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ORIGINAL ARTICLE

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

BCS Sınıf II İlacının Hızlı Dağılabilir Tabletleri için *İn Vitro* Ayırt Edici Çözünme Test Yönteminin Geliştirilmesi ve Validasyonu

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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 ultraviolet 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 pH 6.8, simulated gastric fluid pH 1.2 without enzymes, phosphate buffer solution (pH 6.8) and 0.1 N hydrochloric acid 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% sodium lauryl sulfate (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 % relative standard deviation 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) and 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, fast dispersible tablets (FDTs), domperidone

ÖZ

Amaç: Hızlı dağılabilir tabletler (FDT'ler), çok hızlı dağıldıkları için *in vitro* etken madde salımının ayrımı ve değerlendirilmesi zordur. Bu nedenle, bu çalışmada, BCS sınıf II domperidonun FDT'leri için yeni bir *in vitro* ayırt edici çözünme yöntemi geliştirilmiş ve valide edilmiştir.

Gereç ve Yöntemler: Domperidonun FDT'leri direkt basım yöntemi ile hazırlanmıştır. Çözünme çalışmaları sekiz istasyonlu Electrolab TDT-082 çözünme test cihazında gerçekleştirilmiştir, ultraviyole spektrofotometre ile analiz edilmiş ve taze distile su ile sodyum lauril sülfat (%0,5, % 1,0 ve %1,5), simüle bağırsak sıvısı pH 6,8 ile simüle enzimsiz mide sıvısı pH 1,2, fosfat tampon çözeltisi (pH 6,8) ve 0,1N hidroklorik asit gibi farklı çözünme ortamlarında farklı çalkalama hızlarında değerlendirilmiştir.

Bulgular: Geliştirilen yöntem özgüllük, doğruluk, kesinlik, doğrusallık ve sağlamlık açısından doğrulanmıştır. Farklı ortamlar arasında, distile su ile %0,5 sodyum lauril sülfat (SLS)'nin daha yüksek ayrım gücü ile optimum olduğu bulunmuştur. Geri kazanım yüzdesi %96 ila %100,12 ve kesinlik için bağıl standart sapma değerinin (gün içi ve günler arası) %1'den az olduğu bulunmuştur. Ayrıca hazırlanan FDT'lerin %0,5 SLS içeren distile sudaki çözünme profili, salım profilinde farklılığı gösteren ve geliştirilen yöntemin ayırt edici doğasını doğrulayan benzerlik (f2) ve fark (f1) faktörü hesaplaması kullanılarak karşılaştırılmıştır.

Sonuç: FDT'ler için ayırt edici çözünme yöntemi geliştirilmiş ve valide edilmiştir. Elde edilen tüm sonuçlar tatmin edici, doğru ve aralık içindedir. Mevcut yöntem, formülasyon geliştirilmesi ve FDT'lerin kalitesinin değerlendirilmesi için faydalı olabilir.

Anahtar kelimeler: Validasyon, ayırt edici çözünme yöntemi, hızlı dağılabilir tabletler (FDT'ler), domperidon

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INTRODUCTION

Fast dispersible tablets (FDTs) are one of the formulations that can be used as a substitute for suspensions and they can overcome the problems associated with the swallowing of solid dosage forms. They disperse in liquid to give a homogeneous dispersion before administration and also disperse immediately in the mouth when they come in contact with saliva or rapidly disintegrate in water usually within 3 min to form a stabilized suspension. Such formulations provide an opportunity for those who have difficulty with conventional oral dosage forms, i.e. capsules, tablets, suspensions, and solutions, or who may not have access to water and have problems swallowing etc.[1,2] As the intrinsic solubility of the active pharmaceutical ingredient (API) controls the dissolution rate and as disintegration of FDTs is very rapid, it is difficult to evaluate the effect of the 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 the capability to discriminate between *in vitro* release profiles with different natures, and to detect possible changes if any in the quality of products 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 a drug product is known as its discriminating power and it can be demonstrated by analyzing the dissolution profiles by considering the changes made in the method.[3]

Dissolution is a quantitative and qualitative technique that provides the necessary information regarding bioavailability of a drug to ensure lot-to-lot consistency.

