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Biorelevant Dissolution Method Development for Dutasteride and Tamsulosin Hydrochloride Modified Release Capsule Simulating Post-prandial Condition

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ABSTRACT

Objectives: This research work is aimed to develop bio relevant dissolution method by simulating human gastrointestinal condition at post-prandial state. The quality control dissolution procedure for modified release product using simple buffers of specific pH is not adequate for prediction of *in vivo* performance. **Methods:** Percentage of drug absorbed is derived by deconvolution of drug plasma concentration at post-prandial condition using Wagner-Nelson deconvolution method. Quality control dissolution test is performed using office of generic drugs recommended dissolution method. Bio relevant dissolution method is developed using USP Apparatus 3 (reciprocating cylinder), with quality by design approach. A full factorial design of experiment study is performed for optimization of dips per minute and media volume. Separate dissolution method is developed for tamsulosin and dutasteride, since the formulation design and release profile are different for both drugs. **Results:** The dissolution profile obtained using quality control procedure is observed faster in comparison to percentage of drug absorbed. The bio relevant dissolution method developed for tamsulosin part is, 250ml of Fed state simulated change over dissolution media with 15DPM, based on desirability factor 0.8767 and for dutasteride part is, 100ml of pH 6.5 Fed state simulated intestinal fluid with 20DPM, based on desirability factor 0.5836, achieved from multiple response optimizations. The dissolution results are comparable to percentage of drug absorbed. The regression co-efficient (R^2) value of 0.998 and 0.982 demonstrates a very good *in vitro/in vivo* correlation under post-prandial condition for tamsulosin and dutasteride respectively. **Conclusion:** The developed method shall be used as a predictive *in vitro* tool for evaluation of *in vivo* performance under post-prandial condition.

Key words: Biorelevant, Dutasteride, Tamsulosin, Post-prandial, Deconvolution.

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INTRODUCTION

Dutasteride/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 multi particulates containing tamsulosin hydrochloride 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, absorbed rapidly after oral administration and observed with 60% bioavailability. C_{max} is observed about 4-5hrs, with the biological half-life ($t_{1/2}$) of 50-60hrs, when administered after food.[2] Tamsulosin is absorbed completely after oral administration with 100% bioavailability. C_{max} is observed about 11-12hrs, with the biological half-life ($t_{1/2}$) of 12-13hr, when administered after food.[3]

Plasma drug concentration is based on pharmacokinetic 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.[4] For immediate release products, which are having longer biological half-life, the deconvolution is recommended to evaluate up to the C_{max} of drug product, since, no drug release occurs after stipulated period of time.[5]

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. If individual monograph is not available, USP recommends standard dissolution apparatus and limits based on type of dosage form.[6] 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.[7] 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.[8]

Various research works has been performed on formulation development and analytical method development.[9-11] No research work has been performed on biorelevant dissolution method development of tamsulosin and dutasteride modified-release formulation. USP Apparatus 3 (reciprocating cylinder) is recommended for modified-release dosage of multiparticulate drug delivery system,[12] and it is having the scope to run with multiple dissolution media, by varying the speed. The biorelevant dissolution media for post-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.[13] Method development is 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.[14]

A bio relevant dissolution method, by simulating human gastro-intestinal condition is aimed to develop in this research work, by optimising the factors influencing drug release profile. The correlation between percentage of drug absorbed through *in vivo* study and percentage of drug released through *in vitro* dissolution is established by *in vitro/in vivo* Correlation (IVIVC).

MATERIALS AND METHODS

Combodart(R) is procured from pharmacy. Dutasteride and tamsulosin hydrochloride is obtained as gift sample from Dr. Reddy's Laboratories, Hyderabad. Standard inorganic salts and solvents are 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 Haën), Sodium taurocholate (Prodotti Chimici), Tetrahydro furan (Merck), Pancreatin powder (Scientific Protein Laboratories LLC) are procured from indigenous vendors and used for evaluation. Polyvinyl difluoride filters (0.45micron) are 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

Deconvolution of Plasma profile

The plasma drug concentration time profile obtained at post-prandial state is deconvoluted using Wagner-Nelson deconvolution method, to determine the fraction of drug absorbed.

