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Prediction of In-vivo Performance of Naproxen and Esomeprazole Magnesium Delayed-Release Tablets using Biorelevant Dissolution Tests

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Abstract

Main objective of this research work was to develop a biorelevant dissolution method by correlating the *in-vivo* behavior of Naproxen and Esomeprazole magnesium delayed release tablets 500/20mg, when administered orally under pre-prandial condition. The target dissolution profile for bio-relevant dissolution media was derived, by deconvoluting mean blood plasma concentration time profile of Naproxen and Esomeprazole, achieved after oral administration under pre-prandial condition. The dissolution media volume and RPM were optimized using full factorial design of experiment. The dissolution profile observed with office of generic drugs recommended dissolution media was faster in release for Naproxen part and slower in release for Esomeprazole part in comparison to target release of bio-relevant dissolution method, with the F_2 value of 31 for Naproxen and 29 for Esomeprazole. USP Apparatus-I with fasted state simulated gastro intestinal change over dissolution media were used for method development. Based on ANOVA results, for Naproxen part, 250ml of fasting change over dissolution medium, and 50RPM, with the desirability factor of 0.508 was concluded as bio relevant dissolution medium. For esomeprazole part, the 900ml of fasting change over dissolution medium, and 100RPM, with the desirability factor of 0.479 was concluded as bio-relevant dissolution medium. The F_2 value observed between in-vitro and in-vivo dissolution profile is 64 and 63, the regression co-efficient (R^2) value of 0.987 and 0.997 for Naproxen and Esomeprazole respectively demonstrates a very good *in-vitro/in-vivo* correlation under pre-prandial condition. The developed method shall be used as a predictive in-vitro tool for evaluation Naproxen from Naproxen and Esomeprazole magnesium delayed release tablets, and also gives the advantage for claiming bio-waiver for remaining strengths.

Keywords: Bio-Relevant, Delayed Release, Esomeprazole, magnesium, Naproxen, Pre-prandial

1. Introduction

Naproxen and Esomeprazole magnesium delayed release tablets are used for treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in adults. Naproxen and Esomeprazole magnesium is combination of proton pump inhibitor and a non steroidal anti-inflammatory drug as delayed-release tablet combining an enteric coated Naproxen core and an immediate-release Esomeprazole magnesium layer surrounding the core. Twice a day delayed release tablets are having the oral bioavailability of 95% and 75% with the elimination half-life of approximately 15 hrs and 1.2 hrs for Naproxen and Esomeprazole respectively[1].

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Delayed-Release (DR) formulations are developed to avoid the degradation of drug in stomach or to avoid the irritation in gastric mucosa. The design of delayed release will alter the pharmacokinetic properties of drug. Additional clinical studies were performed to understand the rate of release vs. pharmacokinetics of drug. Hence, biorelevant dissolution method plays a critical role in determining drug product performance[2-4].

Many research works were carried out on estimation of Naproxen and Esomeprazole from blood plasma and chemical characterization, using RP-HPLC. Analytical method for bio-relevant dissolution method was not studied by any researcher[5-7].

Deconvolution is the process, to convert the mean plasma concentration drug profile achieved after oral administration of drug product into cumulative percentage drug release for a certain period of time. Plasma concentration will increase based on rate of absorption up to reaching the C_{max}, and decline in concentration will be observed due to biological half-life and elimination rate of drug. Where as in dissolution cumulative percentage of drug release would be on increasing trend upto 100%. Wagner-Nelson deconvolution procedure is adopted 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[8].

The quality control dissolution procedure is used to characterise the product for completeness of drug solubility in specified medium for a specified period of time from batch to batch, evaluated with regular conventional buffer with or without surfactant, using compendial dissolution apparatus, and the dissolution method is specific to the product[9]. 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 is specific to the human gastrointestinal condition and transit time. The agitation speed and media volume are required to be optimised for the product[10-12].

Several physiologically based dissolution media were developed for simulating gastro intestinal condition, and are used in the present study. Analytical method was developed by using quality by design approach, and the experiments were carried out with full factorial design method[13].

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)[14,15].

The research work is aimed to develop a biorelevant dissolution method by simulating gastro intestinal pH condition of pre-prandial state.

