Asian Journal of Pharmaceutical Research and Health Care, *Vol 12(4), 177-188, 2020*

ISSN (Online) : 2250-1460
DOI: 10.18311/ajprhc/2020/25661

Biorelevant Dissolution Method Development for Dutasteride and Tamsulosin Hydrochloride Modified Release Capsule - A Prognostic Tool for Oral Drug Absorption

Devi Thamizhanban[1]*, Gampa Tulja Rani[2] and Kathiresan Krishnasamy[1]

[1]Department of Pharmacy, Annamalai University, Annamalai Nagar, Chidambaram – 608002, Tamil Nadu, India; devrajmphd@gmail.com, dr.kathiresan123@rediffmail.com

[2]Malla Reddy Pharmacy College, Maisammaguda, Hyderabad – 500014, Telengana, India; tuljapharma@yahoo.com

Abstract

The research work was aimed to develop a biorelevant dissolution method for fixed dose combination containing Dutasteride 0.5 mg in immediate-release form and Tamsulosin 0.4 mg in modified-release form. Mean plasma concentration achieved after oral administration to human under pre-prandial condition are deconvoluted using Wagner-Nelson deconvolution method, to achieve target dissolution profile. The dissolution profile observed using office of generic drugs recommended dissolution media was observed to be faster than the target dissolution profile. Tamsulosin being a modified-release multiparticulate system, biorelevant dissolution method was developed with Fasted state simulated change over dissolution media, using USP Apparatus 3 (reciprocating cylinder). Dutasteride being an immediate-release form, dissolution method was developed with single dissolution media, by extending the dissolution run time upto C_{max}. Dissolution media, media volume and Dips Per Minute (DPM) are optimized by performing full factorial design of experiment. The ANOVA result interprets the biorelevant dissolution media for Tamsulosin part is 250 ml of Fasted state simulated change over dissolution media with 15 DPM, based on desirability factor of 0.7768 and for Dutasteride part 250 ml of pH 6.5 Fasted state simulated intestinal fluids with 7 DPM, based on desirability factor of 0.8988. The regression co-efficient (R^2) value of 0.999 and 0.996 demonstrates a very good *in-vitro/in-vivo* correlation under pre-prandial condition for Tamsulosin and Dutasteride respectively. The developed method shall be used as a predictive *in-vitro* tool for evaluation of *in-vivo* performance under pre-prandial condition.

Keywords: Deconvolution, Dutasteride, Pre-prandial, Tamsulosin

1. Introduction

Dutasteride and Tamsulosin hydrochloride modified release capsule is a hard gelatin capsule consists of an immediate-release soft gelatin capsule containing Dutasteride 500 mcg and modified-release multiparticulate containing Tamsulosin HCl 400 mcg. The combination product is used for the treatment of moderate to severe symptomatic Benign Prostatic Hyperplasia (BPH) in men[1].

Dutasteride is poorly soluble; following oral administration the time to peak serum concentration of Dutasteride is 1 to 3 hrs. The absolute bioavailability is approximately 60%. Tamsulosin is absorbed more than

*Author for correspondence

90% after oral administration. C_{max} is observed at about 5 to 6 hrs, with the biological half-life ($t_{1/2}$) of 10 to13 hrs under fasting condition[2].

Plasma drug concentration is based on pharmacok inetic profile of drug product depends on absorption rate and elimination rate. Whereas, dissolution is based on cumulative percentage of drug released. 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, using one-compartment model[3]. For immediate-release products, which are having longer biological half life, the deconvolution is recommended to evaluate upto the C_{max} of drug product. Since, no drug release occurs after stipulated period of time[4].

Dissolution is a critical quality attribute for solid oral dosage form. Pharmacopoeial or quality control dissolution procedures are mainly used to characterise the extent of dissolution for immediate release formulation, rate and extent of drug release for modified release formulation. USP recommends standard dissolution apparatus and limits based on type of dosage form, if individual monograph is not available[5]. Generally, quality control test for dissolution is performed by using standard buffer, with or without surfactant based on solubility of drug dissolution procedure is different for individual product[6], whereas, bio-relevant dissolution media is based on human gastro intestinal condition and transit time. Dissolution volume and agitation speed are required to be modulated based on *in-vivo* performance product[7].

Various research works have been performed on formulation development and analytical method development[8-10]. No research work has been performed on bio-relevant dissolution method development of Tamsulosin and Dutasteride modified release formulation. USP Apparatus 3 is recommended for modified release dosage of multiparticulate drug delivery system[11] and having the scope to run with multiple dissolution media, by varying the speed. The biorelevant dissolution media for pre-prandial condition simulates the gastro-intestinal pH conditions of stomach, duodenum, jejunum, ileum, distal ileum and colon, with certain enzymes and residence time at each pH condition[12]. Method development was performed using quality by design approach with risk assessment and statistical interpretation of data using appropriate software for multiple factors, instead of evaluating one factor at a time[13].

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

2. Materials and Methods

2.1 Materials

Combodart was procured from pharmacy. Dutasteride and Tamsulosin hydrochloride was obtained as gift sample from Dr. Reddy's laboratories, Hyderabad. Acetonitrile, monobasic potassium phosphate, glacial acetic acid, n-butyl amine, sodium perchlorate, perchloric acid, methanol, standard inorganic salts and solvents were procured from merck. 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) were procured from indigenous vendors and used for evaluation. Polyvinyl difluoride filters (0.45 micron) were purchased from Rankem, India.

