ORIGINAL ARTICLE

A Predictive *In vitro* Biorelevant Dissolution Method Development for Fluvoxamine Extended-Release Capsules by Simulating Preprandial and Postprandial *In vivo* Performance

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Abstract

Aims: This research work was about biorelevant dissolution method development for fluvoxamine extended-release capsule by correlating preprandial and postprandial *in vivo* performance. **Materials and Methods:** The mean plasma concentration profile obtained after oral administration of extended-release capsules was deconvoluted using Wagner-Nelson deconvolution technique, to achieve percentage fraction of drug absorbed, and target dissolution profile was derived. Biorelevant dissolution method was developed using USP Apparatus-3, with dissolution media simulating gastrointestinal tract sink condition. A full factorial design of experiment was carried out for optimizing dissolution volume and dips per minutes, to achieve target dissolution profile. **Results:** The dissolution results observed using office of generic drugs recommend dissolution method were not comparable with target dissolution profile and observed with F_2 value of 37 at preprandial and 43 at postprandial condition. The achieved dissolution profile was comparable with target and observed with F_2 value of 81 at preprandial condition and 85 at postprandial condition. **Conclusion:** The developed dissolution method establishes good correlation between *in vitro* drug release and *in vivo* drug absorption and observed with R^2 value of 0.998 at preprandial condition and 0.997 at postprandial condition. The method gives the advantage of giving biowaiver.

Key words: Biorelevant, deconvolution, fluvoxamine maleate, postprandial, preprandial

INTRODUCTION

Fluvoxamine maleate is a serotonin (5-HT) reuptake inhibitor, chemical name is (E)-5-Methoxy-1-[4-(trifluoromethyl) phenyl]-1-pentanone O-(2-aminoethyl) oxime maleate. It is a white or almost white powder, odorless. Its molecular weight is 434.41, pKa is 6.28, and melting point is between 121°C and 123°C. Fluvoxamine maleate is soluble in acetone and ethanol, sparingly soluble in water and insoluble in ether. Fluvoxamine maleate extended-release capsules 100 mg – once a day formulation is having the bioavailability of approximately 84% and observed with elimination half-life of 15.6 h approximately.[1,2]

Plasma drug concentration is based on drug absorption and drug elimination rate. Whereas, the dissolution is based on cumulative percentage of drug released. The Wagner-Nelson deconvolution method is used to identify the percentage of drug absorbed from drug plasma concentration – time profile, with the aid of elimination rate and half-life of the specific product.[3] Research works were performed for analytical method development for fluvoxamine using HPLC[4] and UV method.[5]

The quality control dissolution procedure is used to the completeness of drug release from batch to batch, evaluated with regular conventional buffer with or without surfactant,

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using compendial dissolution apparatus, and the dissolution method is specific to the product, to detect the process and stability changes. The biorelevant dissolution method is used to predict the *in vivo* performance of product, evaluated with biorelevant dissolution media, using either compendial or non-compendial dissolution apparatus. The dissolution media are specific to the gastrointestinal condition and time. The apparatus, agitation speed, and media volume are required to be optimized for the product.[6-8]

USP Apparatus 3 – reciprocating cylinder is highly recommended for extended-release dosage of multiparticulate drug delivery system, and dissolution run is programmable to run with multiple dissolution media, by varying the speed. pH changes shall be simulated to gastrointestinal physiology. Several physiologically based dissolution media were developed for simulating gastrointestinal condition and are used in the present study.[9-12]

The correlation between percentage of drug absorbed through *in vivo* study and percentage of drug released though *in vitro* dissolution is established by *in vitro/in vivo* correlation (IVIVC) or *in vitro/in vivo* relationship (IVIVR).[13,14]

MATERIALS AND METHODS

Materials

Luvox(R) was procured from the United States of America. Working standards for fluvoxamine maleate were obtained as gift sample from par formulations. Acetonitrile and methanol (Merck, USA), egg phosphatidylcholine (Lipoid EPC®) (Lipoid GmbH), glyceryl monooleate (Rylo MG19 Pharma®) (Danisco Specialities), maleic acid (Sigma-Aldrich), sodium oleate (Riedel-de Haën), sodium taurocholate (Prodotti Chimici), tetrahydrofuran (Merck), and Pancreatin powder (Scientific Protein Laboratories LLC, WI) were used.

Instrumentation

Dissolution was performed using dissolution apparatus USP-II (Electrolab) and dissolution apparatus USP-III (Vankel). The analysis was carried out using Agilent 8453 UV spectrophotometer. Other instruments used for analysis were analytical balance, ultrasonic bath, centrifuge, pH meter, and oven and mechanical shaker. Polytetrafluoroethylene (PTFE) filter used for sample filtration was purchased from Rankem, India.

Methods

The mean plasma concentration data obtained from the study at preprandial and postprandial condition of fluvoxamine maleate from Luvox (SBOA) were deconvoluted using WinNonlin® software to determine the fraction of drug absorbed.

Quality control testing[15]

The quality control dissolution test is performed based on the recommendation from by office of generic drugs. The dissolution of fluvoxamine maleate extended-release capsule is performed in 900 mL of 0.05 M phosphate buffer, pH 6.8 using Apparatus II (paddle) at 50 rpm. Fluvoxamine maleate dissolved in the medium is analyzed by UV method (246 nm). The effect of speed on dissolution was evaluated at 35, 50, and 75 RPM. Experiments were conducted in three replicates. The sampling times were 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, and 16 h. Dissolution media were prepared by dissolving 7.0 g of monobasic sodium phosphate. Sampling was performed automatically through the sampling device. The volume withdrawn was approximately 5 mL for each sampling time point. The samples were filtered through a 0.45 µm PTFE filter and then analyzed using UV spectrophotometer.

