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BIORELEVANT DISSOLUTION METHOD DEVELOPMENT OF MEMANTINE EXTENDED-RELEASE CAPSULES FOR PREDICTION OF PRE-PRANDIAL *IN-VIVO* PERFORMANCE

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Keywords:

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ABSTRACT: The main objective of this research work is to develop biorelevant dissolution method for the Memantine extended-release capsule by correlating pre-prandial *in-vivo* performance. The mean plasma concentration profile obtained after oral administration of extended-release capsules was deconvoluted using the Wagner-Nelson deconvolution technique for deriving the percentage fraction of drug absorbed to achieve the target dissolution profile. The dissolution results obtained by using the office of generic drugs recommended dissolution method was not comparable with the target dissolution profile and observed with an F_2 value of 30. Biorelevant dissolution method was developed using USP Apparatus 3 (reciprocating cylinder), with dissolution media simulating gastrointestinal tract sink condition. A full factorial design of the experiment was carried out for dissolution method development and optimization. Media volume and dips per minute were considered as main factors in the design of the experimental study. The developed biorelevant dissolution method based on statistical interpretation of the main effect, interaction effect, and desirability factor is with media volume 150 ml and 15 dips per minute and observed with the F_2 value (similarity factor) of 90. The developed dissolution method demonstrates a very good *in-vitro*/*in-vivo* correlation under the pre-prandial condition and observed with R^2 value of 0.998. The dissolution method shall be used as a predictive *in-vitro* tool for evaluation Memantine extended-release capsules, and also gives the advantage of claiming bio-waiver.

INTRODUCTION: Memantine hydrochloride is N- methyl- D- Aspartate receptor antagonists, chemically known as 1-amino-3, 5-dimethyl-adamantane hydrochloride, white to off-white crystalline powder, highly soluble in water and alcohol, sparingly soluble in acetone and dimethyl fumarate.

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pKa is 10.27, pH of 3% solution in water is 5.5 [1, 2]. Memantine exhibits high solubility and permeability. Extended-release capsules of 28 mg formulation is having the bioavailability of approximately 86% and observed with a half-life of 60-80 h approximately [3].

Pharmacopoeial or quality control dissolution procedures are mainly used to characterize the extent of dissolution for the immediate-release formulation, rate, and extent of drug release for modified-release formulation. If individual monograph is not available, USP recommends standard dissolution apparatus and limits based on the type of dosage form [5].

The quality control dissolution procedure is used to characterize the product for completeness of drug solubility in a specified medium for a specified period of time form batch to batch, evaluated with a regular conventional buffer with or without surfactant, using compendial dissolution apparatus, and the dissolution method is specific to the product. The biorelevant dissolution method is used to predict the *in-vivo* performance of the product, evaluated with biorelevant dissolution media, using either compendial or non-compendial dissolution apparatus. The dissolution media is specific to the human gastro-intestinal condition and transit time. The agitation speed and media volume are required to be optimized for the product [6, 7].

USP Apparatus 3 (reciprocating cylinder) is recommended for extended-release dosage of multi-particulate drug delivery system, and the dissolution run is programmable to run with multiple dissolution media by varying the speed [8]. pH changes shall be simulated to gastro-intestinal physiology. The human gastrointestinal transit system, pH and transit time is presented in **Table 1**.

Several physiologically based dissolution media were developed for simulating gastrointestinal condition and were used in the present study [9]. The analytical method was developed by using quality by design approach, and the experiments were carried out with full factorial design method [10].

TABLE 1: HUMAN GI TRACT TRANSIT CONDITION AND RESIDUAL TIME

GI tract	Fasting condition		
	Dissolution medium	pH	Residence time
Stomach	FaSSGF	1.6	120
Duodenum / Jejunum	New-FaSSIF	6.5	60
Jejunum/Ileum	Half-FaSSIF	7.0	60
Distal ileum	FaSSIF-sans	7.5	120
Colon	SCoF	5.8	480

The correlation between the percentage of drug absorbed through *in-vivo* study and the percentage of drug released through *in-vitro* dissolution was established by *in-vitro* / *in-vivo* Correlation (IVIVC) or *in-vitro* / *in-vivo* Relationship (IVIVR) [11, 12].