The dissolution test remains incomplete without performing its validation, which ensures accuracy, consistency, and precision with repeatable results. The validation of dissolution can be performed by considering equipment validation that examines the geometrical specifications of the dissolution apparatus and its alignment, and by considering the performance parameters the reliability of the dissolution test is evaluated, especially precision.[4,5]

In the present study a discriminating dissolution test method was developed and validated for FDTs of domperidone, a Biopharmaceutics Classification System Class II drug having poor water solubility and high permeability. It is a D_2 antagonist and is usually prescribed as an antiemetic agent with a molecular weight of 425.91 g/mol, pk_a value of 7.9, and melting point in the range of 244-246°C.

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

MATERIALS AND METHODS

Materials

Domperidone reference standard was supplied by Metrochem API, Pvt. Ltd., Hyderabad, India, 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 sulfate (SLS), disodium hydrogen phosphate, and hydrochloric acid were obtained from Nice Chemicals Pvt. Ltd., Kerala, India. Potassium dihydrogen phosphate, methanol, and sodium bicarbonate were bought from Central Drug House (P) Ltd., New Delhi, India. Sodium chloride was purchased from Chemigens Research and Fine Chemicals, New Delhi, India. Sodium hydroxide pellets, citric acid, magnesium stearate, sodium croscarmellose, and microcrystalline 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. Simulated intestinal fluid (SIF) (pH 6.8), simulated gastric fluid (SGF) (pH 1.2) without enzyme, PBS (pH 6.8), and 0.1 N HCl were prepared according to United States Pharmacopeial Convention (USP) 27.

Instruments and apparatus

To detect absorbance a Shimadzu ultraviolet (UV) - visible spectrophotometer model UV-1800 was used and a digital pH meter (model P101, Hanna Instruments, Italy) was used to determine pH. A water bath incubator (model PLT-113, Remi Equipments, Mumbai, India) was used for shaking. An analytical balance (model-SSI/DB 195, Singla Scientific) was applied for weighing. A rotatory tablet machine (12 station) (model-SSI/RTM/5283, Madhur, India) was used for tablet punching. 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 domperidone in various solvents was determined by flask-shake method. A surplus amount of drug was added to 50 mL of test solvent, sonicated for 10 min, and subjected to continuous shaking for 24 h on a mechanical shaker at normal temperature. To achieve equilibrium the solution was left undisturbed for 1 h; after that it was filtered (Whatman filter paper no. 42; 2.5-µm pore size) and by UV spectrophotometric method the 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, and SIF pH 6.8. The drug content of each solution was determined in triplicate and the results were presented as mean ± standard deviation.[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. $\phi < 1/3$, 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 h on a mechanical shaker at normal temperature. To achieve equilibrium the solution was kept undisturbed for 4 h and then filtered through Whatman filter paper no. 41 and after appropriate dilution the drug content was calculated by UV spectrophotometry 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 and then another screen (40 mesh). Domperidone containing an amount equivalent to 10 mg was blended with the other desired excipients. Sodium bicarbonate and anhydrous citric acid were preheated at 80°C to remove absorbed/residual moisture and were thoroughly mixed in a mortar to get a uniform powder and then mixed with the other ingredients. The blend thus obtained was directly compressed using a 12-station mini press tablet machine equipped with a 9-mm concave punch.[7] The composition of the domperidone FDTs is given in Table 1.

Optimization of dissolution test

On the basis of the results obtained from the solubility study, the optimization of dissolution test for FDTs of domperidone was carried out on two different marketed FDTs of different manufacturer (FDT1 and FDT2). FDTs containing 10 mg of domperidone were used and dissolution studies were carried out using an USP apparatus II. The rate of dissolution was determined in different dissolution media (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), and 0.1 N HCl at different agitation speeds of 50 and 75 rpm (Figures 1-4). Further, the dissolution profiles were compared using one-way ANOVA. A p value <0.05 was considered significant.[8]

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

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

Table 1. Composition of fast dispersible tablets of domperidone

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

Comparison of dissolution profiles by model-independent method

The dissolution profiles of the prepared FDTs (DOM-1 and DOM-2) and marketed FDTs (FDT-1 and FDT-2) were compared by applying a model-independent approach, which was based on the calculation of similarity factor (f_2) and dissimilarity factor