Biorelevant testing

A biorelevant dissolution media used, to simulate the preprandial condition presented in Table 1, using USP dissolution test Apparatus-3 (reciprocating cylinder) to simulate release of fluvoxamine from Luvox in the GI tract. The top and bottom mesh size for the Bio-Dis vessel was 405 µm (40 mesh). The dissolution experimental design was executed using design of experiment (DOE), using Minitab software, a full factorial design, with two factors of dips per minute (DPM) at four levels and media volume at two levels, the response was evaluated at four time points for dissolution. The factor levels and response to be measured are presented in Table 2.

Table 1: Human gastrointestinal transit condition and residual time

GI tract	Fasting condition			Fed condition		
	Dissolution medium	pH	Residence time (min)	Dissolution medium	pH	Residence time (min)
Stomach	FaSSGF	1.6	120	FeSSGF	5.0	120
Duodenum/jejunum	New-FaSSIF	6.5	45	New-FeSSIF	5.8	45
Jejunum/ileum	Half-FaSSIF	7.0	45	Half-FeSSIF	6.5	45
Distal ileum	FaSSIF-sans	7.5	120	FeSSIF-sans	7.5	120
Colon	SCoF	5.8	480	SCoF	5.8	480

Table 2: Factor information

Factors	Levels	Values	Responses			
DPM	4	7, 10, 15, 20	1 h dissolution	4 h dissolution	8 h dissolution	12 h dissolution
Volume	2	100, 250				

Fasted state simulated gastric fluid (FaSSGF)

0.16 g lecithin was dissolved in 1.6 mL of dichloromethane and added to 5 L of purified water. 0.42 g of sodium taurocholate was added to the above solution and stirred for 45 min. 1 g pepsin and 20 g of NaCl were added to the above solution, heated at 40°C, using hot plate under continuous stirring for 30 min. The pH was adjusted to 1.6 using 1 N HCl. The volume was made up to 10 L.

Blank fasted state simulated Intestinal fluid (FaSSIF) pH 6.5, pH 7.0, and pH 7.5

19.77 g of sodium dihydrogen phosphate monohydrate, 1.7 g of sodium hydroxide pellets, and 30.93 g of sodium chloride were dissolved in 5 L of purified water, by stirring for 30 min. The pH was adjusted to exactly pH 6.5 or pH 7.0 or pH 7.5 using 1 N sodium hydroxide solution or 1 N hydrochloric acid solution.

Fasted state simulated intestinal fluid (FaSSIF) pH 6.5, pH 7.0, and pH 7.5

3.3 g sodium taurocholate was dissolved in approximately 500 mL of the blank FaSSIF of specific pH solution. 10 g of lecithin was dissolved in 100 mL of methylene chloride by mixing to achieve the concentration on 100 mg/mL. 11.8 mL of a methylene chloride solution containing 100 mg/mL lecithin was added to blank FaSSIF and stirred well for 15 min. A milky emulsion obtained. The solution was introduced into rotavapor, and methylene chloride was evaporated by heating at 40°C, under vacuum with the RPM of 50. After cooling to room temperature, the weight of the solution was checked again. The water lost to evaporation was replaced with demineralized water to obtain a total weight. Finally, the volume was made up to 2 L using blank FaSSIF.

Fed state simulated gastric fluid (FeSSGF)

138.5 g of sodium chloride and 40.04 g sodium acetate were dissolved in 5 L of purified water. 10 mL of acetic acid added to the above solution and mixed for 5 min. The pH was adjusted to 5.0 using 1 N HCl. The volume was made up to 10 L.

Blank fed state simulated Intestinal fluid (FeSSIF) pH 5.8, pH 6.5, and pH 7.5

20.2 g of sodium hydroxide pellets, 43.25 g of glacial acetic acid, and 59.37 g of sodium chloride were dissolved in 5 L of purified water, by stirring for 30 min. The pH was adjusted to exactly pH 5.8 or pH 6.5 or pH 7.5 using 1 N sodium hydroxide solution or 1 N hydrochloric acid solution.

Fed state simulated intestinal fluid (FeSSIF) pH 5.8, pH 6.5, and pH 7.5

16.5 g sodium taurocholate was dissolved in approximately 500 mL of the blank FeSSIF of specific pH solution. 10 g of lecithin was dissolved in 100 mL of methylene chloride by mixing to the achieve the concentration on 100 mg/mL. 59.08 mL of a methylene chloride solution containing 100 mg/mL lecithin was added to blank FeSSIF and stirred well for 15 min. A milky emulsion obtained. The solution was introduced into rotavapor, and methylene chloride was evaporated by heating at 40°C, under vacuum with the RPM of 50. After cooling to room temperature, the weight of the solution was checked again. The water lost to evaporation was replaced with demineralized water to obtain a total weight. Finally, the volume was made up to 2 L using blank FeSSIF.

Preparation of simulated colonic fluid pH 5.8

1.44 g of dibasic sodium phosphate, 8 g of sodium chloride, 0.2 g of potassium chloride, and 0.24 g of monobasic potassium phosphate in were dissolved in 1 L of purified water. pH was adjusted to pH 5.8 using 1 N sodium hydroxide solution or 1 N hydrochloric acid solution.