2. Materials and Methods

2.1 Materials

Vivomo(R) manufactured by Horizon pharma was procured from pharmacy. Working standards for Naproxen & Esomeprazole magnesium was obtained as gift sample from Dr. Reddy's Laboratories. Trihydroxy methyl amino methane (TRIS), Acetonitrile, Monobasic potassium phosphate, Glacial acetic acid, N-Butyl amine, Acetonitrile, Sodium perchlorate, perchloric acid, Methanol of suitable HPLC and AR grade were purchased from E. Merck Co., Mumbai. Pepsin 3000NF (Meteoric Bio Pharmaceuticals Pvt. Ltd.), Lecithin (Soya lecithin India), Glyceryl monooleate (Danisco Specialities), Maleic acid (Sigma–Aldrich), Sodium oleate (Riedel-de Haen), Sodium taurocholate (Prodotti Chimici), Tetrahydro furan (Merck), Pancreatin powder (Scientific Protein Laboratories LLC) were procured from indigenous vendors and used for evaluation.

2.2 Instrumentation

RP-HPLC system (Agilent 1200 with binary pump and UV detector), Electrolab dissolution test apparatus with paddle system (USP-II), with Japanese sinker and Dissolution apparatus USP-I (Electrolab) with reduced size vessel of 250 ml. The analysis was carried out using Agilent 1200 RP-HPLC system consisting of a pump, an injector, UV detector, with an auto sampler and column heater. Data were collected and processed using Empower software. Other instruments used for analysis were Analytical Balance, Ultrasonic Bath, Centrifuge, pH meter, Oven and Mechanical shaker. Rotavap (type R-114, Buechi, Essen, Germany), Polyvinyl difluoride filters (0.45 micron) used for sample filtration were purchased from Rankem, India.

2.3 Methods

2.3.1 Quality Control Dissolution Testing

Quality control dissolution testing is the procedure generally adopted for release of every batch manufactured at commercial scale using regular buffer, which was performed as per the Office of Generic Drugs (OGD) recommended procedure. Being Esomeprazole highly degradable to acidic environment, the dissolution was performed directly on pH 7.4 phosphate buffer, the samples were analyzed using RP-HPLC method. The standard procedures were followed for characterization as per USP. The effect of speed on dissolution was evaluated for Naproxen at 35, 50 and 75 RPM, and for Esomeprazole, at 50, 75 and 100 RPM.

2.3.2 Biorelevant Testing

A biorelevant dissolution media used, to simulate the pre-prandial condition, using USP apparatus-I, to simulate release of Naproxen and Esomeprazole magnesium delayed release tablet (Vivomo) in the GI tract. The product is recommended to administer 30 minutes before food. Hence, only fasting state simulated dissolution media was evaluated for biorelevant method development. The dissolution experimental design was executed with Design Of Experiment (DOE), using mini tab software, a full factorial design, with 2 factors of RPM at 4 levels and Media volume at 3 levels, the response was evaluated at four time points for dissolution of Naproxen, and two points for dissolution of Esomeprazole. The factor levels and response to be measured were presented in (Table 1).

The following biorelevant dissolution media were used for dissolution testing: Fasted State Simulated Gastric Fluid (FaSSGF), Fasted state simulated intestinal fluid (FaSSIF) pH 6.5, pH 7.0 and pH 7.5. The compositions and preparation of these biorelevant dissolution media have been described in various literature.

3. Results and Discussions

3.1 Deconvolution of Pre-Prandial *in-vivo* Data

The mean blood plasma drug concentration (Cp) of Naproxen and Esomeprazole time profiles after oral administration of VIVOMO 500/20mg at pre-prandial condition were 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 2).

The deconvoluted data indicates that under pre-prandial condition 85% of Naproxen is absorbed in 4 hrs and 98% of Esomeprazole is absorbed at 30 minutes, which directs the simulated dissolution to be performed for 4 hrs for Naproxen and 30 minutes for Esomeprazole, using appropriate dissolution sink conditions.

In-vitro dissolution of Vivomo tablets 500/20mg in OGD recommended dissolution media, and the study on effect of RPM:

A comparative dissolution profile of Vivomo tablets in OGD recommended dissolution media and target dissolution profile, along with the effect of RPM on dissolution profile are presented in (Table 3&4) and (Figure 1&2) and compared for similarity factor with target dissolution profile for Naproxen and Esomeprazole were presented respectively.