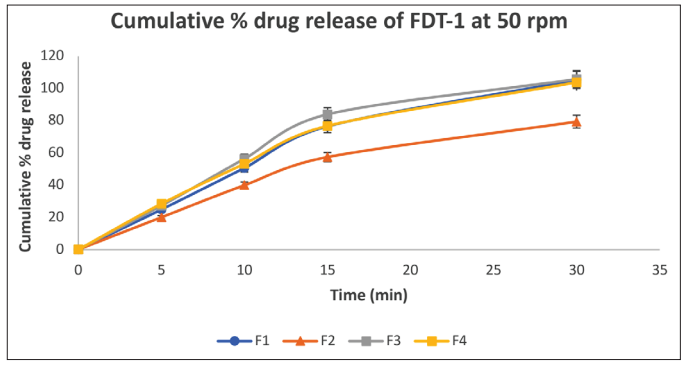

Figure 1. *In vitro* drug release study of marketed fast dispersible tablets (FDTs-1) of domperidonein (F1) 0.1 N HCl, (F2) SGF pH 1.2, (F3) Distilled water with 0.5% SLS, (F4) Distilled water with 1% SLS

FDTs: Fast dispersible tablets, SGF: Simulated gastric fluid, SLS: Sodium lauryl sulfate

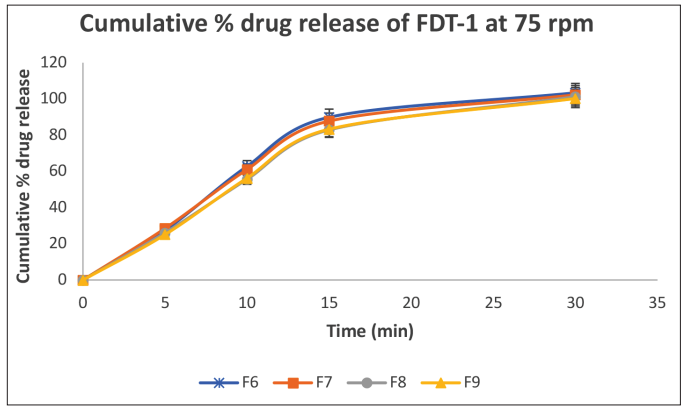

Figure 2. *In vitro* drug release study of marketed fast dispersible tablets (FDTs-1) of domperidone in (F1) 0.1 N HCl, (F2) SGF pH 1.2, (F3) Distilled water with 0.5% SLS, (F4) Distilled water with 1% SLS

FDTs: Fast dispersible tablets, SGF: Simulated gastric fluid, SLS: Sodium lauryl sulfate

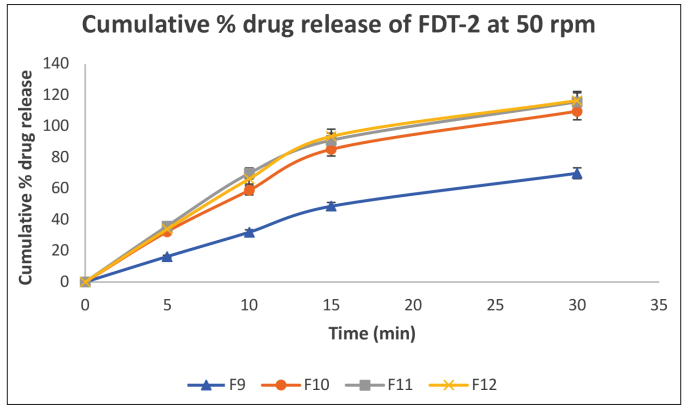

Figure 3. *In vitro* drug release study of marketed fast dispersible tablets (FDTs-1) of domperidone in (F9) SGF pH 1.2, (F10) 0.1 N HCl, (F11) Distilled water with 0.5% SLS, (F12) Distilled water with 1% SLS

FDTs: Fast dispersible tablets, SGF: Simulated gastric fluid, SLS: Sodium lauryl sulfate

(f_1). An f_2 value equal to 50 or greater ensures sameness or equivalence of the two curves and also the performance of the two products. Dissolution profiles of the 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 using equations 1 and 2.

$f_1=\{[\Sigma\ t=1\ n\ |R-T|]\ /\ [\Sigma\ t=1\ n\ R]\} \times 100$.....1

$f_2=50\times\log\{[1+(1/n)\Sigma t=1n(R-T)2]-0.5x100$.....2

Here n is the number of time points, R is the dissolution value of the reference (prechange) batch at time t, and T is the dissolution value of the test (postchange) batch at time t.