RESULTS AND DISCUSSION

Deconvolution of preprandial and postprandial *in vivo* data

The mean plasma drug concentration of fluvoxamine maleate obtained from Luvox 100 mg at preprandial condition and postprandial condition was deconvoluted using Wagner-Nelson numerical deconvolution method. The target dissolution profile was derived from fraction of drug absorbed, and the results are presented in Table 3.[16]

The deconvoluted data indicate that under preprandial condition, 80% of drug is absorbed in 16 h and under postprandial condition, 80% of drug is absorbed at 12 h, which directs the simulated dissolution to be performed for 16 h for preprandial condition and 12 h for postprandial condition, using appropriate dissolution sink conditions.

In vitro dissolution of Luvox capsules 100 mg in OGD recommended dissolution media and the study on effect of RPM

Analytical method was followed as per USP, for evaluation of dissolution, and the standard peak of fluvoxamine is presented in Figure 1.

A comparative dissolution profile of Luvox capsules 100 mg in OGD recommended dissolution media and target dissolution profile, along with the effect of RPM on dissolution profile is presented in Table 4 and Figure 2 and compared for similarity factor with target dissolution profile at preprandial condition and postprandial condition which was presented.

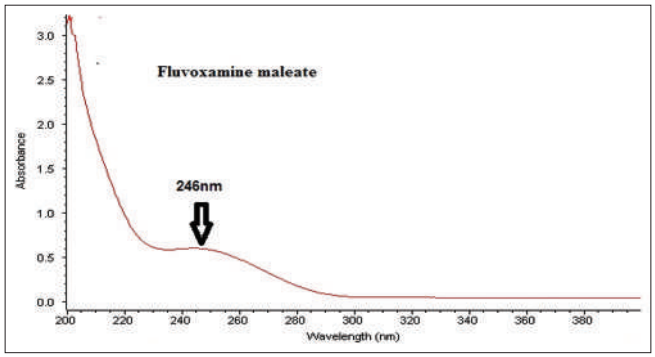

Figure 1: A typical UV spectra for fluvoxamine maleate

A comparative dissolution profile of Luvox capsules in the office of generic drugs recommended dissolution media was evaluated. The target profile achieved from deconvoluted data was not comparable with the dissolution profile achieved even by varying the RPM. The similarity factor (F_2) values observed also below 50%. Hence, it was decided to develop a biopredictive dissolution method to simulate the *in vivo* performance of drug product

Development of biorelevant dissolution method

The dissolution method was aimed to develop using QBD approach. The target profile was defined as deconvoluted dissolution profile. Initial risk assessment of CQA (dissolution profile) on variables is the residence time, molar concentration and pH of buffer, DPM, and media volume, in the biorelevant media dissolution method development. Two factors were evaluated in this study, risk assessment

Table 3: Target dissolution profile deconvoluted from *in vivo* data

Time (h)	Preprandial condition			Postprandial condition		
	Mean drug plasma concentration in human (preprandial) Cp (ng/mL)	Fraction abs. (numerical deconvolution by Wagner-Nelson method)	% absorbed (target profile)	Mean drug plasma concentration in human (postprandial) Cp (ng/mL)	Fraction abs. (numerical deconvolution by Wagner-Nelson method)	%absorbed (target profile)
0	0.000	0.00	0.00	0	0.00	0
1	0.012	0.00	0.0	0.02	0.00	0.0
2	0.393	0.01	1	0.12	0.00	0
3	4.100	0.10	10	0.91	0.02	2
4	10.795	0.27	27	6.68	0.18	18
5	19.964	0.52	52	17.14	0.48	48
6	21.624	0.59	59	25.12	0.71	71
7	23.257	0.66	66	26.66	0.79	79
8	20.653	0.63	63	26.96	0.83	83
9	20.151	0.65	65	27.47	0.88	88
10	20.165	0.68	68	25.67	0.86	86
12	19.705	0.73	73	24.15	0.88	88
14	18.364	0.75	75	22.46	0.90	90
16	18.759	0.82	82	22.78	0.96	96
20	14.254	0.81	81	17.38	0.92	92
24	13.450	0.87	87	15.43	0.95	95
30	11.385	0.94	94	12.08	0.96	96
36	8.387	0.95	95	9.79	0.98	98
48	4.547	0.98	98	6.50	1.02	102
72	1.281	1.00	100	1.54	1.01	101
96	0.228	1.01	101	0.68	1.02	102

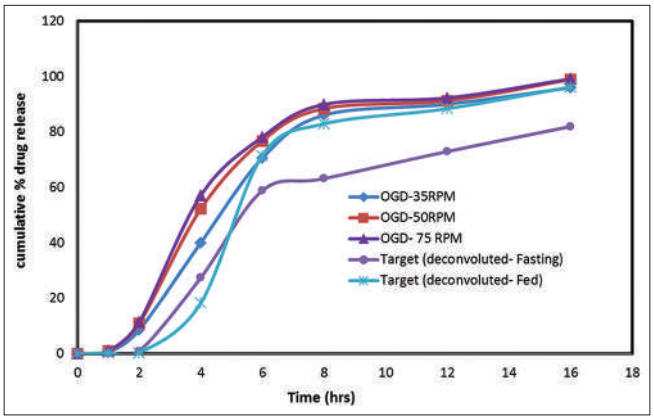

Figure 2: Comparative dissolution profile of Luvox 100 mg in OGD dissolution media at different RPM with target dissolution profile (deconvoluted from *in vivo*)

was performed for both parameters, and the RPN number is presented in Table 5. Study design was established using Minitab.