2.2 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).

2.3 Methods

2.3.1 Deconvolution of Plasma Profile

The mean plasma drug concentration data obtained after administration of Combodart on healthy volunteers were from single dose study at pre-prandial condition was deconvoluted using Wagner-Nelson deconvolution method, using one compartment model to determine the fraction of drug absorbed .

2.3.2 Quality Control Dissolution Testing

The quality control dissolution test was performed based on the recommendation from office of generic drugs. The

dissolution of Dutasteride and Tamsulosin hydrochloride modified release capsules is performed in 0.1 N HCl with 0.2% SLS (Sodium Lauryl Sulpahte) for 2 hrs, followed by pH 7.2 phosphate buffer for 8 hrs by using USP Apparatus 1 and media volume of 900 ml. Chromatographic separation was achieved with Agilent's high performance liquid chromatography with X bridge C18, 5 µm, 4.6 x 150 mm column, mobile phase-1 of 0.05 M phosphate buffer (pH 6.3) and mobile phase-2 of acetonitrile by gradient elution technique. The flow rate was maintained at 1.5 ml/min and the detection wavelength is 225 nm, with sample run time of 18 mins.

2.3.3 Biorelevant Testing

Biorelevant dissolution method is developed by quality by design approach. Tamsulosin being a modified-release pellet, fasted state simulated change over dissolution media was used with the aid of dissolution USP Apparatus 3. Dutasteride being an immediate-release part, dissolution method was developed without change over dissolution condition, by extending the run time, with the aid of dissolution USP Apparatus 3. Initial risk assessment is performed for the dissolution variables, based on the risk priority number, the factors and levels evaluated were presented in (Table 1).

A full factorial design of experiment was carried out using minitab software, with the response of dissolution at different time points. Outcome of the study was interpreted statistically. Bio-relevant dissolution method was finalized based on desirability factor with percentage of drug absorbed. Level-A *In-vitro/In-vivo* correlation was established.

3. Results and Discussions

3.1 Deconvolution of Pre-prandial *In-vivo* Data

The mean blood plasma drug concentration (Cp) of Tamsulosin and Dutasteride profiles after oral administration of Combodart 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 were presented in (Table 2)[14].

The deconvoluted data indicates that under pre-prandial condition 93% of Tamsulosin was absorbed in 8 hrs and 100% of Dutasteride was absorbed at 2.5 hrs, which directs the simulated dissolution to be performed for 8 hrs for Tamsulosin and 2.5 hrs for Dutasteride, using appropriate dissolution sink conditions.

Table 1. Factor information

Factors	Tamsulosin			Dutasteride		
	Levels	Values	Responses	Levels	Values	Responses
DPM	4	7,10,15,20	Dissolution at 2 hrs, 3 hrs, 4 hrs and 8 hrs	2	7,20	Dissolution at 1 hrs, 2 hrs and 2.5 hrs
Volume	2	100 ml and250 ml		2	100 ml and 250 ml	
Media volume	-	-		2	pH 1.6 FaSSGF and pH 6.5 FaSSIF	

Table 2. Fraction of drug absorbed from Combodart at pre-prandial condition

Time (hrs)	Tamsulosin (N = 28)			Dutasteride (N = 28)		
	Mean drug plasma concentration Cp (ng/mL)	Fraction Abs. (Numerical deconvolution)	%Absorbed (Target profile)	Mean drug plasma concentration Cp (ng/mL)	Fraction Abs. (Numerical deconvolution)	%Absorbed (Target profile)
0.0	0.00	0.00	0	0.00	0	0
0.5	-	-	-	0.31	0.12	12
1.0	0.40	0.02	2.5	1.25	0.49	49
1.5	-	-	-	1.54	0.62	62

2.0	3.88	0.24	24	1.85	0.78	78
2.5	-	-	-	2.32	1.00	100
3.0	6.20	0.41	41	1.83	0.98	98
4.0	9.23	0.64	64	1.65	0.99	99
4.5	-	-	-	1.58	0.98	98
5.0	12.12	0.89	89	1.32	0.99	99
5.5	-	-	-	1.15	0.99	99
6.0	10.44	0.89	89	1.09	1.01	101
8.0	8.48	0.93	93	0.94	1.03	103
9.0	7.37	0.93	93	0.81	0.99	99
10.0	5.92	0.90	90	0.77	0.99	99
12.0	4.25	0.89	89	0.65	0.99	99
18.0	2.45	0.95	95	0.32	0.99	99
24.0	0.75	0.93	93	0.18	1.01	101

3.2 Quality Control Dissolution Testing

A comparative dissolution profile of Combodart capsules in OGD recommended dissolution media and target dissolution profile were presented in (Table 3) and (Figures 1 and 2) is compared for similarity factor with target dissolution profile for Tamsulosin and Dutasteride were presented respectively.

The dissolution profile observed from Combodart, using office of generic drugs recommended dissolution media is not comparable to the target dissolution profile required. Hence, it was decided to develop a bio-predictive dissolution method to simulate the *in-vivo* performance of drug product.