MATERIALS AND METHODS:

Materials: Namenda XR(R) was procured from the pharmacy. Working standards for memantine HCl were obtained as gift sample from Mylan. Standard inorganic salts and solvents were procured from Merck. Pepsin 3000 NF (Meteoric biopharmaceuticals Pvt. Ltd), Lecithin (Soya lecithin India), Glyceryl monooleate (Danisco Specialities), Maleic acid (Sigma-Aldrich), Sodium oleate (Riedel-de Haën), Sodium taurocholate (Prodotti Chimici), Tetrahydro furan (Merck), Pancreatin powder (Scientific Protein Laboratories LLC) were procured from indigenous vendors and used for evaluation. Polyvinyl difluoride filters (0.45 micron) were purchased from Rankem, India.

Instrumentation: Dissolution USP Apparatus 1 (Electrolab) and dissolution USP Apparatus 3 (Vankel 25-1000 BIO-DIS Reciprocating cylinder). Agilent 1200 RP-HPLC system consisting of a pump, an injector, UV detector, with an auto sampler and column heater, enabled with Empower software. Analytical Balance, Ultrasonic Bath, Centrifuge, pH meter, Oven, and Mechanical shaker. Rotavap (type R-114, Buechi, Essen, Germany).

Methods: The mean plasma drug concentration data was obtained from a single dose study at pre-prandial condition on human volunteers from Namenda XR was deconvoluted using WinNonlin software to determine the fraction of drug absorbed.

Quality Control Testing: The quality control dissolution test was performed based on the recommendation from by office of generic drugs (OGD). The dissolution of the memantine extended-release capsule was performed in 900 ml of pH 1.2 simulated gastric fluid, using USP Apparatus 1 (basket) at 100 revolutions per minute (RPM). The HPLC column X-bridge C18, 4.6 × 20 mm, 2.5 µ, the column temperature was maintained at 30 °C, with the flow rate of 1.0 ml/min. Memantine being molecule, without chromophore, The sample and test solutions were derivatized before injecting into HPLC. The effect of speed on dissolution was evaluated at 75, 100 & 125 RPM. Experiments were conducted in three replicates. The sampling times were 1 h, 2 h, 4 h, 6 h, 8 h, and 12 h [13]. Dissolution media was prepared by dissolving 2.0 g of sodium chloride, 7.0 ml of concentrated hydrochloric acid in 1000 ml of purified water, and mixed for 10 min; the pH was

adjusted to pH 1.2 using 1N HCl. 0.2% sodium borate buffer and 0.2% flurenylmethyl chloroformate were used for the derivatization of memantine for getting detected using UV detector.

Biorelevant Testing: Fasting simulated state change over dissolution media and USP Apparatus 3 were used to simulate the release of memantine from Namenda XR in the gastrointestinal tract. Dissolution media used were, fasted state simulated gastric fluid (FaSSGF), fasted state simulated intestinal fluid (FaSSIF) pH 6.5, pH 7.0, and pH 7.5, simulated colonic fluid (SCoF) pH 5.8. The top and bottom mesh size for the bio-dis vessel was 405 µm (40 mesh). Initial risk assessment is performed for factors based on the risk priority number; the factors evaluated are DPM at 4 levels and media volume at 3 levels, the response was evaluated at four-time points of 2 h, 4 h, 8 h, and 12 h for dissolution. A full factorial design of the experiment is carried out using Minitab software; the study outcome is interpreted statistically. The factor levels and responses measured were presented in **Table 2**.

Note: Risk assessment was measured in 3 categories, low (1), medium (2) & high (3). The Risk number is the multiplication of all the three. The Risk number more than 9 was considered for the DOE study.

TABLE 2: FACTOR INFORMATION

Factors	Levels	Values	Responses			
DPM	4	7, 10, 15, 20	2 h dissolution	4 h dissolution	8 h dissolution	12 h dissolution
Volume	3	100, 150, 250				

Fasted State Simulated Gastric Fluid (FaSSGF): 0.16 g lecithin was dissolved in 1.6 ml of dichloro-methane, and added to 5 liters of purified water. 0.42 g of sodium taurocholate was added to the above solution and stirred for 4 min.

