastric fluid (SGF) (pH 1.2) were prepared According to USP 27.

Instruments and apparatus

To detect absorbance Shimadzu UV–vis Spectrophotometer Model UV–1800 was used and digital pH meter Model P101 Hanna Instruments, Italy to determine pH. Water bath incubator, Model PLT-113 Remi Equipment's, Mumbai for shaking. Analytical balance Model-SSI/DB 195, Singla Scientific applied for weighing. Rotatory Tablet Machine (12 station) Model-SSI/RTM/5283, Madhur India for tablet puching. An eight-station Electrolab TDT-08L Dissolution Tester and Model TDT-06L dissolution tester apparatus were used as per USP 27 general guidelines.

Determination of solubility

The equilibrium solubility of dompridone in various solvents was determined by flask-shake method. A surplus amount of drug was added in 50 ml of test solvent, sonicated for 10 minutes and provided a continuous shaking for 24 hrs on a mechanical shaker at normal temperature. To achieve equilibrium the solution was kept undisturbed for 1 hr after that it was filtered (Whatman filter paper # 42; 2.5- µm pore size) and by using UV spectrophotometric method drug content was calculated. The saturated solubility was determined in 0.1 N HCl dissolution medium, distilled water, distilled water with SLS (0.5% w/v), distilled water with SLS (1% w/v), distilled water with SLS (1.5% w/v), phosphate buffer (pH 6.8), SGF without enzymes pH 1.2, Simulated intestinal fluid pH 6.8. The drug content of each solution was determined in triplicate and results were presented as mean ± SD [5].

Sink condition

The capability of the medium to dissolve the desired amount of the drug is known as a sink condition. Using sink conditions or too high amount of the sample usually increase the dissolution rate and weaken the discrimination between dissolution profiles. In the European Pharmacopeia, sink conditions are defined as a volume of dissolution medium that is at least three to ten times the saturation volume. In other words, if the maximum concentration of the sample in the dissolution medium is less than 1/3 times the saturation solubility, i.e., $\varphi < 1/3$, it is in sink conditions. Otherwise, it is in non-sink conditions.

The three vessels each containing 10 ml of medium and an excess of drug (100 mg) (n = 3) containing 10 mL of medium were gently rotated for 24 hrs on a mechanical shaker at normal temperature. To achieve equilibrium the solution was kept undisturbed for 4 hrs then filtered through Whatman filter paper no. 41 and after appropriate dilution drug content was calculated by using UV spectrophotometric at 284 nm.

Formulation of Domperidone FDTs

Tablets were prepared as per the previously published method with slight modification. The raw materials were passed through a screen (60 mesh) prior to mixing then a screen (40 mesh). Domperidone containing amount equivalent to 10 mg was blended with the desired other excipients. Sodium bicarbonate and anhydrous citric acid were preheated

at a temperature of 80 °C to remove absorbed/ residual moisture and were thoroughly mixed in a mortar to get a uniform powder and then mixed with other ingredients. The blend thus obtained was directly compressed on a 12-station mini press tablet machine equipped with 9 mm concave punch [7]. Composition of domperidone fast dispersible tablets is given in Table-1.

Table 1 Composition of fast dispersible tablets of domperidone

Ingredient	DOM-1	DOM-2
Drug (Domperidone)	5%	5%
Sodium bi-carbonate	14%	14%
Citric acid	7%	7%
Croscarmellose sodium	6%	----------
Microcrystalline cellulose (MCC)	66.5%	72.5%
Magnesium stearate	1.5%	1.5%

Optimization of dissolution test

On the basis of results obtained from solubility study, the optimization of dissolution test for FDTs of domperidone was carried out on two different marketed fast dispersible tablets of different manufacturer (FDT1 & FDT2). FDTs containing 10 mg of domperidone were used and dissolution studies were carried out using USP apparatus-II. The rate of dissolution was determined in different dissolution mediums (900 ml) i.e. SLS (0.5 %, 1.0%, 1.5%) with fresh distilled water, SIF (pH 6.8), SGF (pH 1.2) without enzyme, PBS (pH 6.8), 0.1N HCl at different agitation speeds of 50 and 75 rpm (Figure 1-4). Further, the dissolution profiles were compared using one-way ANOVA. The p value< 0.05 will be considered as significant [8].