The dissolution profile observed from Vivomo tablets 500/20mg, using office of generic drugs recommended dissolution media was not comparable to the target dissolution profile required for developing bio-relevant

Table 1. Factor information

	Naproxen part			Esomeprazole part		
Factors	**Levels**	**Values**	**Responses**	**Esomeprazole part**		
				Levels	**Values**	**Responses**
RPM	4	35,50,75 & 100	Dissolution at 1hrs, 2hrs, 2hrs & 4hrs	4	35,50,75 &100	Dissolution at 30mins & 1hr
Volume	3	250, 500 & 900ml		2	100ml & 250ml	

Table 2. Target dissolution profile deconvoluted from pre-prandial *In-vivo* data

Time (hrs)	Naproxen			Esomeprazole		
	Mean drug plasma concentration in human pre-prandial) Cp (ng/mL)	Fraction absorbed (Numerical Deconvolution by Wagner-Nelson method)	% Absorbed (Target profile)	Mean drug plasma concentration in human (Pre-prandial) Cp (ng/mL)	Fraction absorbed (Numerical Deconvolution by Wagner-Nelson method)	% Absorbed (Target profile)
0	0.00	0.00	0.00	0.00	0.00	0
0.5	3.27	0.05	5	315.25	0.98	98
1	10.55	0.17	17	180.97	0.93	93
1.5	20.96	0.33	33	109.69	0.92	92
2	34.93	0.56	56	72.52	0.93	93
2.5	40.13	0.66	66	49.82	0.94	94
3	43.40	0.72	72	33.33	0.95	95
3.5	47.26	0.80	80	25.12	0.96	96
4	49.49	0.85	85	16.88	0.97	97
6	50.53	0.94	94	4.66	0.90	90
8	42.65	0.89	89	1.74	0.99	99
10	39.38	0.89	89	1.24	1.00	100
12	35.22	0.88	88	0.25	1.00	100

Table 3. Dissolution profile of Naproxen part from Vivomo Tablets 500/20mg in 0.1N HCl for 2 hrs followed pH 6.8 Phosphate buffer for 2 hrs. USP-II, 1000ml

B. No.	Vivomo 079358			Target profile at fasting for Naproxen
Time (hrs)	35 RPM	50 RPM	75 RPM	
0	0.0	0.0	0.0	0
1	0.4 ± 0.2	1.4 ± 0.2	1.6 ± 0.2	17
2	3.9 ± 0.5	5.8 ± 0.6	5.2 ± 0.4	56
2.5	38.1 ± 2.5	57.2 ± 0.4	56.4 ± 1.7	66
3	75.0 ± 0.6	76.6 ± 0.7	79.8 ± 1.4	72
3.5	98.8 ± 0.6	100.2 ± 0.4	100.6 ± 0.5	80
4	100.0 ± 0.2	100.5 ± 0.3	100.6 ± 0.5	85
Note: mean ± SD, n=3				

Table 4. Dissolution profile of Esomeprazole part from Vivomo tablets 500/20mg in pH 7.4 Phosphate buffer for 2 hrs USP-II, 900 ml

B. No.	Vivomo 079358			Target profile at fasting for Esome prazole
Time (hrs)	50 RPM	75 RPM	100RPM	
0	0.0	0	0.0	0
0.5	34.6 ± 1.5	46.0 ± 0.4	50.7 ± 0.8	98
1	86.5 ± 1.7	93.4 ± 1.7	93.5 ± 0.8	93
1.5	99.1 ± 0.8	99.9 ± 0.9	100.2 ± 0.3	92
2	100.3 ± 0.2	99.6 ± 0.2	100.4 ± 0.2	93
Note: mean ± SD, n=3				

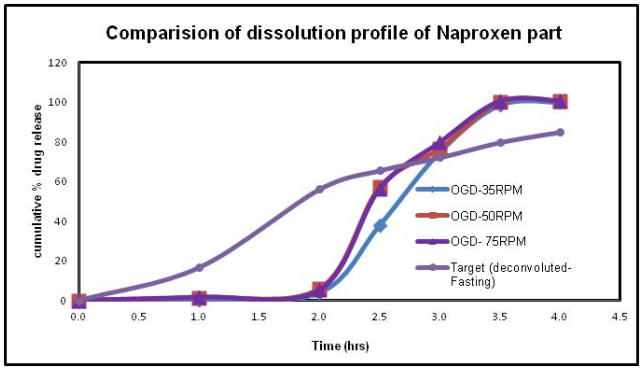


Figure 1. Comparison of dissolution profile of Naproxen from Vivomo in OGD recommended dissolution media at different RPM with target dissolution profile (deconvoluted from *In-vivo*).