A full factorial study was performed, for media volume, two levels were evaluated and, for DPM, four levels were evaluated, for biorelevant dissolution method development at preprandial and postprandial condition. The response was considered as dissolution with four time points of 2 h, 4 h, 8 h, and 12 h. Significant factors for dissolution 2 h, 4 h, 8 h, and 12 h are presented in Figures 3, 4 and Table 6 for preprandial condition, Figure 5, 6 and Table 7 for postprandial condition on main effects and interaction effects.

For all DOE data analysis, the commonly used alpha of 0.05 was chosen to differentiate between significant and not

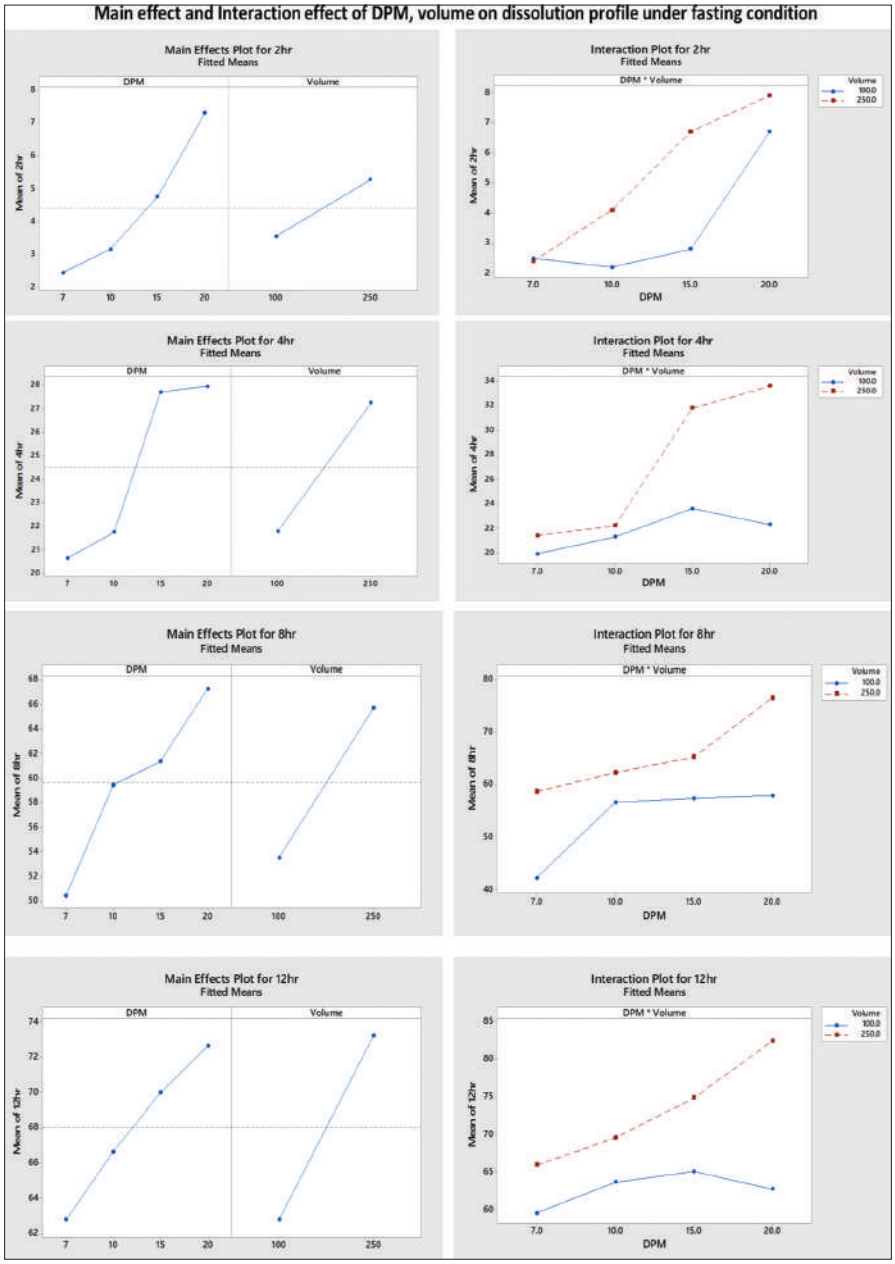

Figure 3: Main effect and interaction effect on dissolution profile under preprandial condition by DPM and media volume

Table 4: Comparative dissolution profile of Luvox capsules 100 mg at different RPM, in 0.05 M pH 6.8 phosphate buffer for 16 h. USP-II, 900 mL

B. No.	079358			Target	
Time (h)	35 RPM	50 RPM	75 RPM	Fasting	Fed
1 h	0.6±0.2	1.0±0.2	1.1±0.4	0	0
2 h	8.6±0.5	11.0±0.7	11.4±0.2	1	0
4 h	40.0±0.5	52.2±0.7	57.1±0.9	27	18
6 h	70.6±0.5	76.8±0.9	78.2±0.3	59	71
8 h	86.1±0.5	88.5±0.2	89.9±0.4	63	83
12 h	90.0±0.1	91.3±1.8	92.3±0.3	73	88
16 h	96.0±0.5	98.9 ±0.6	99.1 ±0.7	82	96
F_2 (with fasting)	43	37	35		
F_2 (with fed)	52	43	40		

Mean±SD, *n*=3

Table 5: Risk assessment for media volume and DPM for the product

Factors	Severity	Probability	Delectability	Risk number	Justification
Media volume	3	3	3	27	Dissolution media volume is directly related to intrinsic solubility of drug, hence, the risk is high.
DPM	3	2	2	12	The agitation speed disrupts the structure to have faster erosion of pellets.