1 g pepsin and 20 g of sodium chloride were added to the above solution, heated at 40 °C, using a hot plate under continuous stirring for 30 min. pH was adjusted to 1.6 using 1N hydrochloric acid. The volume was made up to 10 liters.

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 liters 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 1N sodium hydroxide solution or 1N hydrochloric acid solution.

Fasted State Simulated Intestinal Fluid (FaSSIF) pH 6.5, pH7.0 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 methylene chloride solution containing 100 mg/ml lecithin was added to blank FaSSIF, and stirred well for 15 min. A milky emulsion was 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. Volume was made up to 2 liters using blank FaSSIF.

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 liter of purified water. pH was adjusted to pH 5.8 using 1N sodium hydroxide solution or 1N Hydrochloric acid solution.

RESULTS AND DISCUSSION:

Deconvolution of Pre-prandial *In-vivo* Data: The mean plasma drug concentration of memantine obtained from Namenda XR 28 mg at pre-prandial condition was deconvoluted using Wagner-Nelson numerical deconvolution method. The target dissolution profile was derived from the fraction of the drug absorbed, and the results were presented in **Table 3** [14].

The deconvoluted data indicates that under pre-prandial conditions, 75% of the drug is absorbed in 12 h, which directs the simulated dissolution to be performed for 12 h for the pre-prandial condition using appropriate dissolution sink conditions.

TABLE 3: TARGET DISSOLUTION PROFILE DECONVOLUTED FROM *IN-VIVO* DATA

Time (h)	Pre-prandial condition		
	Mean drug plasma concentration in human (pre-prandial) Cp (ng/ml)	Fraction Abs. (Numerical deconvolution by Wagner-Nelson method)	%Absorbed (Target profile)
0	0.00	0.00	0
0.25	0.03	0.00	0.1
0.5	0.22	0.01	1
1	1.08	0.03	3
2	3.29	0.08	8
3	6.43	0.16	16
4	13.82	0.35	35
6	17.88	0.46	46
8	20.28	0.54	54
12	27.29	0.75	75
24	26.92	0.87	87
30	28.58	0.98	98
36	26.74	1.01	101
48	21.02	0.98	98
72	14.55	1.00	100

***In-vitro* dissolution of Namenda XR 28 mg in OGD Recommended Dissolution Media and the Study on Effect of RPM:** A comparative dissolution profile of Namenda XR 28 mg in OGD recommended dissolution media and target dissolution profile, along with the effect of RPM on dissolution profile were presented in **Table 4** and **Fig. 1**.

TABLE 4: COMPARATIVE DISSOLUTION PROFILE OF NAMENDA XR 28MG AT DIFFERENT RPM, IN pH 1.2SGF FOR 12 h USP APPARATUS-1, 900 ML

Time (h)	Batch Number: 111834			Target (deconvoluted from *In-vivo*)
	75	100	125	
1 hr	10.2 ± 0.7	13.4 ± 0.9	15.2 ± 0.4	3
2 hrs	23.2 ± 0.5	27.4 ± 0.6	29.0 ± 0.5	8
4 hrs	55.7 ± 0.1	57.2 ± 0.4	58.9 ± 0.8	35
6 hrs	73.5 ± 0.8	76.6 ± 0.7	74.3 ± 0.6	46
8 hrs	88.1 ± 1.2	89.8± 0.4	90.5 ± 0.9	54
12 hrs	99.5 ± 1.0	100.6 ± 0.6	100.7 ± 0.4	75
F_2 (Against target)	32	30	29	

Note: mean ± SD, n=3

The target profile achieved from deconvoluted data was not comparable with the dissolution profile achieved by using OGD recommended dissolution media. The change in RPM is also not having any significant impact on the dissolution profile; the similarity factor (F2) was below 50. Hence, it was decided to develop a biorelevant dissolution method to simulate the *in-vivo* performance of drug products.