In-vitro drug release study of prepared fast dispersible tablets (DOM-1 and DOM-2) in selected media

To check the discriminatory power of dissolution media, the *in-vitro* drug release studies was performed using prepared fast dispersible tables DOM-1 and DOM-2 in 0.1 N HCl, and 0.5% SLS with distilled water using USP apparatus II at 50 rpm (Figure 5).

Comparison of Dissolution Profiles by Model-Independent Method

The dissolution profiles of prepared tablets FDTs (DOM-1 & DOM-2) and marketed FDTs (FDT-1 & FDT-2) were compared by applying a model-independent approach, which was based on the calculation of similarity factor (*f*2) and dissimilarity factor (*f*1). A f2 value equals to 50 or greater ensures sameness or equivalence of the two curves and also the performance of the two products. Dissolution profile of FDTs were compared in 0.1 N HCl and 0.5 % SLS with distilled water (as highest drug release was observed in both media) using similarity and dissimilarity factor calculation [9-11].

The similarity factor (*f*2) and dissimilarity factor (*f*1) were calculated by using following equations 1 & 2.

$$f1 = \{[\Sigma\, t = 1\, n\, |R - T|] \,/\, [\Sigma\, t = 1\, n\, R]\} \times 100 \text{.....1}$$

$$f2 = 50 \times log\{[1 + (1/n)\Sigma t = 1n(R - T)2] - 0.5x100 \text{.....2}$$

Here n is number of time points, R is dissolution value of the reference (pre-change) batch at time t, and T is the dissolution value of the test (post-change) batch at time t.

Validation of dissolution test Method

The validation of dissolution method was performed using different parameters such as specificity, linearity, robustness, accuracy and precision [12, 13].

Specificity

A sample of reference commercial formulation (placebo) of tablets was prepared and transferred to the vessel containing 900 ml dissolution media, stirred at 50 rpm using paddle apparatus. The aliquots of sample solution were filtered through Whatman filter paper and analyzed by UV spectroscopy [14].

Accuracy

The domperidone was added to dissolution vessel in known amount at 80%, 100% and 120% level along with each 10 mg domperidone FDT. The dissolution test was performed for 30 min using 900 ml dissolution media (distilled water with 0.5% SLS) at a paddle speed of 50 rpm. Aliquots of 10 ml were filtered through Whatman filter paper and analyzed by UV spectroscopy at a spiked concentration [5].

Linearity

To determine the linearity, a standard plot for domperidone was constructed by plotting average absorbance versus concentration. The linearity was evaluated by linear regression analysis.

Precision

The precision of developed method was determined by repeatability and intermediate precision. For the determination of repeatability the test was performed using six dissolution vessels under the same conditions and results were compared. Intermediate precision was determined by intraday and interday studies. The intraday study was performed by repeating the test for three times in a day[15]. In interday study, the dissolution test was conducted on daily basis for three days and results were compared. An RSD value less than 2% indicates the precision of the developed method.

RESULT AND DISCUSSION

Determination of Solubility and sink condition

The solubility profile of domperidone shows that solubility is pH dependent. The maximum solubility shown by domperidone was observed in 0.1 N HCl and it increases as the pH decrease[16, 17]. The solubility of domperidone in water is very low and is enhanced by the addition of surfactant (SLS). SLS showed increase in the solubility with concentration 0.5% and further increase in concentration had no significant effect on solubility as shown in Table 2. The dose of domperidone in FDTs is 10 mg/tablet. The ratio of solubility to dose ratio (Cs/Cd) represents the closeness to sink condition and it occurs when the amount of drug that can be dissolved is three times higher than the amount of drug to be dissolved. A low ratio of Cs/Cd shows existence of non-sink condition [18, 19].