Risk assessment measured in three categories, low (1), medium (2), and high (3). The risk number is the multiplication of all the three. The risk number more than 9 will be considered for DOE study

Table 6: A full factorial study and responses of the factors for preprandial (fasting) state simulating dissolution method

Run order	Factors		Responses			
	DPM	Volume	Dissoln. 2 h	Dissoln. 4 h	Dissoln. 8 h	Dissoln. 12 h
1	15	100	2.8±0.3	23.6±0.2	57.4±0.2	65.1±0.2
2	15	250	6.7±0.7	31.8±0.7	65.3±0.2	74.9±0.8
3	10	250	4.1±0.5	22.2±0.5	62.3±0.2	69.6±0.7
4	20	250	7.9±0.4	33.6±0.2	76.6±0.2	82.5±0.2
5	7	250	2.4±0.1	21.4±0.2	58.7±0.3	66.0±0.2
6	20	100	6.7±0.2	22.3±0.4	57.9±0.4	62.8±0.3
7	10	100	2.2±0.2	21.3±0.2	56.6±0.2	63.7±0.2
8	7	100	2.5±0.3	19.9±0.5	42.2±0.3	59.6±0.2

Mean±SD, *n*=3

Table 7: A full factorial study and responses of the factors for postprandial (Fed) state simulating dissolution method

Run order	Factors		Responses			
	DPM	Volume	Dissoln. 2 h	Dissoln. 4 h	Dissoln. 8 h	Dissoln. 12 h
1	15	250	0.7±0.2	24.1±0.6	88.6±0.6	93.5±0.8
2	20	100	1.1±0.2	17.5±1.5	71.8±0.3	74.1±0.5
3	7	250	0.5±0.3	15.6±0.5	75.1±0.3	79.6±0.4
4	10	250	0.4±0.2	21.1±0.4	85.5±0.3	90.9±0.6
5	10	100	0.4±0.1	15.3±0.5	68.8±0.3	73.3±0.3
6	20	250	0.9±0.3	25.5±1.0	90.6±0.6	95.4±2.6
7	15	100	0.7±0.1	16.2±0.3	71.0±1.0	75.8±0.7
8	7	100	0.3±0.2	15.0±0.5	65.3±0.5	70.7±0.6

Mean±SD, *n*=3

significant factors. The ANOVA result concludes that the model is significant, and model summary is observed with 100% with no error, results were presented in Table 8 for pre-prandial condition. The response optimization for dissolution graph indicates that the desired DPM is 10 DPM, and media volume was 250 mL, with the composite desirability of 0.589.

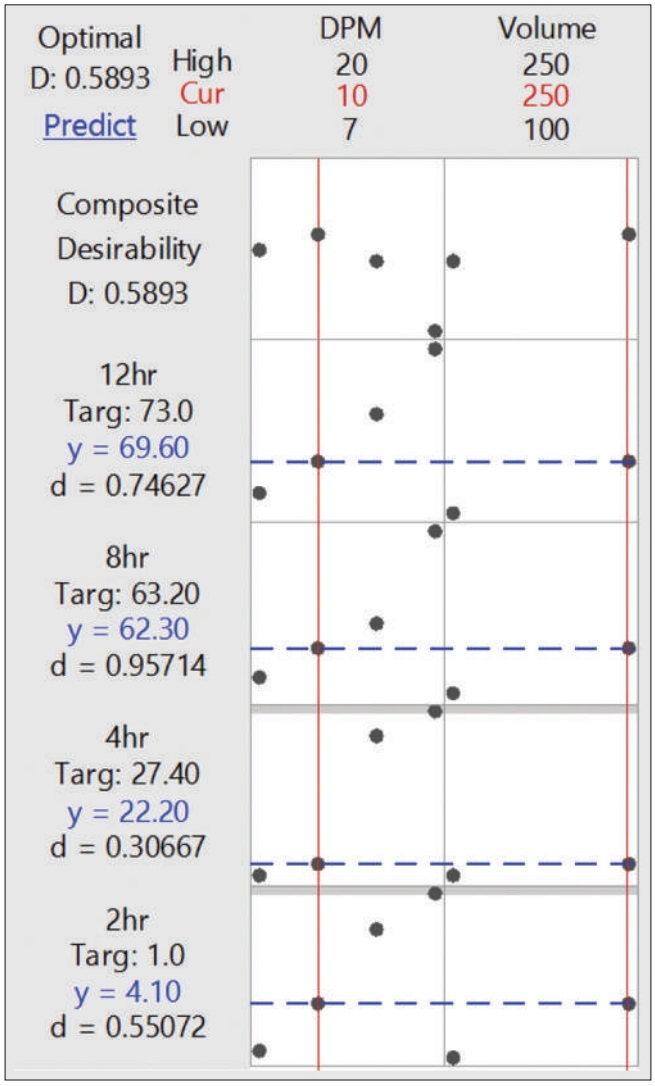

Figure 4: Response optimization for dissolution of fluvoxamine in fasting condition at 2 h, 4 h, 8 h, and 12 h

The ANOVA result concludes that the model is significant, and model summary is observed with 100% with no error, results were presented in Table 9 for post-prandial condition. The response optimization for dissolution graph indicates that the desired DPM is 10 DPM, and media volume was 250 mL, with the composite desirability of 0.629.