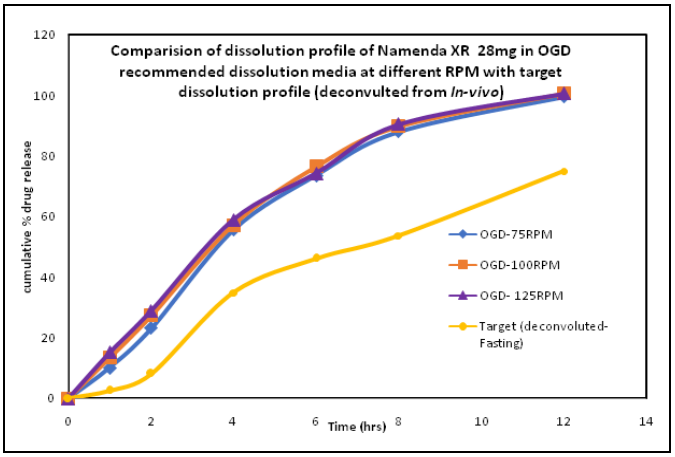


FIG. 1: COMPARISON OF DISSOLUTION PROFILE OF NAMENDA XR IN OGD RECOMMENDED DISSOLUTION MEDIA AT DIFFERENT RPM WITH TARGET DISSOLUTION PROFILE (DECONVOLUTED FROM *IN-VIVO*)

Development of Biorelevant Dissolution Method: The dissolution method was developed by using the quality by design (QBD) approach. The target profile was defined as a deconvoluted dissolution profile. Initial risk assessments of CQA (Dissolution profile) on variables were dissolution apparatus, dissolution media, DPM, and media volume. DPM and media volume were the factors evaluated in this study, based on risk assessment, and details were presented in **Table 5**.

A full factorial design of the experiment study with factors and responses for biorelevant dissolution method at pre-prandial condition was presented in

Table 6. The response was considered as dissolution with 4-time points of 2 h, 4 h, 8 h, and 12 h. For all DOE data analysis, the commonly used alpha of 0.05 was chosen to differentiate between significant and not significant factors.

TABLE 5: RISK ASSESSMENT FOR DISSOLUTION METHOD ON VARIABLES

Factors	Severity	Probability	Delectability	Risk Number	Justification
Dissolution apparatus	2	1	2	4	For modified release capsules, the most recommended apparatus suitable for biorelevant method is USP Apparatus 3, is selected for the dissolution method. Hence, the risk is low.
Dissolution media	1	2	2	4	The dissolution media selected is based on human gastro-intestinal conditions and transit time. Hence, the risk is very low.
Media volume	3	3	3	27	Dissolution media volume is directly related to the intrinsic solubility of drug. Hence, the risk is high.
DPM	3	3	2	18	The agitation speed disrupts the structure to have faster erosion of pellets. Hence, the risk is high.

TABLE 6: A FULL FACTORIAL STUDY AND RESPONSES OF THE FACTORS PRE-PRANDIAL (FASTING) STATE SIMULATING DISSOLUTION METHOD

Run Order	Factors		Responses			
	DPM	Volume	Dissoln 2 h	Dissoln 4 h	Dissoln 8 h	Dissoln 12 h
Target	-	-				
1	7	100	4.5 ± 0.3	19.9 ± 0.5	42.2 ± 0.3	59.6 ± 0.2
2	10	100	5.6 ± 0.2	21.3 ± 0.2	44.6 ± 0.5	63.7 ± 0.2
3	15	100	5.6 ± 0.2	23.6 ± 0.2	45.5 ± 0.2	65.1 ± 0.2
4	20	100	6.1 ± 0.2	22.3 ± 0.4	46.9 ± 0.3	66.2 ± 0.6
5	7	150	2.4 ± 0.1	26.8 ± 0.4	48.8 ± 0.6	70.1 ± 1.0
6	10	150	4.1 ± 0.5	29.1 ± 0.5	51.9 ± 0.6	70.3 ± 0.5
7	15	150	7.4 ± 0.2	34.0 ± 0.7	54.5 ± 0.3	76.0 ± 0.7
8	20	150	7.9 ± 0.4	36.1 ± 0.2	58.7 ± 0.5	83.2 ± 0.3
9	7	250	8.7 ± 0.4	37.2 ± 0.4	58.1 ± 0.4	75.2 ± 0.7
10	10	250	10.6 ± 0.5	38.7 ± 0.4	59.8 ± 0.3	80.8 ± 0.5
11	15	250	11.1 ± 0.4	34.0 ± 0.7	61.1 ± 0.2	81.9 ± 0.4
12	20	250	12.1 ± 0.3	36.1 ± 0.2	61.6 ± 0.8	83.8 ± 0.3