Quality control testing

The quality control dissolution test is performed based on the recommendation from office of generic drugs. The dissolution of dutasteride and tamsulosin hydrochloride modified release capsules is performed in 0.1N HCL with 0.2% SLS for 2hrs, followed by pH 7.2 phosphate buffer for 8hrs by using USP Apparatus 1 and media volume of 900ml. Chromatographic separation was achieved with Agilent's high performance liquid chromatography and bridge C_{18}, 5µm, 4.6 x 150mm column, *with the mobile phase-1* of 0.05M phosphate buffer (pH 6.3) and mobile phase-2 of acetonitrile by gradient elution technique. The flow rate is maintained at 1.5 ml/min and the detection wavelength is 225nm, with sample run time of 18 minutes.

Biorelevant testing

Biorelevant dissolution method is developed by quality by design approach. Tamsulosin being a modified-release pellet, Fed state simulated change over dissolution media are used with the aid of dissolution USP Apparatus 3. Dutasteride being an immediate-release part, dissolution method is 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 factors, based on the risk priority number, the factors evaluated are DPM at 4 levels and media volume at 2 levels for tamsulosin. DPM, media volume and media are the factors evaluated at 2 levels for dutasteride.

A full factorial design of experiment is carried out using minitab software, study outcome is interpreted statistically. Biorelevant dissolution method is finalized based on desirability factor with percentage of drug absorbed. Level-A *in vitro/in vivo* correlation is established.

RESULTS

Deconvolution of plasma profile: The fraction of drug absorbed from Combodart at post-prandial state [15] for tamsulosin and dutasteride are presented in Table 1. Under post-prandial condition 90% tamsulosin absorbed in 12hrs and 93% dutasteride absorbed in 5 hrs, which directs the simulated dissolution method development is recommended to have 12 hr for tamsulosin and 5hr for dutasteride.

Table 1: Fraction of drug absorbed from Combodart at post-prandial condition.

Time (hr)	Tamsulosin (N=45)			Dutasteride (N=45)		
	Mean drug plasma concentration (ng/mL)	Fraction Abs. (Numerical Deconvolution)	%Absorbed (Target profile)	Mean drug plasma concentration Cp (ng/mL)	Fraction Abs. (Numerical Deconvolution)	%Absorbed (Target profile)
0.5	-	-	-	0.0	0.0	1.4
1.0	0.2	0.0	1.6	0.1	0.0	2.6
1.5	-	-	-	0.3	0.1	11.1
2.0	0.9	0.1	6.8	0.5	0.2	22.7
2.5	1.6	0.1	11.9	0.8	0.4	37.2
3.0	2.6	0.2	20.1	1.1	0.5	51.5
4.0	4.8	0.4	37.4	1.4	0.7	70.4
5.0	7.6	0.6	60.1	1.7	0.9	93.3
5.5	8.0	0.65	65.1	1.8	1.0	100.0
6.0	9.1	0.76	75.5			
8.0	9.6	0.88	88.2			
12.0	6.8	0.91	90.9			
24.0	3.3	0.95	95.3			
48.0	0.9	0.97	97.4			

Quality control dissolution testing: Dissolution profile of Combodart is performed using OGD recommended dissolution media. The dissolution of dutasteride is observed more than 90% in 1hr and the percentage absorbed is only 2.6% at 1hr. Similarly, tamsulosin is observed with faster dissolution profile in comparison to percentage drug absorbed. The results are presented in Table 2.