Based on the above results, the target dissolution profile for biorelevant dissolution method has been finalized, lower and upper limits are derived using Minitab, with 95% confidence interval, and the values are presented in Table 10.

Establishment of the IVIVR

A comparative dissolution profile using USP Apparatus-3 and target profile established for biorelevant dissolution method established for preprandial condition is presented in Table 11, Figures 7 and 8.

Percentage of drug absorbed obtained from deconvoluted *in vivo* data was compared with percentage of drug dissolved under simulated fasting condition, and F_2 value is 81.

The fraction of drug released *in vitro* is consistently comparable to the fraction of drug released *in vivo* indicating overdiscriminating dissolution conditions. The regression coefficient (R^2) value of 0.998 also indicates very good predictive capability of the relationship.

A comparative dissolution profile using USP Apparatus-3 and target profile established for biorelevant dissolution method established for postprandial condition is presented in Table 12, Figures 9 and 10.

Percentage of drug absorbed obtained from deconvoluted *in vivo* data was compared with percentage of drug dissolved under simulated fed condition, and F_2 value is 85.

Table 8: ANOVA results for design of experiment for fasting condition

Source	DF	Dissolution at 2 h		Dissolution at 4 h		Dissolution at 8 h		Dissolution at 12 h	
		Adj SS	Adj MS	Adj SS	Adj MS	Adj SS	Adj MS	Adj SS	Adj MS
Model	7	37.93	5.42	188.05	26.86	649.07	92.72	388.91	55.56
Linear	4	33.75	8.44	149.01	37.25	588.34	147.08	327.37	81.84
DPM	3	27.79	9.27	89.05	29.68	290.66	96.89	108.97	36.32
Volume	1	5.95	5.95	59.95	59.95	297.68	297.68	218.41	218.41
Two-way interactions	3	4.18	1.40	39.04	13.01	60.74	20.25	61.55	20.52
DPM*Volume	3	4.18	1.40	39.04	13.01	60.74	20.25	61.55	20.52
Error	0								
Total	7	37.929		188.05		649.07		388.91	
Model summary (R^2)		100%		100%		100%		100%	