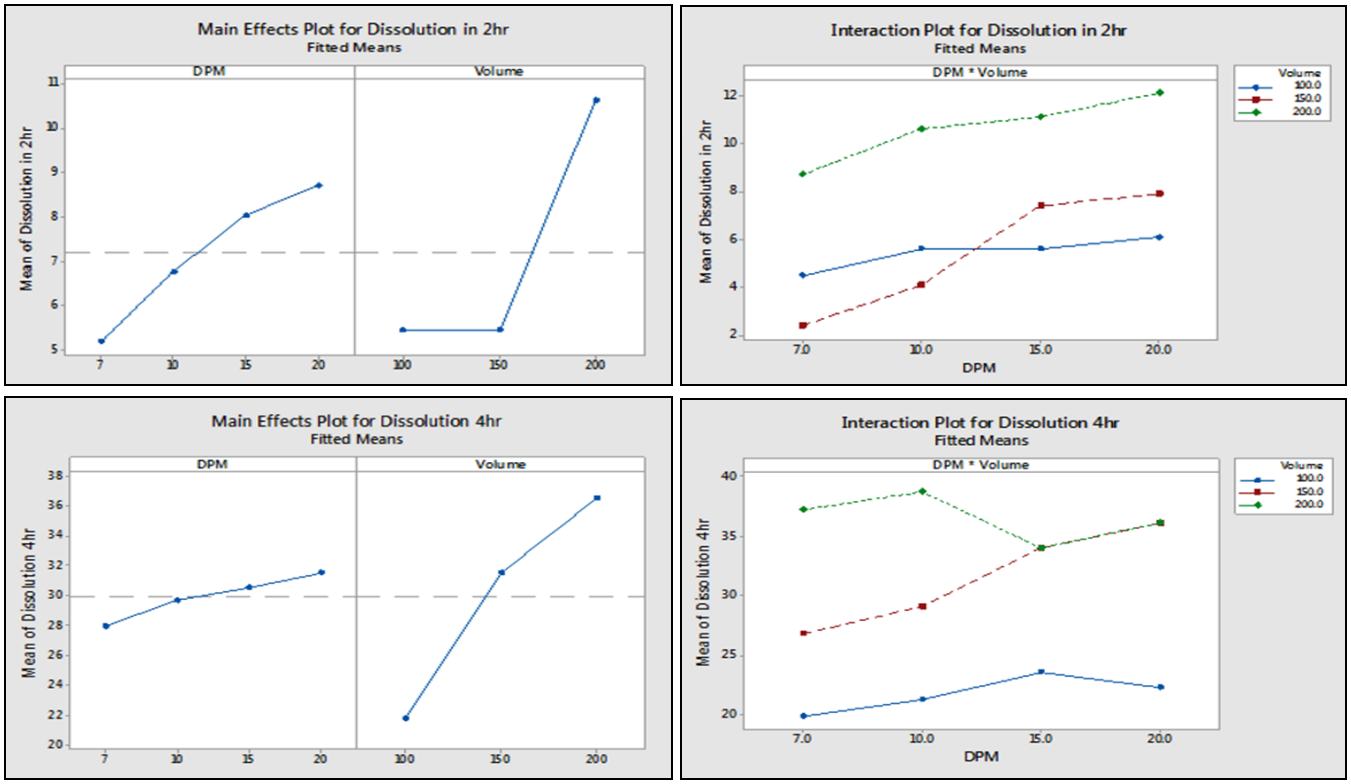
Note: mean ± SD, n=3

TABLE 7: ANOVA RESULTS FOR DESIGN OF EXPERIMENT

Source		Dissolution at 2 h		Dissolution at 4 h		Dissolution at 8 h		Dissolution at 12 h	
	DF	Adj SS	Adj MS	Adj SS	Adj MS	Adj SS	Adj MS	Adj SS	Adj MS
Model	11	99.82	9.08	522.88	47.54	545.63	49.60	764.97	69.54
Linear	5	92.80	18.56	468.74	93.75	532.45	106.49	729.35	145.87
DPM	3	21.39	7.13	20.21	6.74	58.54	19.51	144.70	48.23
Volume	2	71.42	35.71	448.53	224.27	473.91	236.96	584.65	292.33
2-Way Interactions	6	7.02	1.17	54.14	9.02	13.18	2.20	35.62	5.94
DPM*Volume	6	7.02	1.17	54.14	9.02	13.18	2.20	35.62	5.94
Total	11	99.82		522.88		545.63		764.97	
Model summary (R^2)		100%		100%		100%		100%	