Table 2 Solubility and sink condition of domperidone in different media

Dissolution medium	Solubility(µg/ml)	Sink condition(Cs/Cd)
Distilled water	3.56	0.356
Simulated intestinal fluid (pH 6.8)	8.38	0.838
SGF (pH 1.2) without enzymes	214.3	21.43
Phosphate Buffer solution (pH 6.8)	16.09	1.609
0.1N HCl Solution	268.7	26.87
0.5%SLS with distilled water	28.9	2.89
1%SLS with distilled water	23.8	2.38
1.5%SLS with distilled water	19.2	1.92

Characterization of Domperidone FDTs

The friability, hardness, disintegration time, wetting time, drug content and weight of formulated tablets were determined. Hardness of all the formulation was in range of 3.37 -3.55 kg/cm^2. Friability of all the formulation was below 1% indicates that the tablets had good mechanical resistance. Drug content was found to be in range of 100.9 -103.95%. disintegration time of DOM-1 and DOM-2 was found to be 31 and 50 seconds respectively, which clearly indicated that the use of disintegrating agent in combination with effervescent material have a great impact on disintegration time. The weight variation results revealed that average % deviation of 20 tablets of each formulation was less than ±7.5%, which provide good uniformity in all formulation.

Optimization of dissolution test condition

On the basis of screening study conducted on fast dispersible tablets of domperidone, two different marketed fast dispersible tablets of different manufacturer (FDT1 & FDT2), it was found that FDT-1 and FDT-2 exhibited similar dissolution profile at 50 & 75 rpm. The highest drug release was observed in 0.1 N HCl and SGF without enzymes (pH 1.2) due to high solubility to dose ratio (as shown in Table 2), but no significant difference in drug release was observed in both media. The use of 0.5% SLS in distilled water increases the solubility and more than 100 % of drug release was observed within 30 min

at paddle speed of 50 rpm. Moreover, irrespective of paddle speed, the dissolution rate was relatively slower and consistent. A further increase in SLS did not increase the dissolution significantly. The use of dissolution medium containing surfactant at small amount less than its critical micelles concentration is often sufficient to solubilize certain poorly soluble drugs. The use of slowest paddle speed (50 rpm) and dissolution media 0.1 N HCl and distilled water containing 0.5 % SLS showed better release profile. The drug release of FDT-1 and FDT-2 was found similar (*f*2>50) in both media, which may be due to the similar formulation parameters in both the tablets [8, 20].

Confirmation of discriminating dissolution test condition

The different dissolution profiles were obtained for FDTs of varying nature (Figure 5 and 6). In present study dissimilarity in drug release was observed with the fast-dispersible tablet (DOM-1) than compared to DOM-2 in 0.5% SLS (*f*2=26) and similarity in drug release was observed with 0.1N HCl (*f*2=58). Based upon these results, the developed dissolution test method is considered discriminatory because it discriminates between products having differences in pharmaceutical attributes. From the above results it is possible to establish a dissolution method that can be used as an alternative to the official dissolution test for domperidone FDTs. In the present study distilled water containing 0.5% SLS at stirring speed of 50 rpm was found to be optimum [9-11].