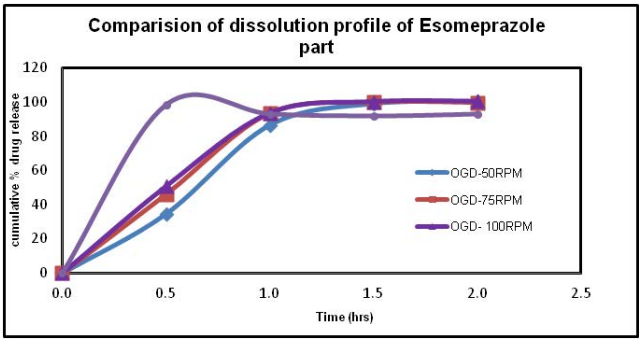


Figure 2. Comparison of dissolution profile of Esomeprazole from VIVOMO in OGD recommended dissolution media at different RPM with target dissolution profile (deconvoluted from *In-vivo*).

dissolution method. The change is RPM of dissolution was not having any significant impact on dissolution profile the similarity factor (F_2) values observed also below 50%. Hence, it was decided to develop a bio-predictive dissolution method to simulate the *in-vivo* performance of drug product.

3.2 Development of Bio-Relevant Dissolution Method

The dissolution method was developed using a quality by design approach. The variables in dissolution method are dissolution apparatus, dissolution media, dissolution media volume and agitation speed. For each factor, risk assessment was preformed and, based on the risk assessment, dissolution media volume and agitation speed is required to be optimized. The risk assessment was presented in (Table 5), and Risk Priority Number (RPN) was derived based on risk assessment.

Risk assessment measured in 3 categories, low (1), medium (2) & high (3). The Risk number is the multiplication of all the three. The risk numbers more than 9 will be considered for DOE study. A complete full factorial design was established using minitab software, for two variables of media volume and agitation speed (RPM), and the parameters are optimized with the response factor of dissolution, at various time intervals.

The response was considered as cumulative percentage drug release at 1hr, 2hrs, 3hrs and 4hrs time interval for Naproxen part, 30 minutes and 1hr time interval for Esomeprazole part of naproxen and esomeprazole magnesium delayed release tablets 500/20mg. A full factorial study with variables for bio-relevant dissolution method was presented in (Table 6) for Naproxen part and (Table 7) for Esomeprazole part along with the dissolution as response.

Main effects and interaction effect of RPM and dissolution media volume on dissolution profile of naproxen part from delayed release tablets of Naproxen

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

Factors	Severity	Probability	Delectability	Risk Number	Justification
Dissolution apparatus	2	1	2	4	The most suitable apparatus for delayed release tablet is USP apparatus -1(basket) or apparatus -2 (paddle) with sinker. Apparatus-1 is selected for dissolution method, hence risk is low.
Dissolution media	1	2	2	4	The dissolution media selected is based on human gastro intestinal condition and transit time. Hence, the risk is very low.
Media volume	3	3	3	27	Dissolution media volume is directly related to intrinsic solubility of drug, hence the risk is high.
RPM	3	3	2	12	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 for Naproxen part at pre-prandial (Fasting) state simulating dissolution method