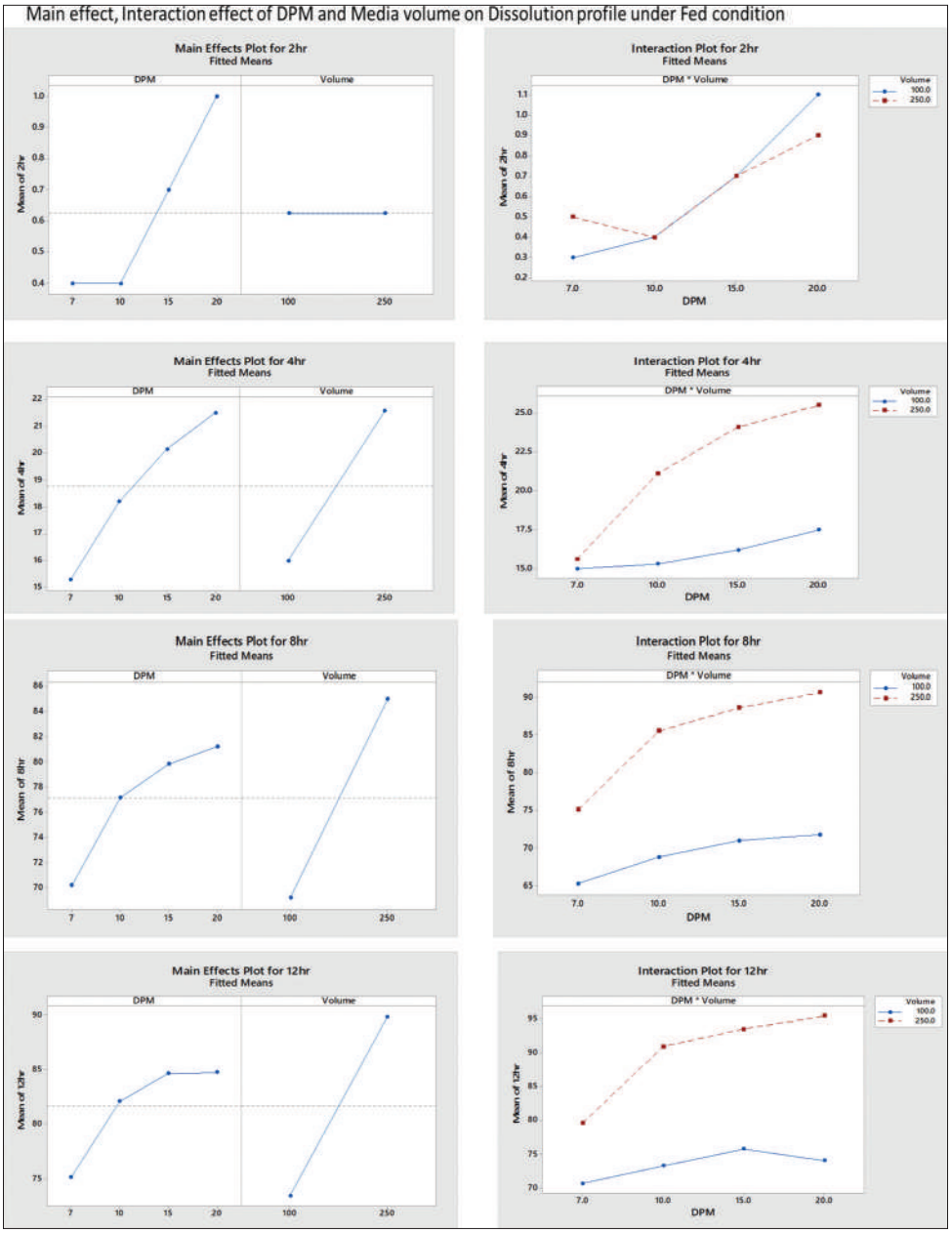

Figure 5: Main effect and interaction effect on dissolution profile under preprandial condition by DPM and media volume

Table 9: ANOVA results for design of experiment for fed condition

Source	DF	Dissolution at 2 h		Dissolution at 4 h		Dissolution at 8 h		Dissolution at 12 h	
		Adj SS	Adj MS	Adj SS	Adj MS	Adj SS	Adj MS	Adj SS	Adj MS
Model	7	0.54	0.08	123.65	17.66	662.49	94.64	700.10	100.01
Linear	4	0.50	0.12	105.61	26.40	637.98	159.49	658.41	164.60
DPM	3	0.50	0.17	43.44	14.48	143.42	47.81	122.12	40.71
Volume	1	0.00	0.00	62.16	62.16	494.55	494.55	536.28	536.28
Two-way interactions	3	0.04	0.01	18.04	6.02	24.51	8.17	41.69	13.90
DPM*Volume	3	0.04	0.01	18.04	6.02	24.51	8.17	41.69	13.90
Error	0								
Total	7	0.54		123.65		662.49		700.10	
Model summary (R^2)		100.00%		100.00%		100.00%		100.00%	

Table 10: Target and ranges recommended for the fasting state and fed state simulating biorelevant dissolution study

Response	Goal	Fasting state			Fed state		
		Lower	Target	Upper	Lower	Target	Upper
Dissoln. 12 h	Target	59.6	73.0	82.5	70.7	88.0	95.4
Dissoln. 8 h	Target	42.2	63.2	76.6	65.3	82.9	90.6
Dissoln. 4 h	Target	19.9	27.4	33.6	15.0	18.3	25.5
Dissoln. 2 h	Target	0.9	1.0	7.9	-0.0	0.0	1.1

Table 11: *In vitro* and *in vivo* dissolution of Luvox 100 mg at preprandial (fasting) condition

Dissolution (time)	Cumulative dissolution time	Cumulative % drug release	Target profile
FaSSGF pH 1.6 for 60 min	1 h	0.5±0.3	0
FaSSGF pH 1.6 for 120 min	2 h	4.1±0.5	1
pH 6.5 FASSIF for 45 min and pH 7.0 half-FaSSIF for 45 min and pH 7.5 FaSSIF-sans for 30 min	4 h	22.2±0.5	24
pH 7.5 FaSSIF-sans for 90 min and pH 5.8 SCoF for 30 min	6 h	56.5±0.3	59
150 min	8 h	62.3±0.3	63
pH 5.8 SCoF for 390 min	12 h	69.6±0.7	73
630 min	16 h	80.8±1.1	82
F_2		81	

Mean±SD, *n*=3

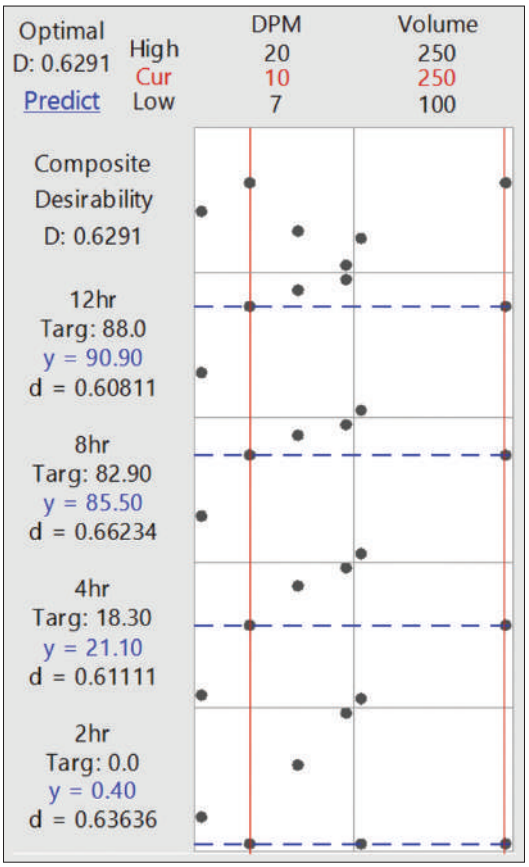

Figure 6: Response optimization for dissolution of fluvoxamine in fed condition at 2 h, 4 h, 8 h, and 12 h