Biorelevant testing: Biorelevant dissolution method is developed by using quality by design (QBD) approach. Initial risk assessment is performed on variables such as residence time, pH of buffer, dissolution media, agitation speed and media volume. Risk assessment is measured in 3 categories, low (1), medium (2) and high (3). The risk number is the multiplication of all the three. The risk number more than 9 is considered for DOE study. Dissolution apparatus, dissolution media, media volume and DPM are considered as factors for dissolution evaluation. Based on the risk priority number (RPN) achieved, media volume and DPM are the two factors studied for tamsulosin. Media volume, dissolution media and DPM are the three factors studied for dutasteride. A full factorial design of experiment is established by using minitab software.

Dissolution media used for bio relevant dissolution method development are, Fed state simulated gastric fluid (FeSSGF), Fed state simulated intestinal fluid (FeSSIF) pH 5.8, pH 6.5 and pH 7.5, Simulated colonic fluid (SCoF) pH 5.8. The composition and preparation of bio relevant dissolution media is followed as per literature.

A full factorial design of experiment study with factors and responses for biorelevant dissolution method is presented for tamsulosin in Table 3 and for dutasteride in Table 4. The dissolution media selected for evaluation of tamsulosin is Fed state simulated change over dissolution media (pH 5.0 FeSSGF for 2hr, pH 5.8 FeSSIF for 1hr, pH 6.5 FeSSIF for 1hr, pH 7.5 FeSSIF for 2hrs and pH 5.8 SCoF for 6hr). The dissolution media selected for dutasteride is pH 5.0 Fed state simulated gastric fluid and pH 6.5 Fed state simulated intestinal fluid.

Each dissolution study is performed using 3 units of Combodart, with the combination of different factors. The standard deviation below 2% confirms no significant variation within units. Dissolution data is further evaluated for statistical interpretation using minitab software for main effect, interaction effect of DPM and media volume on dissolution. Increase in DPM and media volume shows increase in drug release,

Table 2: Comparative dissolution profile of Combodart in 0.1N HCl with 0.2% SLS for 2hr, pH 7.2 phosphate buffer for 8hr. USP Apparatus 1, 900ml, with target release profile.

Time (hrs)	Combodart 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	1.4	5.9 ± 0.4	-
1	92.7 ± 0.5	2.6	11.7 ± 0.6	1.6
1.5	98.5 ± 0.4	11.1	13.1 ± 0.2	-
2	100.2 ± 0.1	22.7	15.9 ± 0.3	6.8
3	-	-	46.7 ± 0.5	20.1
4	-	-	75.5 ± 0.7	37.4
6	-	-	98.6 ± 0.3	75.5
8	-	-	99.6 ± 0.1	88.2
F_2	7		30	

Note: mean ± SD, n=3

Table 3: Full factorial study design and responses on dissolution of tamsulosin from Combodart capsules under fed change over dissolution condition.

Run Order	Factors		Responses		
	DPM	Volume	Dissolution 4 hr	Dissolution 6hr	Dissolution 12hr
Target	-	-	37.4	75.5	90.0
1	7	100	15.8 ± 0.6	36.3 ± 0.5	64.3 ± 1.1
2	10	100	24.0 ± 0.5	41.7 ± 0.4	72.7 ± 0.5
3	15	100	30.4 ± 0.4	53.2 ± 0.6	75.0 ± 0.3
4	20	100	34.0 ± 0.4	62.0 ± 0.7	72.5 ± 0.2
5	7	250	28.0 ± 0.5	63.1± 0.6	81.5 ± 1.2
6	10	250	31.7 ± 0.7	65.2 ± 0.4	83.4 ± 0.9
7	15	250	34.1 ± 0.5	69.0 ± 0.6	88.8 ± 0.6
8	20	250	38.2 ± 0.3	76.3 ± 0.5	90.7 ± 0.5

Note: mean ± SD, *n*=3

Table 4: Full factorial study design and responses on dissolution of dutasteride from Combodart capsules.