3.3 Biorelevant 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. Based on the risk assessment,

Table 3. Dissolution profile of Combodart in quality control dissolution medium

Time (hrs)	Combodart (bath number: 10367998A)			
	Dutasteride		Tamsulosin	
	Cumulative % drug release	Target release (deconvoluted)	Cumulative % drug release	Target release (deconvoluted)
0	0	0	0	0
0.5	70.8 ± 0.6	12.0	5.9 ± 0.4	-
1	92.7 ± 0.5	48.7	11.7 ± 0.6	2.5
1.5	98.5 ± 0.4	62.5	13.1 ± 0.2	-
2	100.2 ± 0.1	77.9	15.9 ± 0.3	23.9
3	-	-	46.7 ± 0.5	41.1
4	-	-	75.5 ± 0.7	64.4
6	-	-	98.6 ± 0.3	89.0
8	-	-	99.6 ± 0.1	93.1
F_2	**19**		**43**	
Note: mean ± SD, n=3				

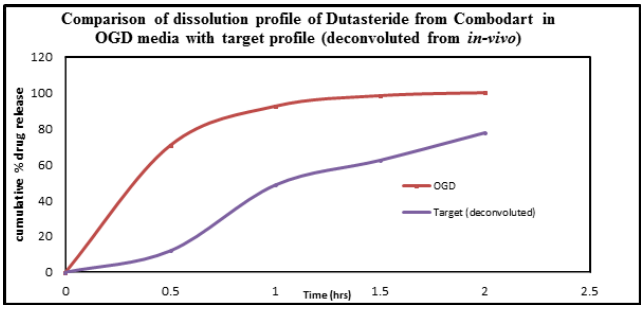

Figure 1. Comparison of dissolution profile of Dutasteride from Combodart in OGD recommended dissolution media with target dissolution profile (deconvoluted from *in-vivo*).

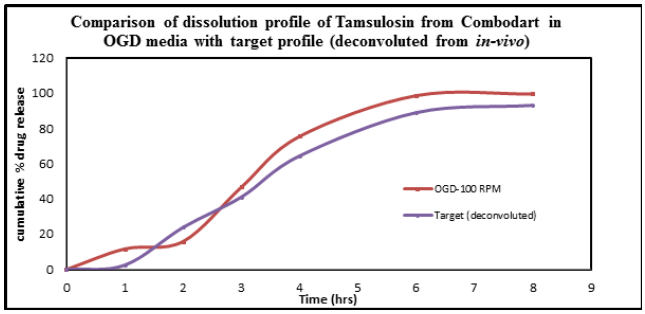

Figure 2. Comparison of dissolution profile of Tamsulosin from Combodart in OGD recommended dissolution media with target dissolution profile (deconvoluted from *in-vivo*).

dissolution media volume and agitation speed required was optimized. The risk assessment was presented in (Table 4) and Risk Priority Number (RPN) was derived based on risk assessment.

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

Based on the Risk Priority Number (RPN) achieved, two factors, media volume and dips per minute were studied for Tamsulosin and three factors, dissolution media, media volume and dips per minute were studied for Dutasteride. A full factorial design of experiment was established by using minitab software and the parameters were optimized with the response factor of dissolution at various time intervals.

Dissolution media used for biorelevant dissolution method were, Fasted State Simulated Gastric Fluid (FaSSGF), Fasted State Simulated Intestinal Fluid (FaSSIF) pH 6.5, pH7.0 and pH 7.5, Simulated colonic fluid (SCoF) pH 5.8. The composition and preparation of biorelevant dissolution media have been followed as per literature.

A full factorial design of experiment study with variables for biorelevant dissolution method was presented (Table 5) for Tamsulosin and (Table 6) for Dutasteride along with the dissolution as response. The dissolution media selected for Tamsulosin was Fasted state simulated change over dissolution media, pH 1.6 FaSSGF for 2 hrs, followed by pH 6.5 FaSSIF for 1 hr, pH 7.0 FaSSIF for 1 hr, pH 7.5 FaSSIF for 2 hrs and pH 5.8

Table 4. 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 dissolution method. Hence, the risk is low.
Dissolution media (Tamsulosin)	1	2	2	4	The dissolution media selected is based on human gastro intestinal condition and transit time. Hence, the risk is very low.
Dissolution media (Dutasteride)	2	3	3	18	Being an immediate release part, change over dissolution media is not suitable. Hence, the risk is high.
Media volume	3	3	3	27	Dissolution media volume is directly related to 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.

SCoF for 2 hrs. For Dutasteride the dissolution media selected is pH 1.6 Fasted state simulated gastric fluid, and pH 6.5 Fasted state simulated intestinal fluid.

Each dissolution study was performed using three units of Combodart, with the combination of different factors. The dissolution values observed were not having significant variation within units. Dissolution data was further evaluated for statistical interpretation. Main effect, interaction effect of DPM and media volume on dissolution were presented in (Figure 3), desirability factor for suitable dissolution medium closest to the target dissolution profile was derived by response optimization plot, and presented in (Figure 4) for Tamsulosin. ANOVA results of DOE study and model summary were presented in (Table 7) for Tamsulosin.

For all DOE data analysis, the commonly used alpha of 0.05 is chosen to differentiate between significant and not significant factors. The ANOVA result indicates the model is significant with model summary of more than 95%. The interpretation of interaction between DPM and media volume are not having significant impact on dissolution.