Validation of dissolution test method

The validation of the dissolution method was tested 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 a vessel containing 900 mL of dissolution media and stirred at 50 rpm using a paddle apparatus. The aliquots of sample solution were filtered through Whatman filter paper and analyzed by UV spectroscopy.[14]

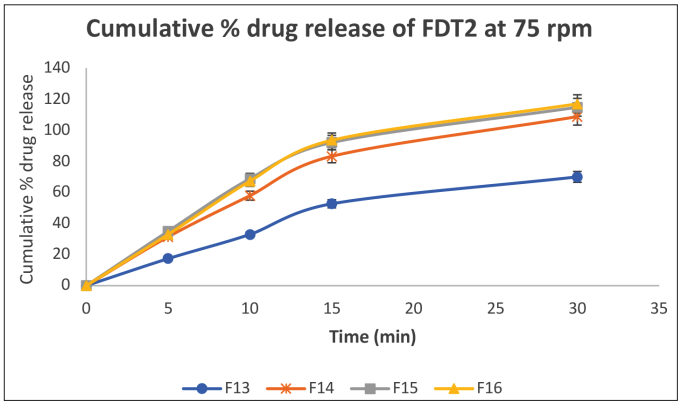

Figure 4. *In vitro* drug release study of marketed fast dispersible tablets (FDTs-1) of domperidone in (F13) SGF pH 1.2, (F14) 0.1 N HCl, (F15) Distilled water with 0.5% SLS, (F16) Distilled water with 1% SLS

FDTs: Fast dispersible tablets, SGF: Simulated gastric fluid, SLS: Sodium lauryl sulfate

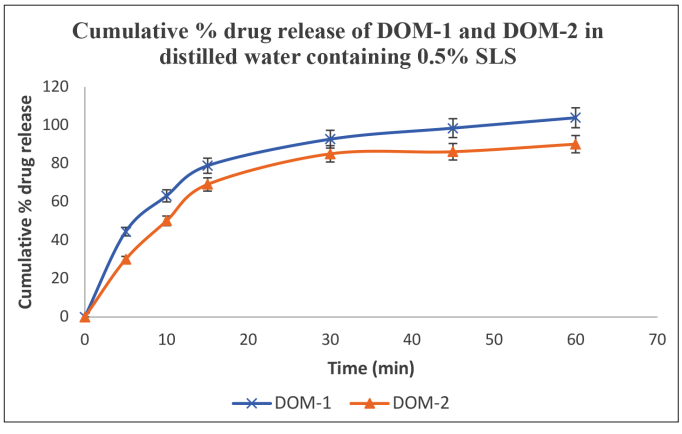

Figure 5. *In vitro* drug release study of prepared fast dispersible tablets (DOM-1 and DOM-2) in distilled water containing 0.5% SLS

SLS: Sodium lauryl sulfate

Accuracy

The domperidone was added to a dissolution vessel in known amount at 80%, 100%, and 120% level along with each 10 mg of domperidone FDT. The dissolution test was performed for 30 min using 900 mL of 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 the 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 the results were compared. Intermediate precision was determined by intraday and interday studies. The intraday study was performed by repeating the test three times in a day.[15] In the interday study, the dissolution test was conducted on a daily basis for 3 days and the results were compared. An relative standard deviation (RSD) value less than 2% indicates the precision of the developed method.

RESULTS 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 increased as the pH decreases.[16,17] The solubility of domperidone in water is very low and is enhanced by the addition of surfactant (SLS). SLS caused an increase in the solubility with concentration 0.5% and a further increase in concentration had no significant effect on solubility as shown in Table 2. The dose of domperidone in the FDTs was 10 mg/tablet. The 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 the existence of nonsink condition.[18,19]

Characterization of domperidone FDTs

The friability, hardness, disintegration time, wetting time, drug content, and weight of the formulated tablets were determined. The hardness of all the formulation was in the range of 3.37-3.55 kg/cm^2. The friability of all the formulations was below 1%, which indicates that the tablets had good mechanical resistance. Drug content was in the range of 100.9%-103.95%. The disintegration time of DOM-1 and DOM-2 was 31 and 50 s, respectively, which clearly indicated that the use of a

disintegrating agent in combination with effervescent material had 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%, providing good uniformity in all formulations.