Run Order	Factors			Responses		
	DPM	Volume	Dissolution media	Dissolution 1hrs	Dissolution 3hrs	Dissolution 5hrs
Target				**2.6**	**51.1**	**93.3**
1	7	100	pH 5.0FeSSGF	5.2 ± 0.4	51.1 ± 1.1	93.5 ± 0.9
2	20	100	pH 5.0FeSSGF	9.9 ± 0.4	62.7 ± 0.5	97.3 ± 1.1
3	7	250	pH 5.0FeSSGF	16.5 ± 0.9	66.0 ± 0.8	98.1 ± 0.7
4	20	250	pH 5.0FeSSGF	22.9 ± 0.5	73.6 ± 1.6	98.5 ± 0.1
5	7	100	pH 6.5 FeSSIF	8.8 ± 0.4	61.2 ± 0.7	93.1 ± 0.4
6	20	100	pH 6.5 FeSSIF	12.2 ± 0.3	64.5 ± 0.9	94.8 ± 0.5
7	7	250	pH 6.5 FeSSIF	18.8 ± 0.4	68.8 ± 0.5	99.0 ± 0.7
8	20	250	pH 6.5 FeSSIF	25.7 ± 1.0	75.4 ± 0.7	99.2 ± 0.3

Note: mean ± SD, *n*=3

the response is presented in Figure 1, desirability factor is derived from response optimization, presented in Figure 2 for tamsulosin. ANOVA results of DOE study and model summary are presented in Table 5 for tamsulosin. The p value observed was less than 0.05, which confirms the model is significant.

For dutasteride, the design of experiment study performed through various dissolution run for evaluating the impact of dissolution media, DPM and media volume. Statistical interpretation of data on main effect, interaction effect of dissolution media, DPM and media volume on dissolution are presented in Figure 3, desirability factor is derived by response optimization plot, presented in Figure 4 for dutasteride. ANOVA results of DOE study and model summary are presented in Table 5 for dutasteride.

Dissolution profile is compared using optimised method for tamsulosin and percentage drug absorbed, the results are presented in Table 6 and Figure 5.

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

Table 5: ANOVA results for Design of experiment – Combodart.

Source	Degrees of freedom	Dutasteride dissolution at			Degrees of freedom	Tamsulosin dissolution at		
		1hr	3 hrs	5 hrs		4hrs	6 hrs	12 hrs
		Adjusted sum square				Adjusted sum square		
Model	7	361.9	409.4	43.9	7	342.9	1308.4	571.4
Linear	3	358.0	385.2	37.3	4	319.8	1254.1	553.9
DPM	1	57.2	105.9	4.7	3	223.2	446.1	105.4
Media Volume	1	285.6	245.3	32.4	1	96.6	808.0	448.5
Media	1	15.1	34.0	0.2	-	-	-	-
2-Way Interactions	3	3.5	17.5	6.2	3	23.1	54.3	17.5
DPM*Media Volume	1	3.4	0.1	3.0	3	23.1	54.3	17.5
DPM*Media	1	0.1	10.8	0.7	-	-	-	-
Media Volume*Media	1	0.1	6.7	2.5	-	-	-	-
3-Way Interactions	1	0.4	6.7	0.5	-	-	-	-
DPM*Media Volume*Media	1	0.4	6.7	0.5	-	-	-	-
Variance Inflation Factor	-	1.50	1.50	1.50	-	1.0	1.0	1.0