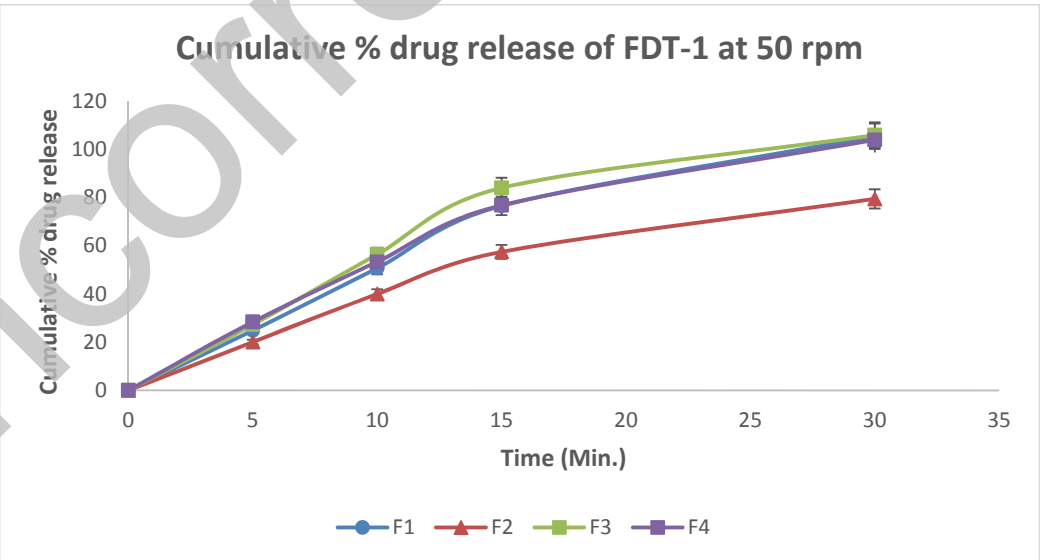

Figure 1: *In-vitro* drug release study of marketed fast dispersible tablets (FDTs-1) of domperidonein (F1) 0.1 N HCl, (F2) SGF pH 1.2, (F3) Distilled water with 0.5% SLS, (F4) Distilled water with 1% SLS.

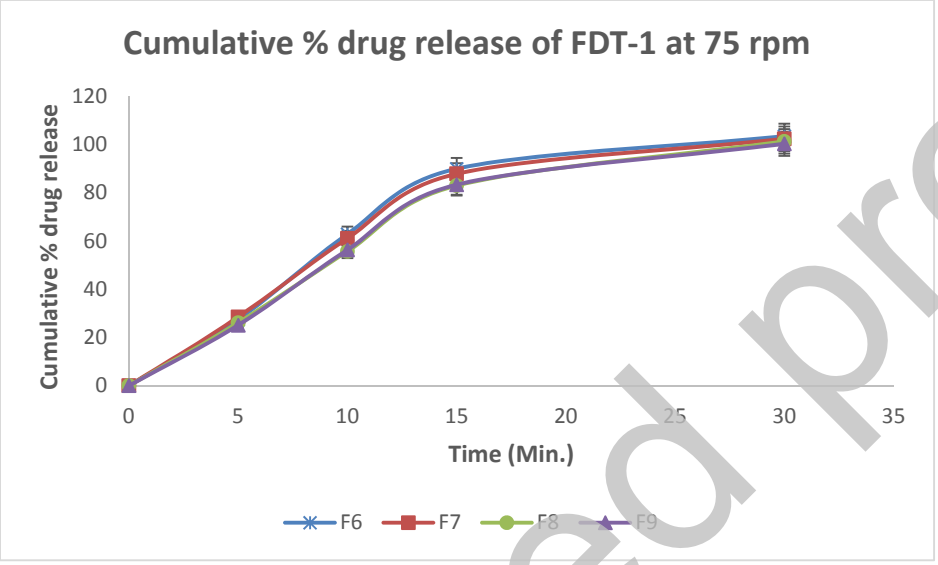

Figure 2: *In-vitro* drug release study of marketed fast dispersible tablets (FDTs-1) of domperidone in (F1) 0.1 N HCl, (F2) SGF pH 1.2, (F3) Distilled water with 0.5% SLS, (F4) Distilled water with 1% SLS.