The multiple response graph presented in (Figure 4), indicates the predicted biorelevant dissolution method for Tamsulosin from Combodart was 15 DPM and 250 ml of Fasted change over dissolution media, with the composite desirability of 0.7768.

Table 5. A Full factorial study and responses of the factors for Tamsulosin at pre-prandial (Fasted) state simulating dissolution method

Run Order	Factors		Responses			
	DPM	Volume	Dissolution 2 hrs	Dissolution 3 hrs	Dissolution 4 hrs	Dissolution 8 hrs
Target	-	-	**23.9**	**41.1**	**64.4**	**93.1**
1	7	250	11.2 ± 0.7	27.3 ± 1.4	46.4 ± 1.0	79.5 ± 0.7
2	10	250	13.9 ± 0.5	34.2 ± 0.9	51.3 ± 1.0	80.7 ± 0.5
3	15	250	18.3 ± 0.4	37.1 ± 1.3	57.7 ± 0.5	85.2 ± 0.5
4	20	250	24.5 ± 0.5	42.2 ± 0.4	65.8 ± 0.5	93.5 ± 0.8
5	7	100	7.3 ± 0.4	15.0 ± 0.6	27.2 ± 0.7	55.2 ± 0.7
6	10	100	9.8 ± 0.4	19.0 ± 0.5	30.7 ± 0.5	60.5 ± 0.3
7	15	100	10.8 ± 0.3	20.8 ± 0.4	36.3 ± 0.6	68.2 ± 0.6
8	20	100	11.8 ± 0.4	25.0 ± 0.6	50.3 ± 1.3	73.9 ± 0.4
Note: mean ± SD, n=3						

Table 6. A full factorial study and response of the factors for Dutasteride at pre-prandial (Fasted) state simulating dissolution method

Run Order	Factors			Responses		
	DPM	Volume	Dissolution media	Dissolution 1 hrs	Dissolution 2 hrs	Dissolution 2.5 hrs
Target				**48.7**	**77.9**	**100**
1	7	250	pH 1.6 FaSSGF	33.3 ± 0.9	51.7 ± 0.3	52.5 ± 0.1
2	20	250	pH 1.6 FaSSGF	37.6 ± 0.9	57.7 ± 0.9	58.7 ± 0.3
3	7	100	pH 1.6 FaSSGF	23.8 ± 1.1	45.6 ± 0.3	46.0 ± 0.7
4	20	100	pH 1.6 FaSSGF	27.2 ± 0.4	49.0 ± 0.7	50.9 ± 0.6
5	7	250	pH 6.5 FaSSIF	46.1 ± 0.6	80.1 ± 0.4	97.1 ± 1.3
6	20	250	pH 6.5 FaSSIF	55.9 ± 0.7	93.7 ± 0.6	100.2 ± 0.1
7	7	100	pH 6.5 FaSSIF	25.8 ± 0.7	50.2 ± 0.4	52.2 ± 0.6
8	20	100	pH 6.5 FaSSIF	30.3 ± 0.2	54.7 ± 0.5	54.5 ± 0.6
Note: mean ± SD, n=3						