Each dissolution study was performed using 3 units of Namenda XR, with a combination of different factors. The standard deviation below 2% confirms no significant variation within units. Dissolution data were further evaluated for statistical inter-pretation using Minitab software for the main effect, interaction effect of DPM, and media volume on dissolution. The degrees of freedom observed was 11, which was less than 12 of executed runs. Hence, the error value is 0, and the model is significant. An increase in DPM and media volume shows an increase in drug release, and the interaction effect cumulatively increases the drug release. The main effect and interaction effect of DPM and media volume was presented in **Fig. 2**. Multiple response prediction was interpreted with the target value. The best fit method was optimized based on dissolution response with 95% confidence interval. The dissolution method with highest desirability was optimized as a suitable

method, with three levels presented in **Fig. 3**. ANOVA results of the DOE study and model summary were presented in **Table 7**. The response optimization for the dissolution graph indicates the desired parameter is 15DPM, and 150 ml media volume, with the composite desirability of 0.9090.



MAIN EFFECT AND INTERACTION EFFECT OF DPM, VOLUME ON DISSOLUTION PROFILE OF NAMENDA XR UNDER FASTING CONDITION

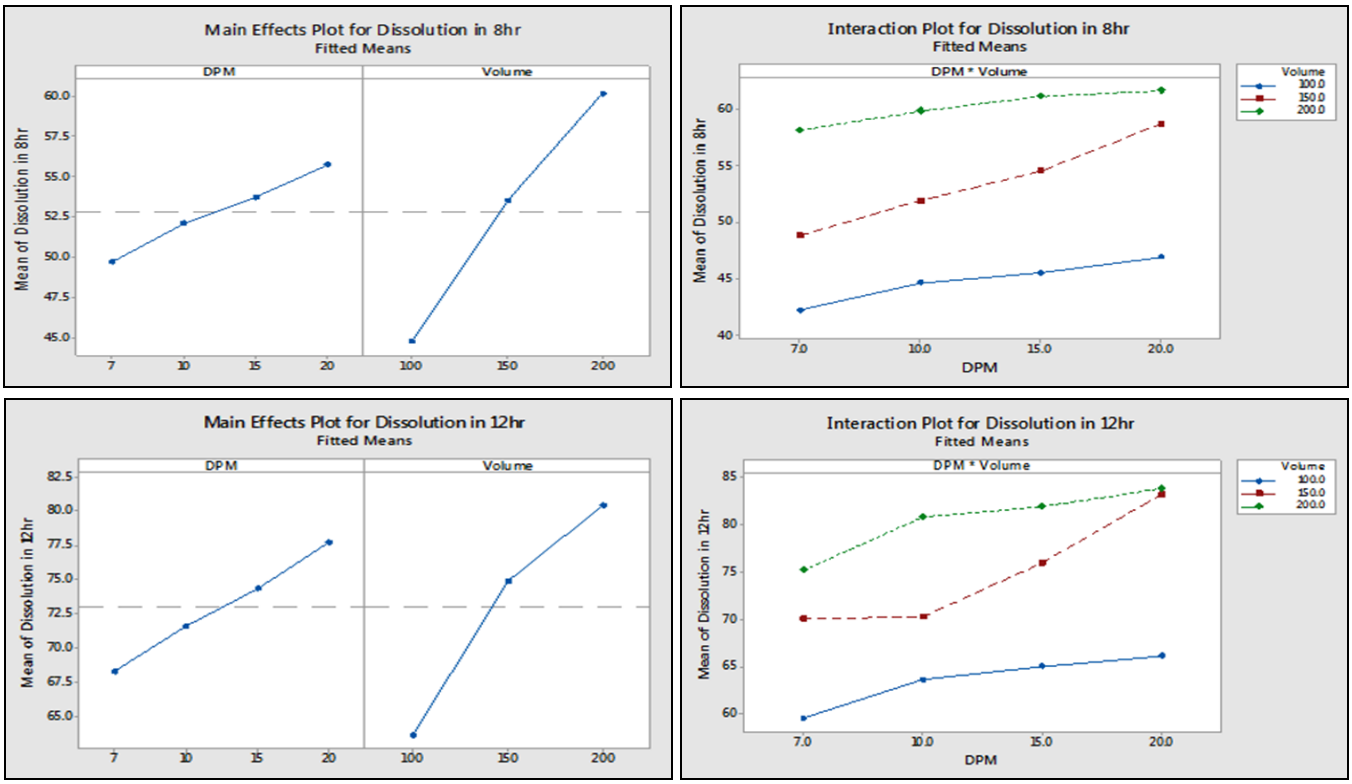


FIG. 2: MAIN EFFECT AND INTERACTION EFFECT ON DISSOLUTION PROFILE UNDER PRE-PRANDIAL CONDITION BY DPM AND MEDIA VOLUME

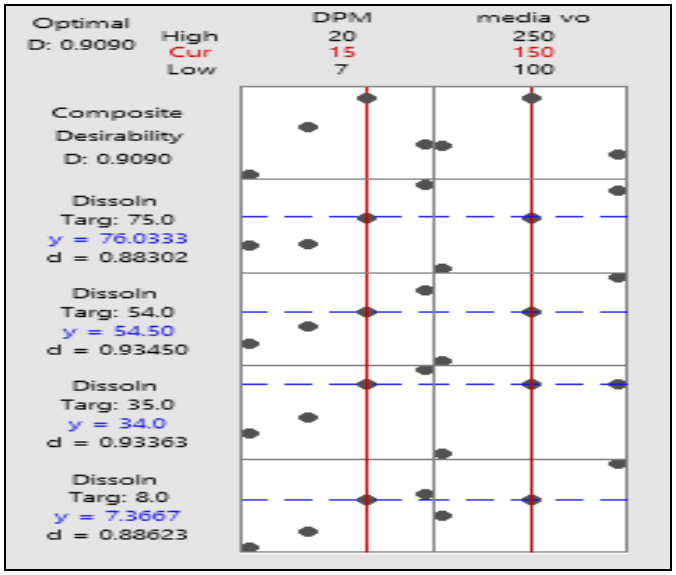


FIG. 3: RESPONSE OPTIMISATION FOR DISSOLUTION OF NAMENDA XR 28 MG IN FASTING CONDITION AT 2H, 4H, 8 H, AND 12 H

TABLE 8: TARGET AND RANGES RECOMMENDED FOR THE FASTING STATE AND FED STATE SIMULATING BIORELEVANT DISSOLUTION STUDY

Response	Cumulative % drug release target and tolerance		
	Lower	Target	Upper
Dissoln 12 h	59.6	75	83.8
Dissoln 8 h	42.2	54	61.6
Dissoln 4 h	19.9	35	38.7
Dissoln 2 h	2.4	8	12.1

Based on the dissolution results the target dissolution profile for biorelevant dissolution method has been finalised, lower and upper limits were derived using Minitab, with 95% confidence interval, and the values were presented in **Table 8**.

Establishment of the IVIVR: A comparative dissolution profile using USP Apparatus 3 and target profile established for biorelevant dissolution method under pre-prandial condition was presented in **Table 9**, **Fig. 4** and **5**.