Optimization of dissolution test conditions

On the basis of the screening study conducted on FDTs of domperidone and two different marketed FDTs of different manufacturer (FDT1 and FDT2), it was found that FDT-1 and FDT-2 exhibited similar dissolution profiles at 50 and 75 rpm. The highest drug release was observed in 0.1 N HCl and SGF without enzymes (pH 1.2) due to the high solubility to dose ratio (as shown in Table 2), but no significant difference in drug release was observed in either medium. The use of 0.5% SLS in distilled water increased the solubility and more than 100% drug release was observed within 30 min at a paddle speed of 50 rpm. Moreover, irrespective of paddle speed, the dissolution rate was relatively slow and consistent. A further increase in SLS did not increase the dissolution significantly. The use of a dissolution medium containing surfactant in small amounts less than its critical micelles concentration is often sufficient to solubilize certain poorly soluble drugs. The use of the slowest paddle speed (50 rpm) and dissolution media 0.1 N HCl and distilled water containing 0.5% SLS resulted in a better release profile. The drug release of FDT-1 and FDT-2 was similar (f_2>50) in both media, which may be due to the similar formulation parameters in both tablets.[8,20]

Confirmation of discriminating dissolution test conditions

Different dissolution profiles were obtained for FDTs of varying nature (Figures 5 and 6). In the present study dissimilarity in drug release was observed with DOM-1 compared to DOM-2 in 0.5% SLS (f_2=26) and similarity in drug release was observed with 0.1 N 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 a stirring speed of 50 rpm was optimum.[9-11]

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
0.1 N 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

SGF: Simulated gastric fluid, SLS: Sodium lauryl sulfate

Validation of the dissolution method[21-23]

Specificity

When tablets were subjected to dissolution testing and absorbance was recorded, the corresponding absorbance was equivalent to 1.38% 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 specific.

Accuracy

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

Linearity

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

Precision

The results for repeatability and intermediate precision are summarized in Tables 4-6. The RSD value was less than 1%,

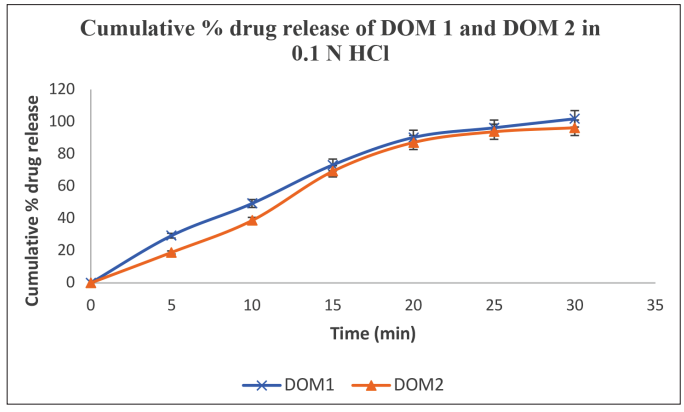

Figure 6. *In vitro* drug release study of prepared fast dispersible tablets (DOM-1 and DOM-2) in 0.1 N HCl

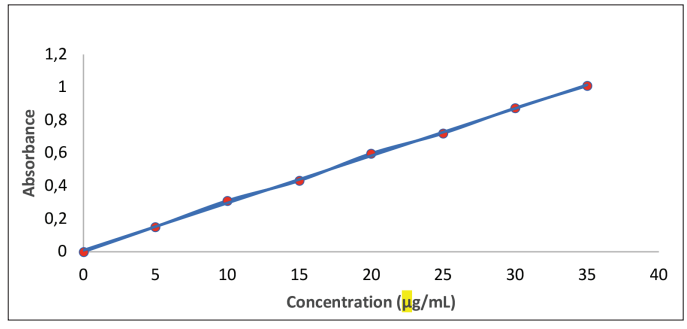

Figure 7. Calibration curve of domperidone in distilled water containing 0.5% SLS

SLS: Sodium lauryl sulfate

which shows that the developed dissolution method has good precision.

CONCLUSION

A dissolution test for domperidone FDTs was developed and validated as per ICH guidelines. The dissolution profiles of FDTs of domperidone were evaluated in different media (900 mL) at different stirring speeds (50 and 75 rpm). The use of distilled water containing 0.5% SLS as dissolution medium at 37±0.5°C and stirring speed of 50 rpm produced satisfactory results. The dissolution testing of domperidone FDTs formulated with different excipients showed different release profiles, which confirms the discriminatory nature of the developed method. The model independent method was used to evaluate the similarity of dissolution profiles. The developed method was found to be adequate for use in quality control testing of domperidone FDTs.

Conflicts of interest: No conflict of interest was declared by the authors.

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 ± standard deviation (n=3)

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

Dissolution vessels	Average % drug release ± SD (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

SD: Standard deviation, RSD: Relative standard deviation

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

Time	Average % drug release ± SD (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

SD: Standard deviation, RSD: Relative standard deviation

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

Day	Average % drug release ± SD (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

SD: Standard deviation, RSD: Relative standard deviation

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