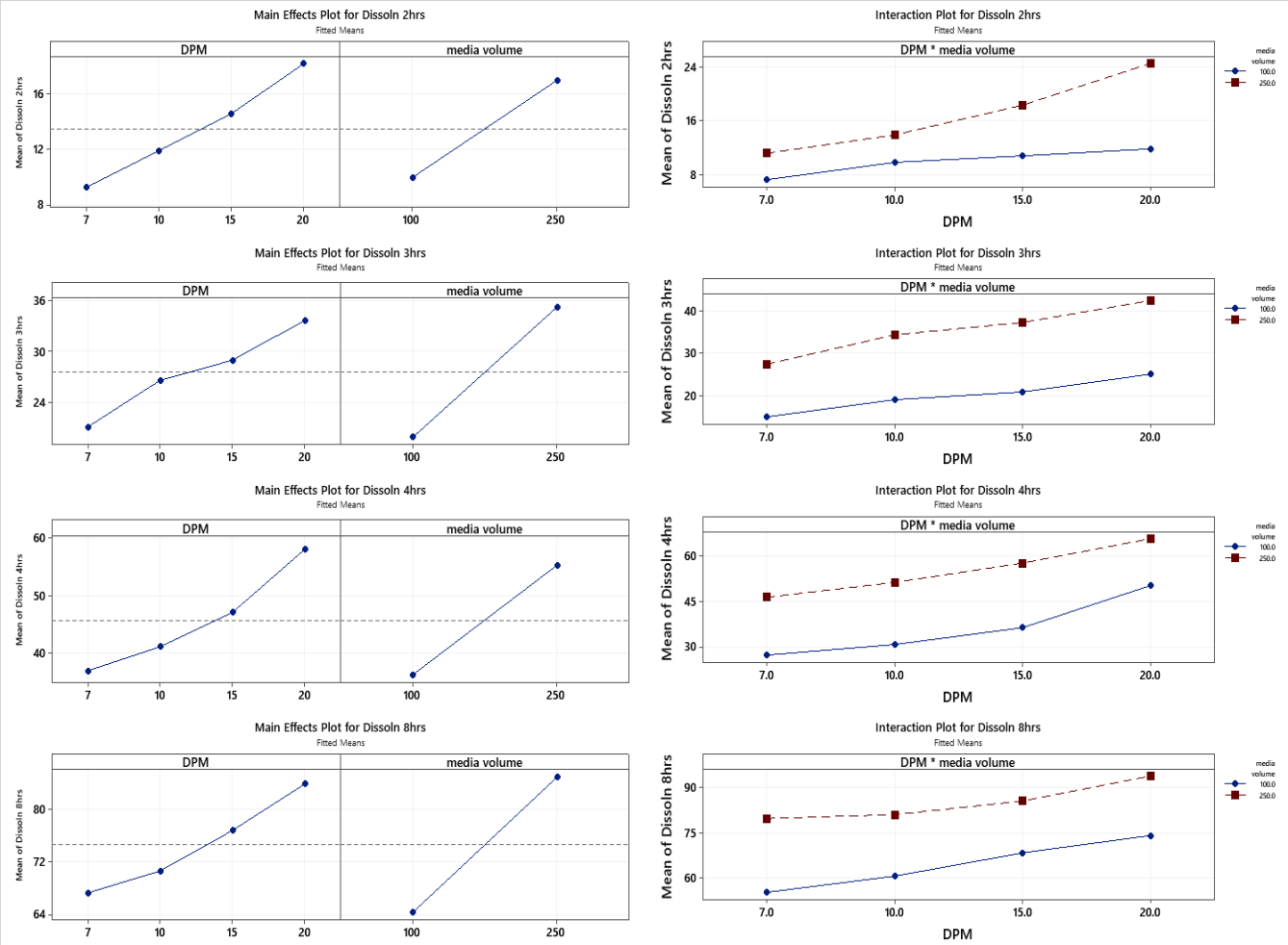

Figure 3. Main effect and interaction effect on DPM and media volume on dissolution profile of Tamsulosin under pre-prandial condition at 2 hrs, 3 hrs, 4 hrs, 8 hrs.

Table 7. ANOVA results for design of experiment for Tamsulosin

Source		Dissolution at 2 hrs		Dissolution at 3 hrs		Dissolution at 4 hrs		Dissolution at 8 hrs	
	Degrees of freedom	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	3	209.6	69.9	623.2	207.7	1238.9	413.0	1139.2	379.7
Linear	2	194.8	97.4	623.2	311.6	1218.2	609.1	1110.3	555.1
DPM	1	86.5	86.5	152.3	152.3	500.2	500.2	310.8	310.8
Volume	1	108.4	108.4	470.8	470.8	718.0	718.0	799.5	799.5
2-Way Interaction	1	23.7	23.7	5.8	5.8	3.4	3.4	6.3	6.3
DPM*Volume	1	23.7	23.7	5.8	5.8	3.4	3.4	6.3	6.3
Error	4	2.2	0.5	9.5	2.4	17.7	4.4	8.2	2.0
Total	7	211.8		632.8		1256.6		1147.4	
Model summary (R^2)		98.98%		98.49%		98.59%		99.29%	

For Dutasteride, the design of experiment study was performed through various dissolution run for evaluating the impact of dissolution media, DPM and volume of media.

Dissolution data was further evaluated for statistical interpretation. Main effect, interaction effect of dissolution media, DPM and media volume on dissolution were presented in (Figure 5), desirability factor for suitable dissolution medium closest to the target dissolution profile was derived by response optimization plot, and presented in (Figure 6) for Dutasteride. ANOVA results of DOE study and model summary were presented in (Table 8) for Dutasteride.

For all DOE data analysis, the commonly used alpha of 0.05 was chosen to differentiate between significant and not significant factors. The ANOVA result indicates the model is significant with model summary of more than 95%. Dissolution media is having significant impact on dissolution, which may be connected to solubility of drug substance. The interpretation of interaction between DPM and media volume are not having significant impact on dissolution, whereas the interaction effect dissolution media and volume are having significant impact on dissolution.

The multiple response graph presented in (Figure 6), indicates the predicted biorelevant dissolution method for Dutasteride from Combodart is 7 DPM and 250 ml of pH 6.5 Fasted state simulated intestinal fluid dissolution media, with the composite desirability of 0.9002.

3.4 Establishment of the IVIVR

A comparative dissolution profile using USP Apparatus 3, 15 DPM with 250 ml of Fasted state change over dissolution medium and target profile established for biorelevant dissolution method at pre-prandial condition for Tamsulosin was presented in (Table 9) and (Figure 7).

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 95.