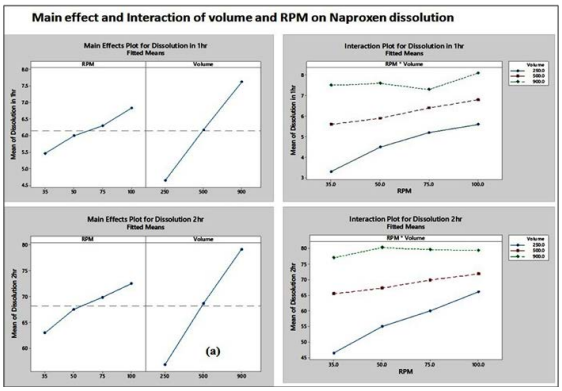
Run order	Factors		Responses			
	RPM	Volume	Dissolution 1 hr	Dissolu-tion 2 hrs	Dissolution 3 hrs	Dissolution 4 hrs
1	35	900	7.5± 0.9	77 .0± 1.4	99.3 ± 0.3	100.4 ± 0.2
2	50	900	7.6 ± 0.5	80.3 ± 0.2	100.4 ± 0.2	100.2 ± 0.2
3	75	900	7.3 ± 0.2	79.6 ± 0.2	99.9 ± 0.4	99.8 ± 0.4
4	100	900	8.1 ± 0.5	79.4 ± 1.2	100.0 ± 0.4	99.9 ± 0.5
5	35	500	5.6 ± 0.5	65.5 ± 0.9	88.7 ± 0.2	100.2 ± 0.4
6	50	500	5.9 ± 0.5	67.3 ± 0.9	90.4 ± 0.7	99.9 ± 0.3
7	75	500	6.4 ± 0.2	69.9 ± 0.2	90.6 ± 0.5	99.8 ± 0.1
8	100	500	6.8 ± 0.3	71.9 ± 0.7	92.2 ± 0.6	99.3 ± 0.7
9	35	250	3.3 ± 0.4	46.5 ± 0.7	66.9 ± 1.2	82.6 ± 0.7
10	50	250	4.5 ± 0.3	55.0 ± 0.7	73.4 ± 0.8	86.6 ± 0.7
11	75	250	5.2 ± 0.4	60.0 ± 1.2	79.4 ± 0.9	90.6 ± 0.5
12	100	250	5.6 ± 0.5	66.1 ± 0.4	85.6 ± 0.9	97.8 ± 1.1

Note: mean ± SD, n=3

and Esomeprazole magnesium were presented in (Figure 3). ANOVA results and model summary were presented in (Table 8) for Naproxen part, which concludes the model is significant.

The multiple response graph presented in (Figure 4), indicates the predicted bio-relevant dissolution method for Naproxen part from the delayed release dosage form is 50 RPM and 250 ml of change over dissolution media, with the composite desirability of 0.508. For all DOE data analysis, the commonly used alpha of 0.05 was chosen to differentiate between significant and not significant factors.

Main effects and interaction effect of RPM and dissolution media volume on dissolution profile of Esomeprazole part from delayed release tablets of Naproxen and Esomeprazole magnesium were presented in (Figure 5). ANOVA results and model summary were presented in (Table 9) for Esomeprazole part, which concludes the model is significant.



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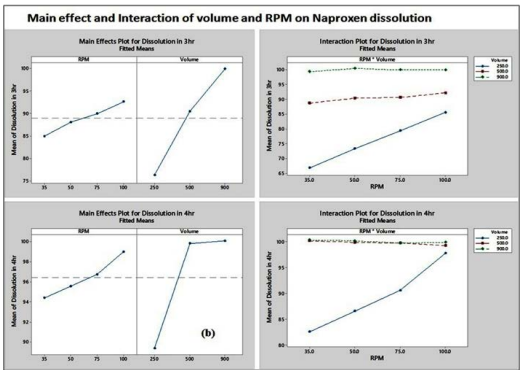

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Figure 3. Main effect and interaction effect on RPM and media volume on dissolution profile of Naproxen part under pre-prandial condition: (a) at 1 hr & 2 hrs, and (b) 3 hrs & 4 hrs..

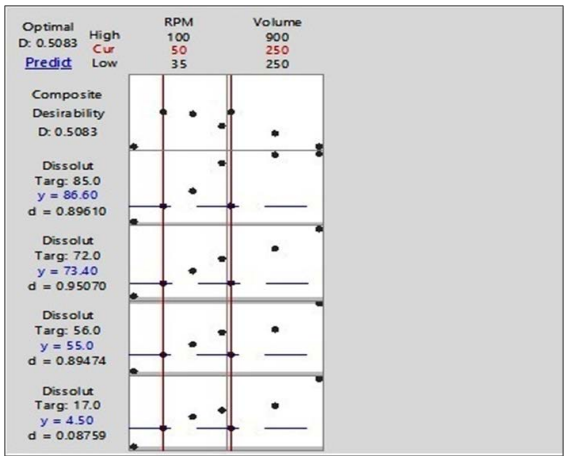

Figure 4. Response optimization for dissolution of Naproxen from Vivomo in fasting condition at 1 hr, 2 hrs, 3 hrs and 4 hrs..