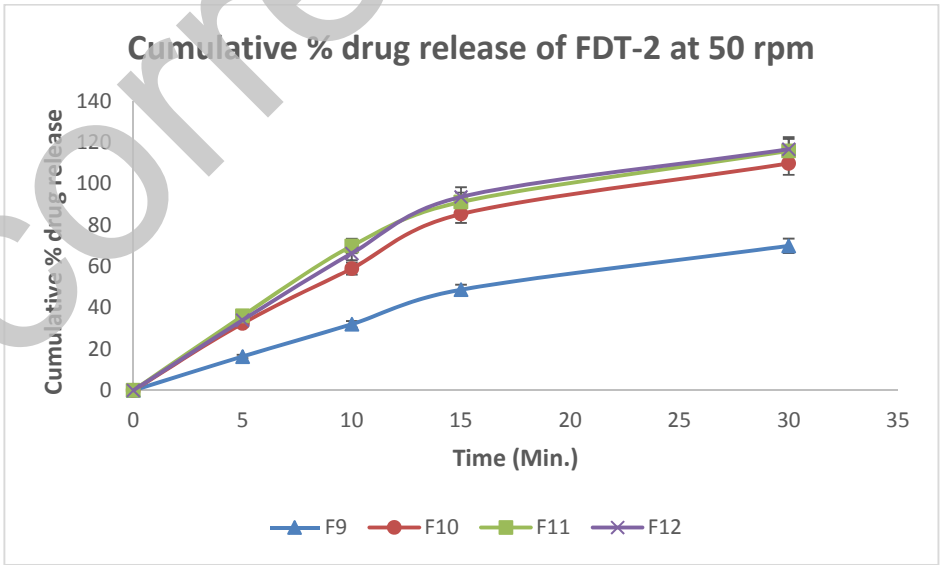

Figure 3: *In-vitro* drug release study of marketed fast dispersible tablets (FDTs-1) of domperidone in (F9) SGF pH 1.2, (F10) 0.1 N HCl, (F11) Distilled water with 0.5% SLS, (F12) Distilled water with 1% SLS.

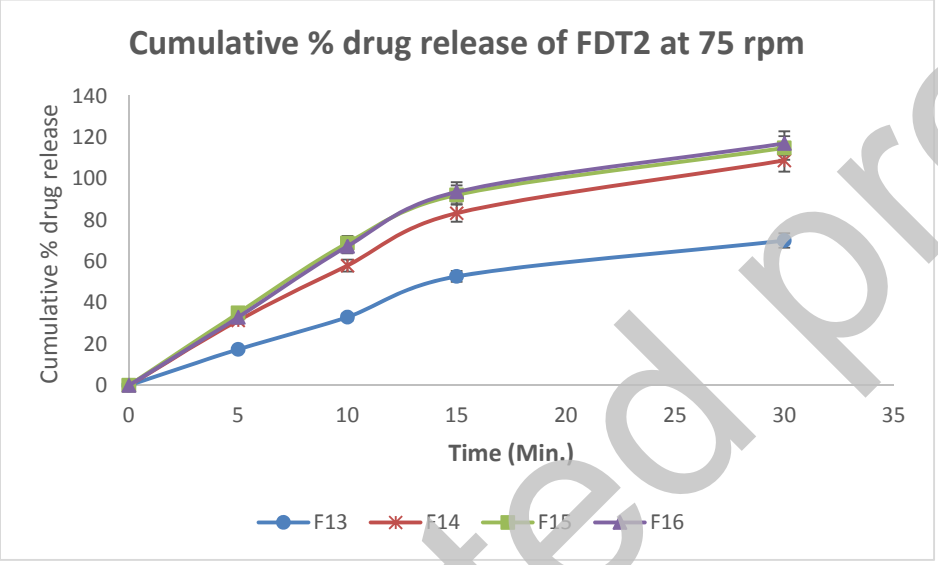

Figure 4: *In-vitro* drug release study of marketed fast dispersible tablets (FDTs-1) of domperidone in (F13) SGF pH 1.2, (F14) 0.1 N HCl, (F15) Distilled water with 0.5% SLS, (F16) Distilled water with 1% SLS.