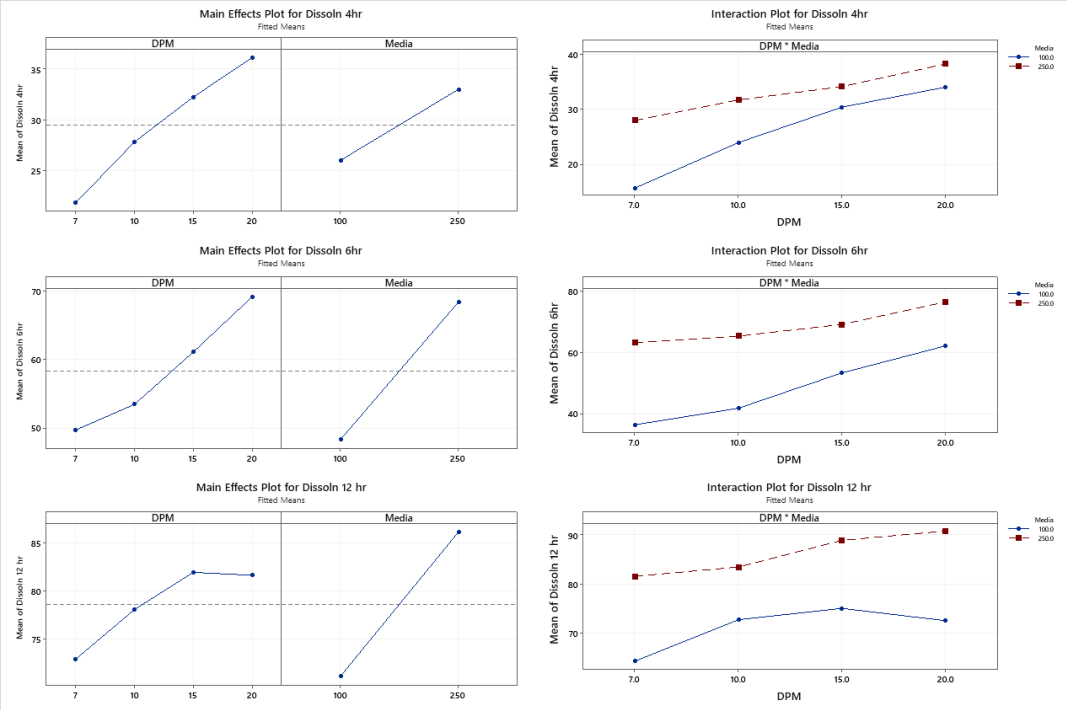

Figure 1: Main effect and interaction effect on DPM and media volume on dissolution profile of tamsulosin under post-prandial condition.

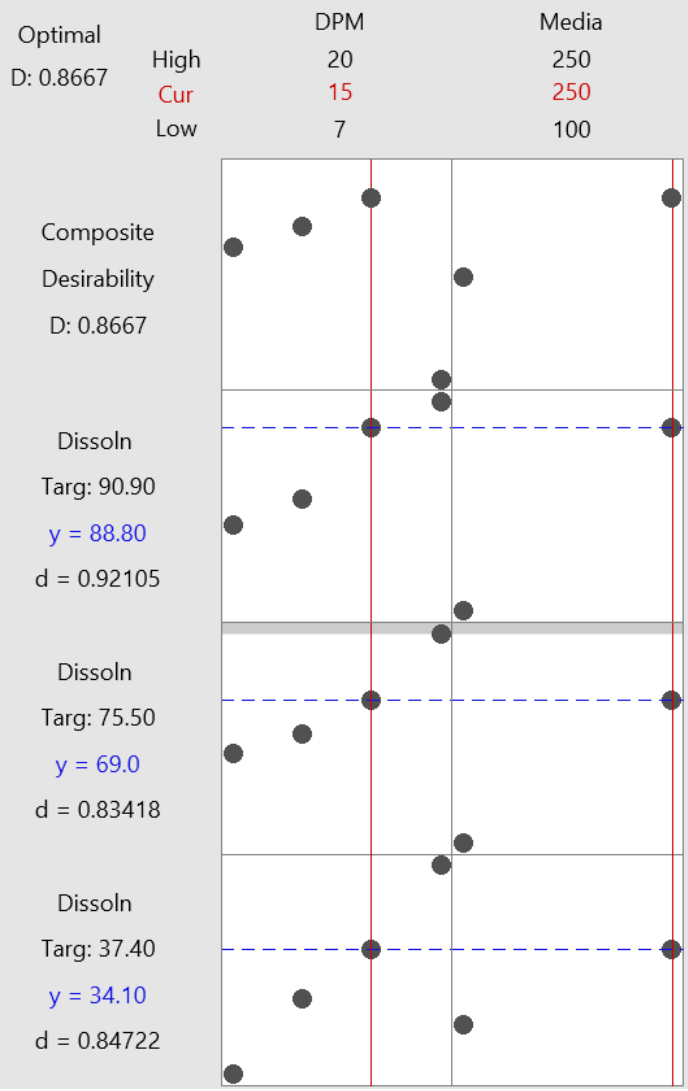

Figure 2: Response optimisation for dissolution of tamsulosin from Combodart under post-prandial condition at 4hr, 6hr and 12hr.