The multiple response graph presented in (Figure 6), indicates the predicted bio-relevant dissolution method for Esomeprazole part from the delayed release dosage form is 100 RPM and 900 ml of pH 7.4 phosphate buffer, with the composite desirability of 0.479. Main effects and interaction effect of RPM and dissolution media volume on dissolution profile of Esomeprazole part from delayed release tablets of naproxen and esomeprazole magnesium were presented in (Figure 6). 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), for both Esomeprazole part and Naproxen part of delayed release formulation of Naproxen and Esomeprazole delayed release tablets.

3.3 Establishment of the IVIVR

A comparative dissolution profile using USP apparatus -I, with 250 ml of dissolution medium, and 50 RPM established for biorelevant dissolution method and target profile at pre-prandial condition for Naproxen part is presented in (Table 11) and (Figure 7&8).

Percentage of drug absorbed obtained from deconvoluted *in-vivo* data was compared with percentage of drug dissolved under simulated fasting condition, and the F_2 value is 64.

The fraction of drug released in-vitro is consistently comparable to the fraction of drug released in-vivo indicating discriminating dissolution conditions. The regression co-efficient (R^2) value of 0.987 also indicates very good predictive capability of the relationship.

Table 7. A Full factorial study and Response of the factors for Esomeprazole part at pre-prandial (Fasting) state simulating dissolution method

Run order	Factors		Response	
	RPM	Volume	Dissolution 30 minutes	Dissolution 1 hr
1	35	900	91.7 ± 1.4	100.3 ± 0.2
2	50	900	96.5 ± 1.5	100.2 ± 0.4
3	75	900	99.5 ± 0.4	100.2 ± 0.3
4	100	900	100.1 ± 0.5	100.9 ± 0.3
5	35	500	83.9 ± 1.6	100.5 ± 0.3
6	50	500	85.2 ± 0.5	100.6 ± 0.2
7	75	500	90.5 ± 0.3	100.3 ± 0.5
8	100	500	95.2 ± 0.8	99.8 ± 0.4
9	35	250	75.8 ± 0.5	95.2 ± 0.4
10	50	250	78.3 ± 0.4	98.8 ± 0.4
11	75	250	80.9 ± 0.7	100.1± 0.5
12	100	250	86.5 ± 3.5	100.1 ± 0.5

Note: mean ± SD, n=3

Table 8. ANOVA results for design of experiment for Naproxen part

Source	Degrees of freedom	Dissolution at 1 hr		Dissolution at 2 hrs		Dissolution at 3 hrs		Dissolution at 4 hrs	
		Adjusted sum square	Adjusted mean square	Adjusted sum square	Adjusted mean square	Adjusted sum square	Adjusted mean square	Adjusted sum square	Adjusted mean square
Model	11	21.95	2.00	1220.71	110.97	1326.08	120.55	422.98	38.45
Linear	5	20.64	4.13	1129.70	225.94	1219.43	243.89	330.94	66.19
DPM	3	2.94	0.98	145.07	48.36	92.98	30.99	34.69	11.56
Vol.	2	17.71	8.85	984.63	492.32	1126.45	563.22	296.26	148.13
2-Way Interaction	6	1.31	0.22	91.01	15.17	106.66	17.78	92.04	15.34
RPM*Volume	6	1.31	0.22	91.01	15.17	106.66	17.78	92.04	15.34

Table 9. ANOVA results for design of experiment for Esomeprazole part

Source	Degrees of freedom	Dissolution at 30 minutes		Dissolution at 1 hr	
		Adjusted sum square	Adjusted mean square	Adjusted sum square	Adjusted mean square
Model	11	737.46	67.04	25.47	2.32
Linear	5	723.73	144.75	13.63	2.73
DPM	2	549.46	274.73	8.66	4.33
Vol.	3	174.27	58.09	4.97	1.66
2-Way Interactions	6	13.73	2.29	11.84	1.97
DPM* Volume	6	13.73	2.29	11.84	1.97