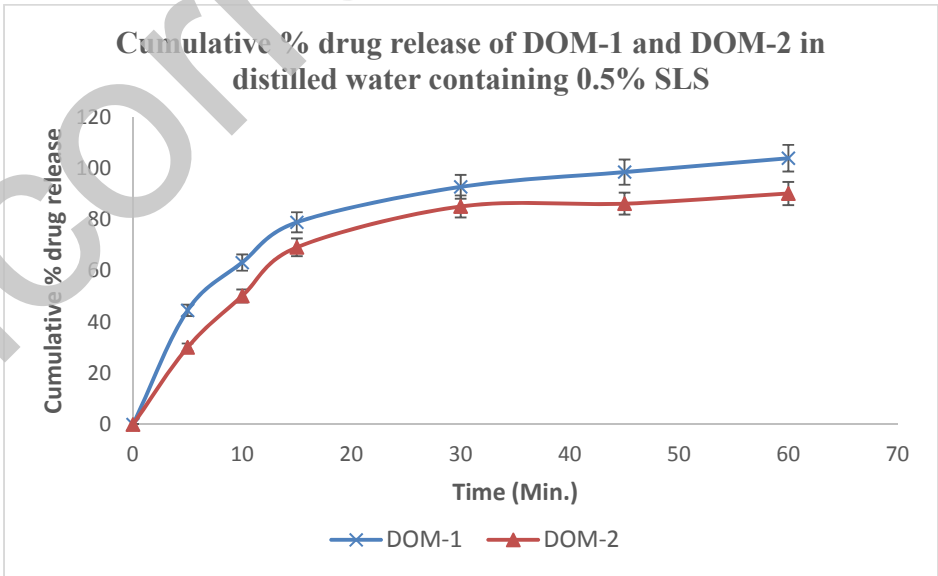

Figure 5*: In-vitro* drug release study of prepared fast dispersible tablets (DOM-1 and DOM-2) in Distilled water containing 0.5% SLS.

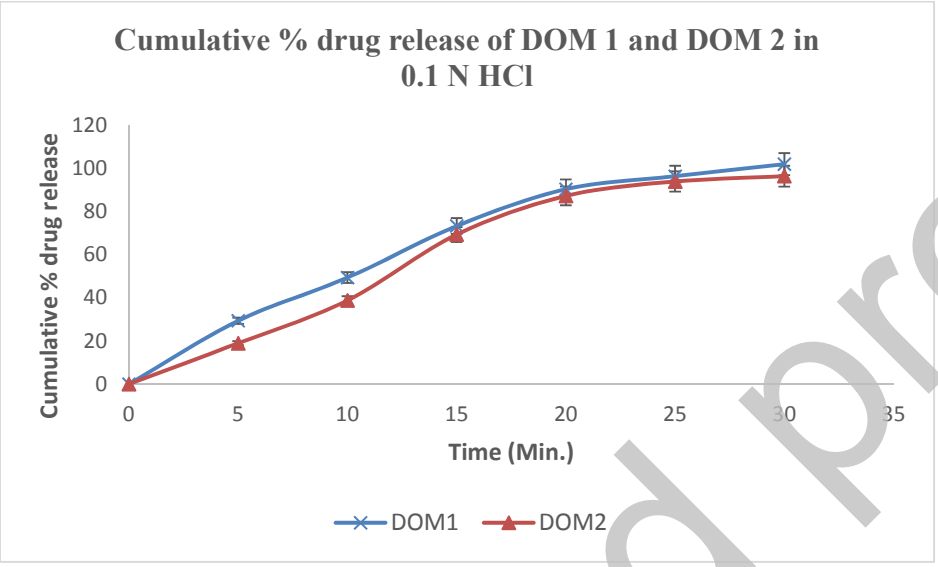

Figure 6: *In-vitro* drug release study of prepared fast dispersible tablets (DOM-1 and DOM-2) in 0.1N HCl

Validation of dissolution method

Specificity

When tablets were subjected to dissolution test and absorbance was taken, the corresponding absorbance was found to be equivalent to 1.38% of domperidone concentration. As per the ICH guidelines, the dissolution method is specific if the interference is not more than 2%. Hence, the developed method was found to be specific [21, 22].

Accuracy

The accuracy of developed method was evaluated on the basis of percent recovery. For accuracy test, recommended percent recovery should be in between 95.0 to 105.0%. The mean recovery of domperidone is shown in Table 3, indicating that dissolution method is accurate.

Table 3 Accuracy test result for domperidone

Sr.no.	Parameter	Levels		
1	Tablet amount (mg)	10	10	10
2	Level of addition (%)	80	100	120
3	Amount added (mg)	8	10	12
4	Average amount recovered (mg)	17.40	20.08	21.59
5	Average % recovery*	96.66± 1.132	100.40±1.82	98.13±1.49

*Each reading is mean± SD (n=3)

Linearity

The standard curve (Figure 7) depicts good linearity in the range of (5-35 µg / mL). The equation of line was y = 0.0287x + 0.0093 with slope 0.0287 and r^2 = 0.9992. The RSD was found to be less than 2%. The data clearly indicates that the method is linear and with a specified limit.