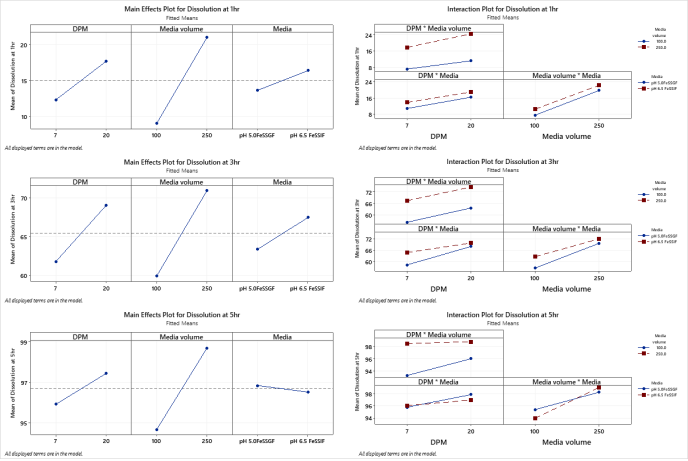

Figure 3: Main effect and interaction effect on DPM, media and media volume on dissolution profile of dutasteride under post-prandial condition.

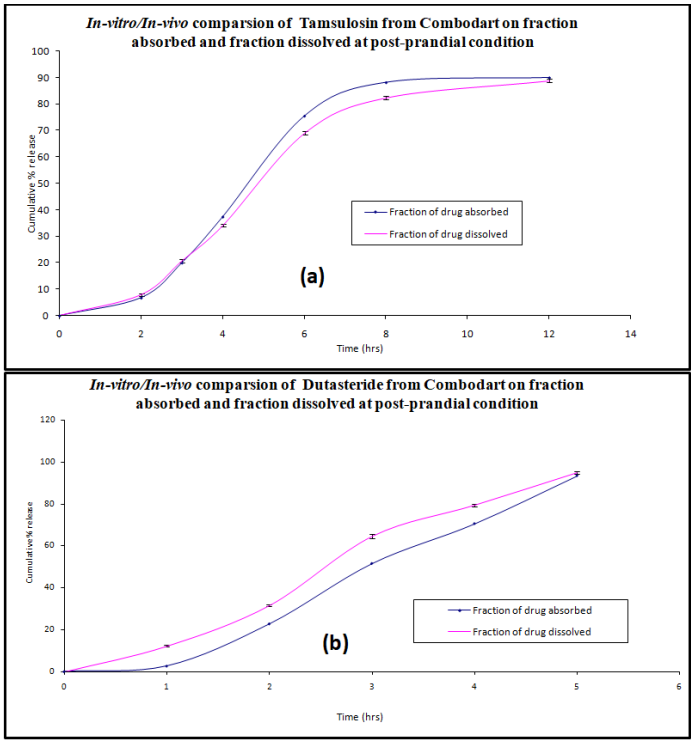

Figure 5: *In vitro/in vivo* comparison of Combodart - on fraction of drug absorbed by *in vitro* and fraction of drug dissolved by *in vitro*- a) Tamsulosin b) Dutasteride. The y-axis represents % drug release and the x-axis denotes times in hours. Data represent mean ± standard deviation, $n = 3$.