Percentage of drug absorbed obtained from deconvoluted *in-vivo* data was compared with percentage of drug dissolved under simulated fasting condition. The fraction of drug released *in-vitro* is consistently comparable to the fraction of drug absorbed *in-vivo* indicating over-discriminating dissolution conditions. The slope observed by correlating *in-vitro/in-vivo* is y =

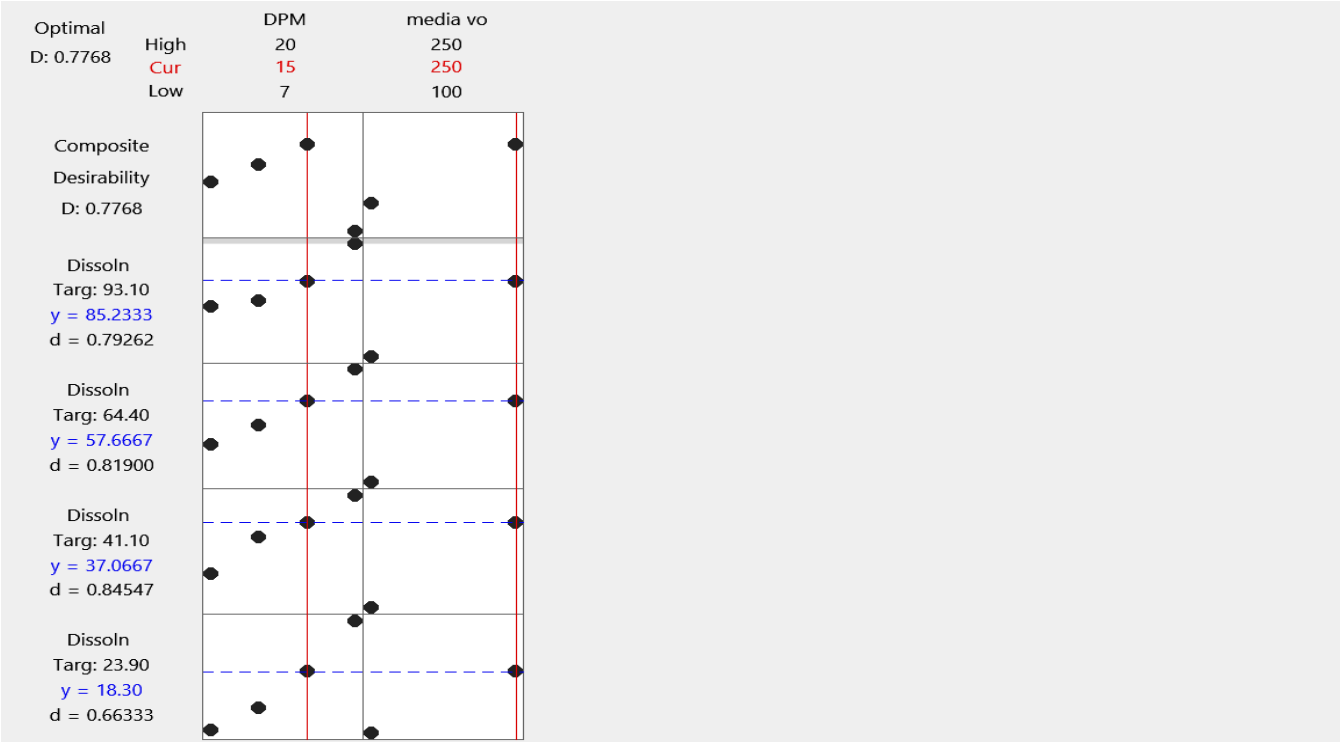

Figure 4. Response optimisation for dissolution of Tamsulosin from Combodart capsules under fasting condition at 2hrs, 3 hrs, 4 hrs and 8 hrs,

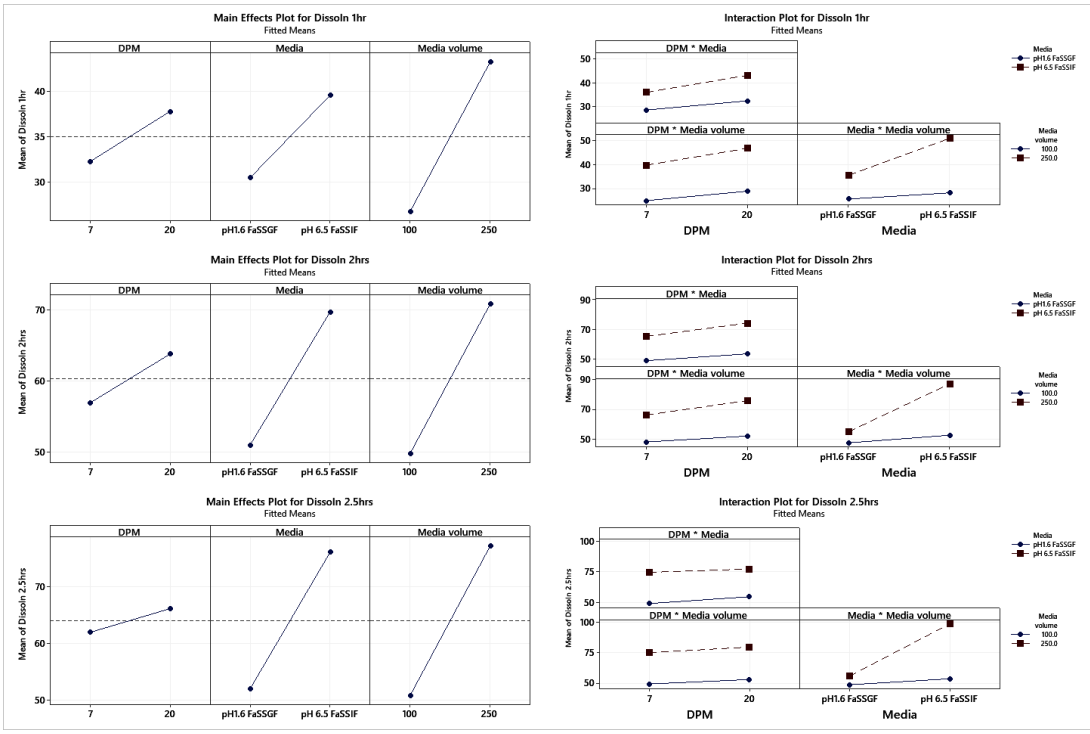

Figure 5. Main effect and interaction effect on DPM and media volume on dissolution profile of Dutasteride under pre-prandial condition at 1 hr, 2 hrs and 2.5 hrs.