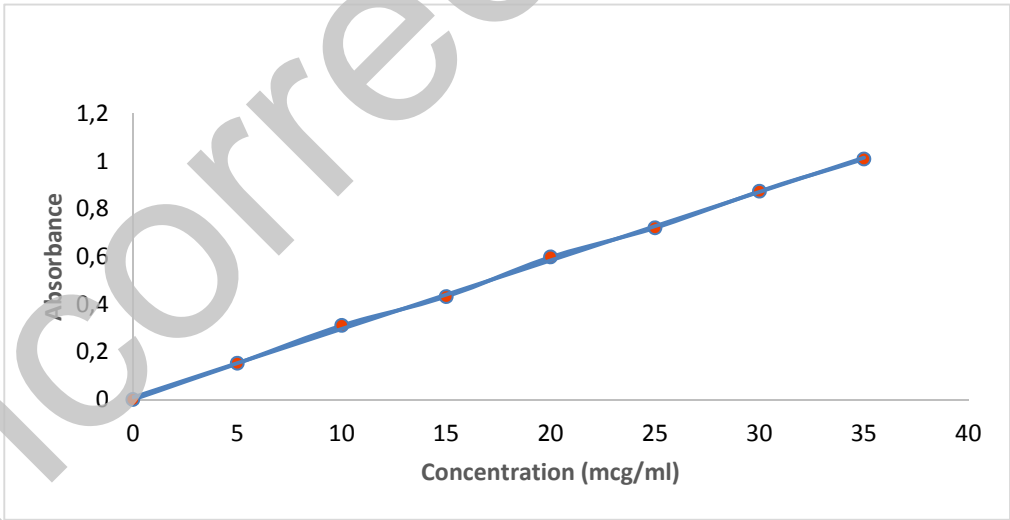

Figure 7. Calibration curve of domperidone in Distilled water containing 0.5% SLS

Precision:

The result for repeatability and intermediate precision are summarized in Table 4-6. The RSD value was found to be less than 1% which shows that the developed dissolution method has good precision.

Table 4. Dissolution test precision (repeatability) result for domperidone

Dissolution vessels	Average % drug release ± S.D. (n=3)	% RSD
Vessel 1	98.82± 0.81	0.81
Vessel 2	99.71± 0.59	0.59
Vessel 3	100.28 ± 0.38	0.37
Vessel 4	99.31 ± 0.75	0.76
Vessel 5	100.89 ± 0.35	0.34
Vessel 6	100.06 ± 0.91	0.90

Table 5. Dissolution test precision (intraday) result for domperidone

Time	Average % drug release ± S.D. (n=3)	% RSD
8.30 a.m.	99.71 ± 0.89	0.89
1.30 p.m.	100.01 ± 0.57	0.56
6.30 p.m.	100.09 ± 0.71	0.70

Table 6. Dissolution test precision (interday) result for domperidone

Day	Average % drug release ± S.D. (n=3)	% RSD
Day 1	100.07 ± 0.79	0.79
Day 2	99.23 ± 0.68	0.68
Day 3	99.01 ± 0.51	0.52

Conclusion

The dissolution test for domperidone fast dispersible tablets was developed and validated as per ICH guidelines. The dissolution profiles of FDTs of domperidone were evaluated in different mediums (900 ml) at different stirring speed (50 and 75 rpm). The use of

distilled water containing 0.5% SLS as dissolution media at 37 ± 0.5 ^{0}C and stirring speed of 50 rpm produced satisfactory results. The dissolution testing of domperidone FDTs formulated with different excipients showed different release profile, which confirms the discriminatory nature of developed method. The model independent method was used to evaluate the similarity of dissolution profile. The developed method is found to be adequate for use in quality control testing of domperidone fast dispersible tablets.

Conflict of interest

The author(s) declares no conflict of interest.

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