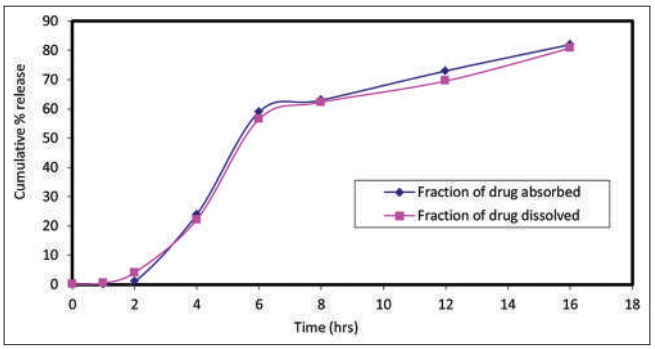

Figure 7: *In vitro-in vivo* comparison of Luvox 100 mg capsules – on fraction of drug absorbed by *in vivo* and fraction of drug dissolved by *in vitro*

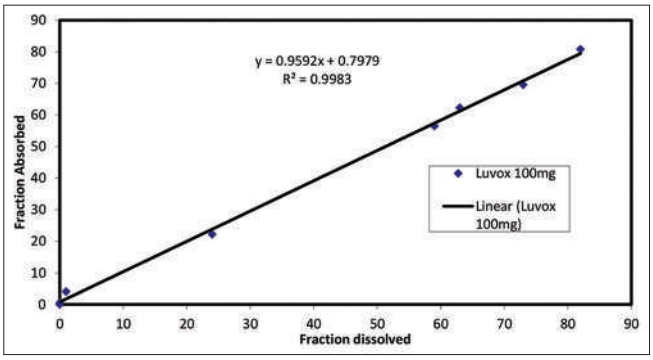

Figure 8: *In vitro-in vivo* level – a correlation of Luvox extended-release capsules under fasting condition

The fraction of drug released *in vitro* is consistently comparable to the fraction of drug released *in vivo* indicating overdiscriminating dissolution conditions. The regression coefficient (R^2) value of 0.997 also indicates very good predictive capability of the relationship.

Table 12: *In vitro* and *in vivo* dissolution of Luvox 100 mg at postprandial condition

Dissolution (time)	Cumulative dissolution time	Cumulative % drug release	Target profile
FeSSGF pH 5.0 for 120 min	2 h	0.4±0.2	0
pH 5.8 FeSSIF for 45 min and pH 6.5 half-FeSSIF for 45 min and pH 7.5 FeSSIF-sans for 30 min	4 h	21.1±0.4	18
pH 7.5 FeSSIF-sans for 60 min	5 h	45.6±0.7	48
pH 7.5 FeSSIF-sans for 30 min and pH 5.8 SCoF for 30 min	6 h	75.2±0.7	71
pH 5.8 SCoF for 150 min	8 h	85.5±0.3	83
pH 5.8 SCoF for 390 min	12 h	90.9±0.6	88
F_2		85	

Mean±SD, *n*=3

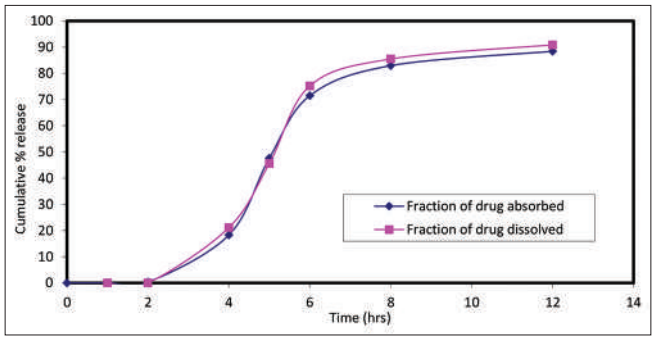

Figure 9: *In vitro-in vivo* comparison of Luvox 100 mg capsules – on fraction of drug absorbed by *in vivo* and fraction of drug dissolved by *in vitro* under fed condition

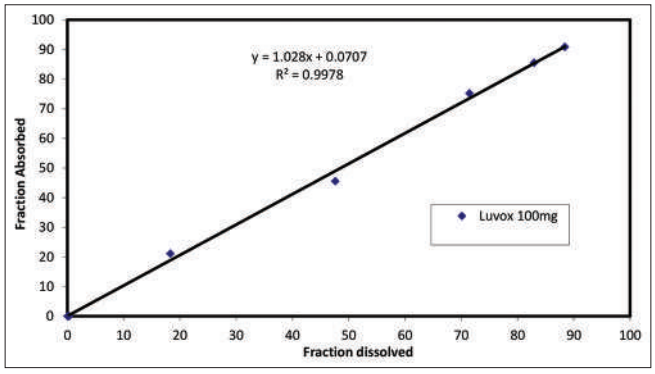

Figure 10: *In vitro-in vivo* level – a correlation of Luvox extended-release capsules under fed condition

CONCLUSION

The finished product is not having any impact by agitation speed, which reveals that the functional coating is robust. However, F_2 value with target dissolution profile deconvoluted from *in vivo* was observed below 50. A suitable biorelevant dissolution method by simulating preprandial and postprandial conditions was developed, using design of experiment study. Hence, the dissolution method using USP Apparatus 3 at 10 DPM with 250 mL of change over media simulating preprandial condition shall be used as a biorelevant dissolution method, based on the established IVIVC. The upper and lower limits were fixed based on 95% CI of the target dissolution profile.

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