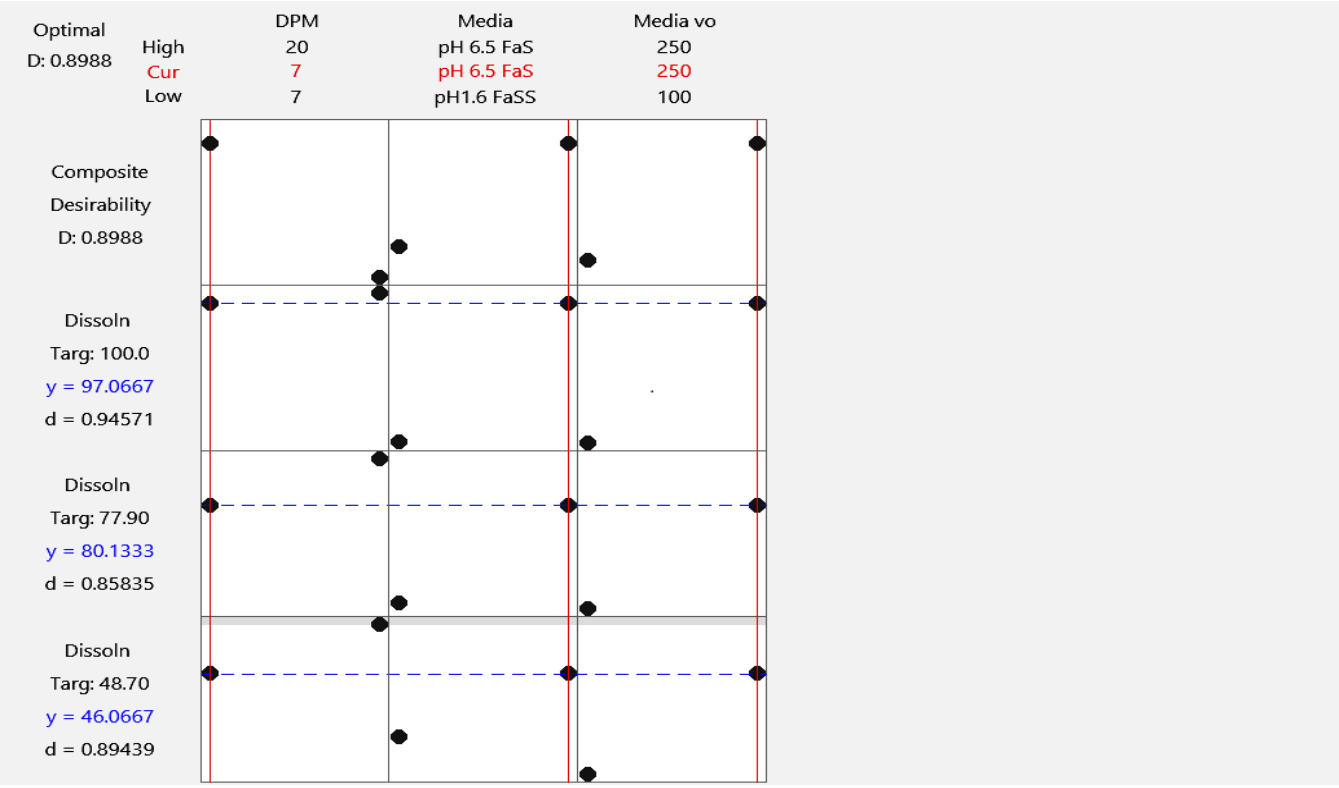

Figure 6. Response optimisation for dissolution of Dutasteride from Combodart capsules under fasting condition at 1 hr, 2 hrs and 2.5 hrs.

Table 8. ANOVA results for design of experiment for Dutasteride

Source	Degrees of freedom	Dissolution at 1 hr		Dissolution at 2 hrs		Dissolution at 2.5 hrs	
		Adjusted sum square	Adjusted mean square	Adjusted sum square	Adjusted mean square	Adjusted sum square	Adjusted mean square
Model	7	862.7	123.2	2065.5	295.1	3291.5	470.2
Linear	3	765.5	255.2	1667.8	555.9	2559.1	853.0
DPM	1	60.5	60.5	94.5	94.5	34.0	34.0
Media Volume	1	541.2	541.2	875.7	875.7	1375.5	1375.5
Media	1	163.8	163.8	697.5	697.5	1149.6	1149.6
2-Way Interactions	3	94.8	31.6	392.4	130.8	732.3	244.1
DPM* Media Volume	1	4.8	4.8	17.1	17.1	0.6	0.6
DPM* Media	1	5.4	5.4	9.5	9.5	4.1	4.1
Media Volume* Media	1	84.5	84.5	365.9	365.9	727.7	727.7
3-Way Interactions	1	2.4	2.4	5.3	5.3	0.0	0.0
DPM* Media Volume* Media	1	2.4	2.4	5.3	5.3	0.0	0.0