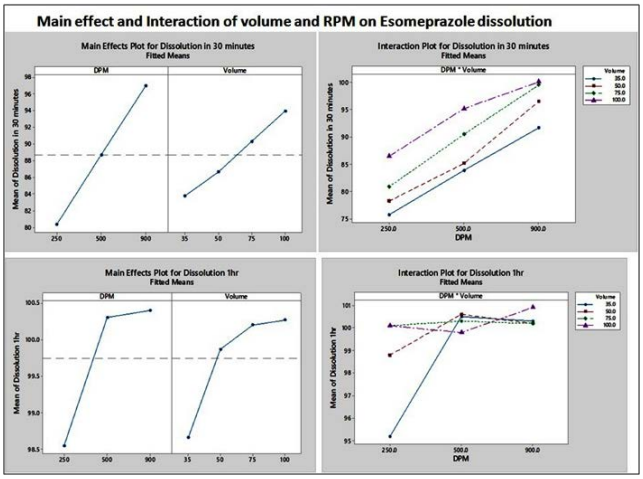

Figure 5. Main effect and interaction effect on RPM and media volume on dissolution profile of Esomeprazole part under pre-prandial condition.

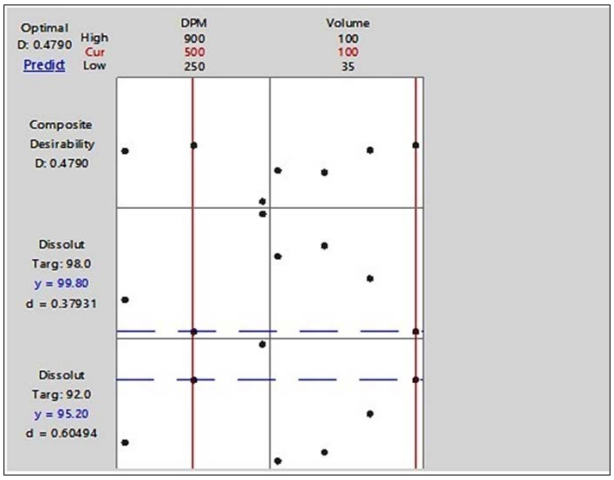

Figure 6. Response optimisation for dissolution of Esomeprazole from Vivomo in fasting condition at 30 minutes and 1 hour.

Table 10. Target and ranges recommended for Naproxen and Esomeprazole simulating biorelevant dissolution study

Response	Goal	Naproxen part			Esomeprazole part		
		Lower	Target	Upper	Lower	Target	Upper
Dissolution 4 hours	Target	82.6	85	100.4	-	-	-
Dissolution 3 hours	Target	66.9	72	100.4	-	-	-
Dissolution 2 hours	Target	46.5	56	80.3	-	-	-
Dissolution 1 hour	Target	3.3	17	18.7	82.8	92	100.9
Dissolution 30 minutes	Target	-	-	-	75.8	98	100.1

Table 11. *In-Vitro* and *In-Vivo* dissolution of Naproxen part of VIVOMO at pre-prandial (Fasting) condition

Dissolution (time)	Cumulative dissolution time	Cumulative % drug Release	Target profile
FaSSGF pH 1.6 for 60 minutes	1 hour	4.5 ± 0.3	17
pH 6.5 FASSIF for 60 minutes	2 hours	55.0 ± 0.7	56
pH 7.0 Half-FaSSIF for 60 minutes	3 hours	73.4 ± 0.8	72
pH 7.5 FaSSIF-sans for 60 minutes	4 hours	86.6 ± 0.7	85
F_2		**64**	

Note: mean ± SD, n=3

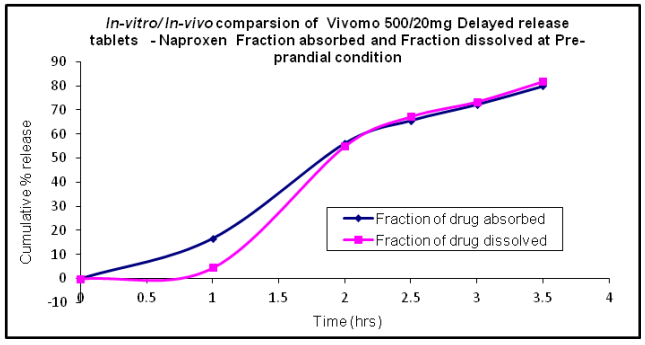

Figure 7. *In-vitro/In-vivo* comparison of Naproxen from Vivomo tablets 500/20mg- on fraction of drug absorbed by *in-vivo* and fraction of drug dissolved by *in-vitro*.