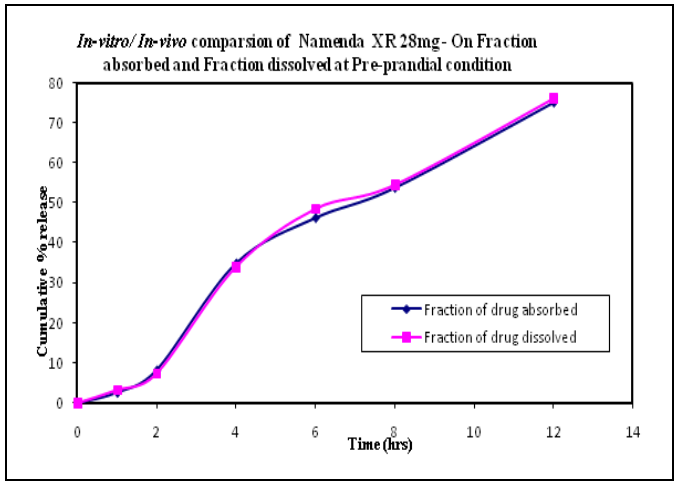


FIG. 4: *IN-VITRO* / *IN-VIVO* COMPARISON OF NAMENDA XR 28 mg - ON FRACTION OF DRUG ABSORBED BY *IN-VIVO* AND FRACTION OF DRUG DISSOLVED BY *IN-VITRO*

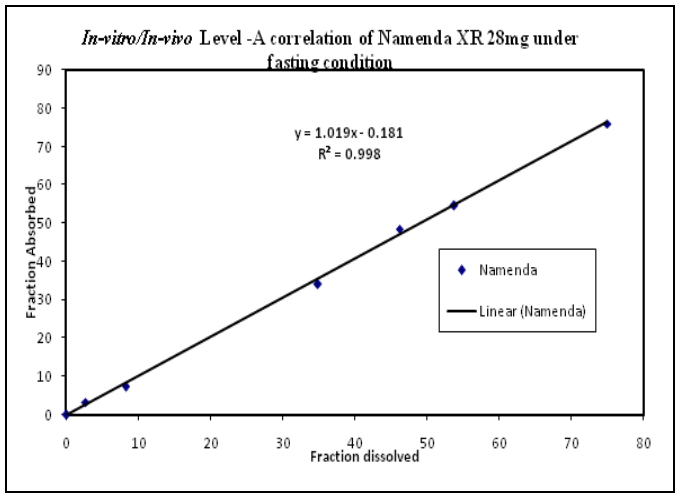


FIG. 5: *IN VITRO-IN VIVO* LEVEL -A CORRELATION OF NAMENDA XR 28 mg EXTENDED RELEASE CAPSULES UNDER FASTING CONDITION

Percentage of drug absorbed obtained from deconvoluted *in-vivo* data was compared with percentage of drug dissolved under simulated fasting condition and the F2 value was 90.

TABLE 9*: IN-VITRO* AND *IN-VIVO* DISSOLUTION OF NAMENDA XR 28 mg AT PRE-PRANDIAL (FASTING) CONDITION

Dissolution (time)	Cumulative dissolution time	Cumulative % drug Release	Target profile
FaSSGF pH 1.6 for 60 min	1 h	3.3 ± 0.2	3
FaSSGF pH 1.6 for 120 min	2 h	7.4 ± 0.2	8
pH 6.5 FaSSIF for 60 min followed by pH 7.0 FaSSIF for 60 min	4 h	34.0 ± 0.7	35
pH 7.5 FaSSIF for 120 min	6 h	48.5 ± 0.2	46
pH 5.8 SCoF for 120 min	8 h	54.5 ± 0.3	54
pH 5.8 SCoF for 240 min	12 h	76.0 ± 0.7	75
F_2		90	
Note: mean ± SD, n=3			

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

The conventional approach is to recommend the dissolution profile closest to the target profile. Whereas, QBD approach recommends the desirable dissolution profile by considering multiple factors, main effect, and interaction effect.
The developed biorelevant dissolution method shall be used when there is a change in batch size, process change, API change, excipient change, or equipment change.

CONCLUSION: The finished product is not having any impact by agitation speed, which reveals the functional coating is robust. However, the F2 value with the target dissolution profile deconvoluted from *in-vivo* was observed below 50. The dissolution responses interpreted statistically for the main effect, interaction effect, and composite desirability indicates the developed biorelevant dissolution method for prediction of *in-vivo* performance was USP Apparatus 3, 15 DPM, and 150 ml of Fasting simulated state change over dissolution media, with the composite desirability of 0.9090.

Based on the established IVIVC with R^2 value of 0.998, the method shall also be used as a waiver for the remaining strengths of memantine extended-release capsules, by which human volunteers consumption for biostudy shall be reduced. The upper and lower limits were fixed based on 95% CI of the target dissolution profile.

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CONFLICTS OF INTEREST: We declare no conflict of interest.

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