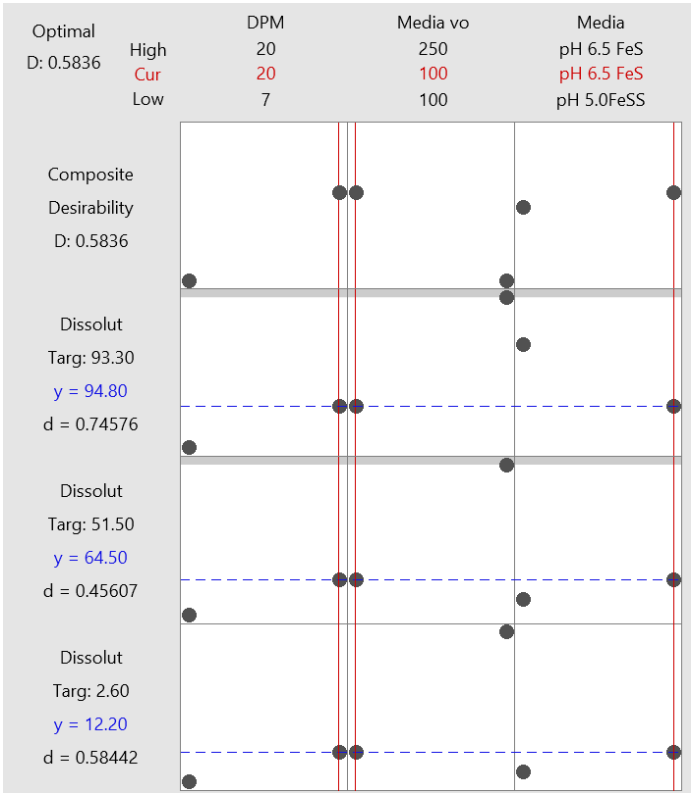

Figure 4: Response optimisation for dissolution of dutasteride from Combodart under post-prandial condition at 1hr, 3hr and 5hr.

Table 6: *In-vitro*/*In-vivo* comparison of dutasteride and tamsulosin from Combodart on fraction absorbed and fraction dissolved at post-prandial condition.

Dissolution (time)	Cumulative Time (hrs)	Cumulative % drug release	Target profile (% absorbed)
Tamsulosin Part			
FeSSGF pH 5.0 for 120 mins	2 hrs	7.9 ± 0.4	6.8
pH 5.8 New- FeSSIF for 60 mins	3 hrs	20.7 ± 0.5	20
pH 6.5 Half-FeSSIF for 60 mins	4 hrs	34.1 ± 0.5	37.4
pH 7.5 FeSSIF- sans for 120 mins	6hrs	69.0 ± 0.6	75.5
pH 5.8 SCoF for 120 mins	8 hrs	82.4 ± 0.6	88.2
pH 5.8 SCoF for 240 mins	12 hrs	88.8 ± 0.6	90.9
F2		70	
Dutasteride Part			
pH 6.5 FeSSIF for 1 hour	1 hour	12.2 ± 0.3	2.6
pH 6.5 FeSSIF for 2 hours	2 hours	31.6 ± 0.5	22.7
pH 6.5 FeSSIF for 3 hours	3 hours	64.5 ± 0.9	51.5
pH 6.5 FeSSIF for 4 hours	4 hours	79.3 ± 0.7	70.4
pH 6.5 FeSSIF for 5 hours	5 hours	94.8 ± 0.5	93.3
F2		52	

Note: mean ± SD, n=3

correlating *in vitro/in vitro* is y = 0.913x + 0.991. The regression co-efficient (R^2) value of 0.998 also indicates very good predictive capability of the relationship.

Dissolution profile is compared using optimised method for dutasteride and percentage drug absorbed, the results are presented in Table 6 and Figure 5.

Percentage of drug absorbed obtained from deconvoluted *in vivo* data for dutasteride is compared with percentage of drug dissolved under simulated fed condition. The fraction of drug released *in vitro* is consistently comparable to the fraction of drug released *in vitro* indicating over discriminating dissolution conditions. The slope observed from *in vitro/in vitro* correlation is y = 0.997x + 7.072. The regression co-efficient (R^2) value of 0.982 also indicates very good predictive capability of the relationship.