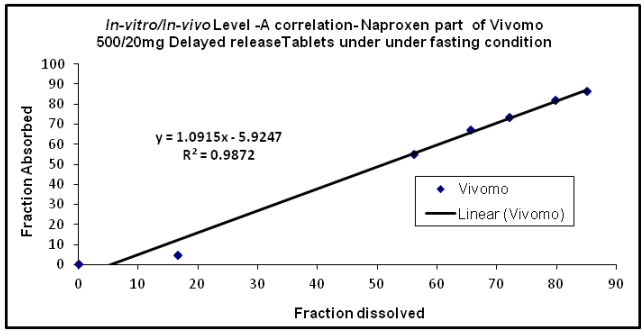

Figure 8. *In-vitro/In-vivo* level -A correlation- Naproxen part of Vivomo 500/20mg delayed release tablets under fasting condition.

Table 12. *In-Vitro* and *In-Vivo* dissolution of Esomeprazole part of VIVOMO at pre-prandial (fasting) condition

Dissolution (time)	Cumulative dissolution time	Cumulative % drug Release	Target profile
pH 6.5 FASSIF for 30 minutes	30 minutes	100.1 ± 0.5	98
pH 6.5 FASSIF for 60 minutes	60 minutes	100.9 ± 0.3	93
F_2		**63**	

Note: mean ± SD, n=3

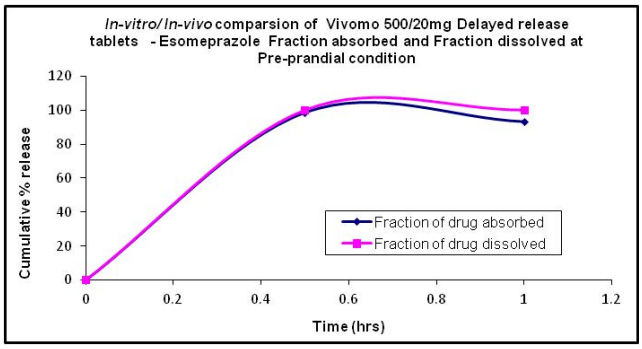

Figure 9. *In-Vitro/In-Vivo* comparison of Esomeprazole part from Vivomo tablets 500/20mg - on fraction of drug absorbed by *In-Vivo* and fraction of drug dissolved by *In-Vitro*.

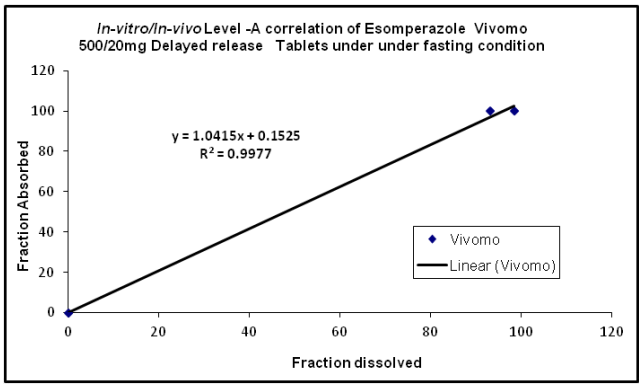

Figure 10. *In-vitro/In-vivo* level-A correlation-Esomeprazole part of Vivomo 500/20mg delayed release tablets under fasting condition.

A comparative dissolution profile using USP apparatus -I, with 900 ml of dissolution medium, and 100 RPM established for biorelevant dissolution method and target profile at pre-prandial condition for Esomeprazole part is presented in (Table 12) and (Figure 9&10).

Percentage of drug absorbed obtained from deconvoluted *in-vivo* data was compared with percentage of drug dissolved under simulated fasting condition, and the F_2 value is 63.

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 co-efficient (R^2) value of 0.997 also indicates very good predictive capability of the relationship.

4. Conclusion

Biorelevant dissolution method developed using USP apparatus-I, coupled with a deconvolution approach successfully correlating the *in-vivo* performance of Naproxen and Esomeprazole delayed release tablets after oral administration under the fasted state. Among the dissolution methods studied, 250 ml of change over media with 50 RPM, was closest to the target under fasted state for Naproxen part, and 900 ml pH 6.5 fasted state simulated change over media with 100 RPM, was closest to the target under fasted state for Esomeprazole part, based on the established IVIVC, where regression co-efficient was close to 1.0.

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