Table 9. *In-vitro* and *In-vivo* dissolution of Tamsulosin from Combodart at pre-prandial (Fasted) condition

Dissolution (time)	Time (hrs)	Cumulative % drug Release	Target profile
FaSSGF pH 1.6 for 60 mins	1 hr	2.6 ± 0.1	2.5
FaSSGF pH 1.6 for 120 mins	2 hrs	24.5 ± 0.5	23.9
pH 6.5 FaSSIF for 60 mins	3 hrs	42.2 ± 0.4	41.1
pH 7.0 FaSSIF for 60 mins	4 hrs	65.8 ± 0.5	64.4
pH 7.5 FaSSIF for 120 mins	6 hrs	89.1 ± 0.9	89.0
pH 5.8 SCoF for 120 mins	8 hrs	93.5 ± 0.8	93.1
F_2		**95**	
Note: mean ± SD, n=3			

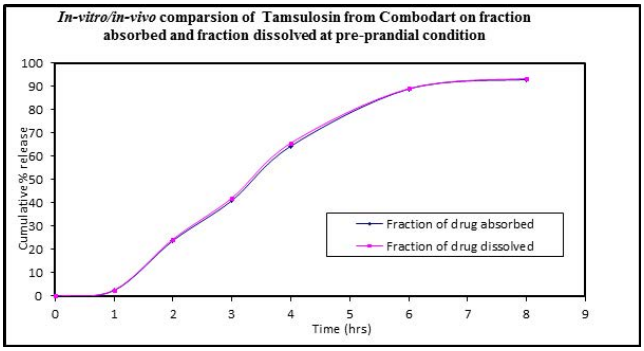

Figure 7. *In-vitro/in-vivo* comparison of Tamsulosin from Combodart - on fraction of drug absorbed by *in-vivo* and fraction of drug dissolved by *in-vitro.*

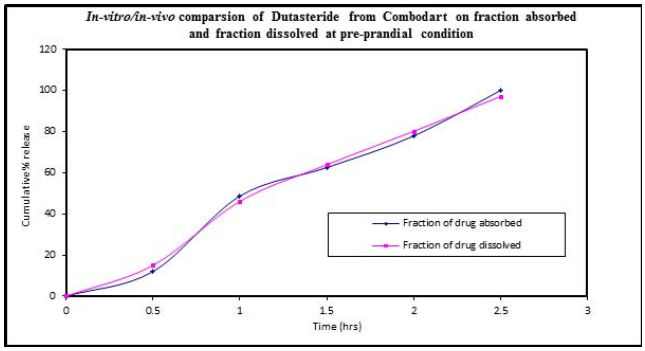

Figure 8. *In-vitro/in-vivo* comparison of Dutasteride from Combodart - on fraction of drug absorbed by *in-vivo* and fraction of drug dissolved by *in-vitro.*

1.003x + 0.393. The regression co-efficient (R^2) value of 0.999 also indicates very good predictive capability of the relationship.

A comparative dissolution profile using USP Apparatus 3, 7 DPM with 250 ml of pH 6.5 Fasted state simulated intestinal fluid as dissolution medium and target profile established for biorelevant dissolution method at pre-prandial condition for Dutasterideis presented in (Table 10) and (Figure 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 78.

The fraction of drug released *in-vitro* was consistently comparable to the fraction of drug released *in-vivo* indicating over-discriminating dissolution conditions. The slope observed from *in-vitro/in-vivo* correlation wasy = 0.976x + 1.394. The regression co-efficient (R^2) value of 0.996 also indicates very good predictive capability of the relationship.

4. Conclusion

The conventional approach is to recommend the dissolution profile closest to target profile. Whereas, QBD approach recommends the desirable dissolution profile, by considering multiple factors, main effect and interaction effect. Biorelevant dissolution methods shall be used when there were change in batch size, process change, API change, excipient change or equipment change. The developed dissolution method shall be used as a predictive tool for *in-vivo* absorption and potential tool for the establishment of IVIVC.

5. Acknowledgements

Authors are thankful to Malla Reddy Pharmacy College, Hyderabad and Dr. Reddy's Laboratories for providing all necessary facilities for conducting the study.

Table 10. *In-vitro and In-vivo* dissolution of Dutasteride from Combodart at pre-prandial (Fasted) condition

Dissolution (time)	Time (hrs)	Cumulative % drug Release	Target profile
pH 6.5 FaSSIF for 30 mins	0.5 hrs	15.0 ± 0.7	12.0
pH 6.5 FaSSIF for 60 mins	1 hr	46.1 ± 0.6	48.7
pH 6.5 FaSSIF for 90 mins	1.5 hrs	63.9 ± 1.2	62.5
pH 6.5 FaSSIF for 120 mins	2 hrs	80.1 ± 0.4	77.9
pH 6.5 FaSSIF for 150 mins	2.5 hrs	97.1 ± 1.3	100.0
F_2		**78**	
Note: mean ± SD, n=3			

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