DISCUSSION

Biorelevant dissolution methods are the predictive tool for *in vivo* performance of drug product. The percentage of drug absorbed is determined by deconvolution of plasma profile shows the difference in release profile, more than 85% of drug is absorbed for tamsulosin at 8hrs and dutasteride at 5hrs[15], which recommends developing biorelevant dissolution method for certain dissolution run duration. Combodart is evaluated for dissolution using quality control method resulted in faster dissolution profile in comparison to percentage of drug absorbed, with the F_2 value 7 for dutasteride and 30 for tamsulosin.

Hence, a bio-predictive dissolution method to characterize the *in vivo* performance of drug product is developed. This dissolution method involves incorporation of multiple dissolution medium and preparation of dissolution medium used to simulate the gastrointestinal condition.[8] Tamsulosin being modified-release dosage form, change over dissolution media simulating post-prandial condition is used for dissolution evaluation up to 12hr. Dutasteride being an immediate-release dosage form, single dissolution media is used by extending the dissolution run time upto 5hrs. A separate biorelevant dissolution method is developed, based on the formulation design and release profile of dutasteride and tamsulosin. A quality by design approach is adopted. The initial risk assessment performed on factors affecting dissolution performance directs, DPM and media volume are the significant factors to be studied for tamsulosin. DPM, media volume and media are the significant factors to be studied for dutasteride. A full factorial design of experiment study was performed.[14]

For tamsulosin, increase in agitation speed and media volume is having increase in dissolution. From the ANOVA results, *p* value less than 0.05% and the total sum of square attributed only to the factors without residual error concludes the model is significant, with the model summary of 100%. Interaction effect is not having significant contribution in model. The dissolution response at 4hrs, 6hr and 12hr are evaluated by varying the factors and multiple responses is plotted using minitab software, indicates the predictive biorelevant dissolution method for tamsulosin from Combodart is USP Apparatus 3, 15DPM and 250ml of change over dissolution media, with the composite desirability of 0.8767. The composite desirability is not based on closeness of dissolution with percentage drug absorbed, it includes other variable factors studied throughout the experiment. The dissolution profile of optimized biorelevant dissolution method, with inclusion of multiple dissolution time points compared with fraction of drug absorbed, resulted F_2 value of 70 and complies to level a *in vitro/in-vivo* correlation, with regression co-efficient value of 0.998. USP apparatus 3 is programmable to run dissolution in different media and at different speed at various time intervals.[12]

For dutasteride, increase in agitation speed and media volume is having increase in dissolution. Change in dissolution media is not having significant impact on dissolution. 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 dissolution response at 1hr, 3hr and 5hr evaluated by varying the factors and multiple response was plotted using minitab software, indicates the predicted biorelevant dissolution method for dutasteride from Combodart is USP Apparatus 3, 20DPM and 100ml of pH 6.5 Fed state simulated intestinal fluid dissolution media, with the composite desirability of 0.5836. The dissolution profile of optimized biorelevant dissolution method, with inclusion of multiple dissolution time points compared with fraction of drug absorbed, resulted the F_2 value of 52 and complies to level a *in vitro/in vitro* correlation, with regression co-efficient value of 0.982.

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 is 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.

CONCLUSION

Biorelevant dissolution method developed using USP Apparatus 3, coupled with a deconvolution approach is found to be successfully correlating the *in vivo* performance of tamsulosin and dutasteride modified-release capsules after oral administration under the fed state.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

USP: United States of Pharmacopeia; **OGD:** Office of Generic Drugs; **DPM:** Dips per minute; **NF:** National Formulary; **RP-HPLC:** Reverse phase High performance liquid chromatography; **HCl:** Hydrochloric acid; **SLS:** Sodium lauryl sulphate; **USFDA:** United States Food and Drugs Administration; **DOE:** Design of Experiment; **RPN:** Risk priority number; **SD:** Standard deviation; **ANOVA:** Analysis of variance.

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