ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 8, Issue 4, 2015

ISSN - 0974-2441

Research Article

IN VITRO IN VIVO CORRELATION OF DEXTROMETHORPHAN HYDROBROMIDE MODIFIED RELEASE TABLETS: AN INTERNAL VALIDATION EVALUATION

RAMESH N[1]*, SOCORRINA COLACO[2], RAMAKRISHNA SHABARAYA[1], SEKAR RAJAN[3]*, SUBRAMANIA NAINAR MEYYANATHAN[3]

[1]Department of Pharmaceutics, Srinivas College of Pharmacy, Mangalore - 574 143, Karnataka, India. [2]Department of Pharmacology, Srinivas Institute of Medical Sciences & Research Centre, Mangalore - 575021, Karnataka, India. [3]Department of Pharmaceutical Analysis, J.S.S. College of Pharmacy, Rocklands, Ooty - 643 001, Tamil Nadu, India. Email: ramesh7779@gmail.com

Received: 09 March 2015, Revised and Accepted: 30 March 2015

ABSTRACT

Objectives: The purpose of this study was to develop and validate *in vitro* and *in vivo* correlation (IVIVC) for newly developed dextromethorphan hydrobromide sustained-release (SR).

Methods: During the development of a once-daily SR tablet of dextromethorphan hydrobromide, an extrapolative *in vitro* drug release method was designed and statistically evaluated using three formulations with varying release rates. The similarity factor (f_2) was used to analyze the dissolution data. Three-way crossover study design was conducted in six healthy human subjects under fasting condition.

Result: The formulations were evaluated by using area under the plasma concentration-time curve, ($AUC_{0-\infty}$), time to reach peak plasma concentration, Tmax, and peak plasma concentration C_{max}, while correlation was determined between *in-vitro* release and *in-vivo* absorption. A linear correlation was observed between the absorption and dissolution profiles of the drug. The prediction error (%) was determined to check how well a given model can accurately predict a pharmacokinetic parameter of the drug. The predicted C_{max} and AUC found to be −6.98 and −8.55 and for AUC was 7.76 and 8.82% respectively.

Conclusion: In conclusion, a Level A IVIVC explaining the complete time-course of plasma concentrations was developed and validated, internally for developed dextromethorphan hydrobromide SR formulations.

Keywords: Dextromethorphan hydrobromide, Dissolution, Bioavailability, Sustained-release, *In vitro* and *in vivo* correlation.

INTRODUCTION

The United States Food and Drug Administration (FDA) recommended that formulations with three or more release rates shall be essential to develop *in vitro* and *in vivo* correlation (IVIVC). Estimation of the model's capability to illustrate data is referred to as internal validation. The model should be competent to predict the area under the plasma concentration curve (AUC) and the peak plasma concentration (C_{max}) to within limits as set by the FDA [1].

IVIVC, particularly for solid oral dosage forms, has be en developed to presume drug bioavailability from *in vitro* dissolution. IVIVC can be used to set dissolution specifications; and as a surrogate for bioequivalence in case of any modification with respect to formulation, process, or manufacturing site.

Dextromethorphan hydrobromide is a synthetic antitussive compound used with an antihistamine in the treatment of cough. Dextromethorphan suppresses cough by central action on the cough center in the medulla. The drug usually administered 3-4 times a day due its short half-life [2]. A sustained-release (SR) formulation can guide to the decline in number of doses administered, less probability of an overdose, and especially good to treat asthma patient's night time cough [3]. No IVIVC work was carried out for dextromethorphan hydrobromide. Numerous literature were utilized as guidance for developing and validating IVIVC for the selected drugs [4-18].

The objective in this study was to develop and validate an IVIVC for newly developed dextromethorphan SR tablet. Further SR dosage units from each formulation are administered in healthy human subjects under the fasting condition, as crossover design pattern, and plasma drug concentrations are measured by using the validated analytical method. *In vitro* and *in vivo* studies were performed and data were used for IVIVC.

METHODS

Dissolution studies

The dissolution characteristics were test and reference formulations of dextromethorphan hydrobromide studied using a Type II paddle apparatus based on a method described in the USP (XXIII dissolution apparatus). The dissolution medium was 900 ml in volume and experiments were performed at different pH 1.2, 4.5, 5.5, 6.8 and 7.2 buffers maintained at 37.0±0.5°C at 50 and 75 rpm. 5 ml of samples were withdrawn were withdrawn at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 hrs. Samples were filtered through a 0.45 mm membrane filter and analyzed by using high-performance liquid chromatography (HPLC) at a wavelength of 280 nm. All the experiments were carried out using six tablets for dextromethorphan SR newly developed formulation i.e. slow, fast release (test) and immediate release tablet (reference).

Human pharmacokinetic study

The study was an open-label, randomized, three-treatment, three-period, six-sequence, single-dose, crossover, bioavailability study in six healthy, adult human male subjects under fasting conditions. The study was approved by the ethics committee. The study was performed in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Informed consent was obtained prior to the study. The subjects, who fulfilled the inclusion and exclusion criteria, were allowed to participate in the study. The test product of dextromethorphan SR newly developed formulation i.e. slow, fast

release and the immediate release formulation (reference) product were administered as per the randomization schedule. Blood samples were collected at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 hrs. Blood samples were centrifuged at 3500 rpm and stored at 30°C until assay. The calibration curve was 110.00-3000.00 ng/mL. Acceptable intra-day and inter-day precision (<15%) and accuracy (<10% difference) were observed. The percentage recovery of the analyte was 97.43%. The samples were analyzed by using validated HPLC method.

RESULTS AND DISCUSSION

In vitro dissolution data analysis

The dissolution profiles were estimated by plotting the cumulative percent drug dissolved at various time points. The dissolution were compared using the similarity factor (f_2) presented in the equation,

$$f_2 = 50 \log\left[1 + 1/n \sum_{t=1} (R_t - T_t)^{-2}\right]^{n^{-0.5}} \times 100 \quad (1)$$

Where, R_t and T_t are the percent dissolved at each time point for the reference product and the test product, respectively. Using the f_2 values, dissolution profiles were determined the dissimilarity.

Dissolution tests were performed at pH 1.2 buffer, pH 4.5, pH 5.5, buffer and pH 6.8 at 50 and 75 rpm, the release was identical for the slow and fast formulations. The f_2 value for pH 1.2 buffer, pH 4.5, pH 5.5, buffer and pH 6.8 at 50 rpm was 60.61,42.06, 60.72 and 48.79, respectively, but at 75 rpm, the f_2 value was 61.49, 59.62, 43.64 and 52.02, respectively. The higher f_2 values (more than 50) authenticate that the two dissolution profiles are indistinguishable and therefore not considered further for the study. At pH 7.4 buffer and 50 rpm as well as 75 rpm dissimilarities between the formulations were more apparent. The f_2 value for pH 7.4 buffer at 50 rpm was 34.44 whereas, at 75 rpm, the f_2 value was 41.49. The computed similarity factors (f_2) confirmed the conclusion refer Table 1, that pH 7.4 buffer at 75 rpm was more discriminating dissolution mediums and hence selected for IVIVC model development. The percentage drug releases calculated at various times are presented in Tables 2 and 3 and in Figs. 1 and 2. The similarity factor (f_2) was presented in Table 1.

Pharmacokinetics analysis

The pharmacokinetic parameters C_{max}, AUC_{0-t}, $AUC_{0-¥}$, T_{max}, $t_{½}$ and elimination rate constant for dextromethorphan were calculated by using non-compartmental model by using Winnonlin® Software (Version 5.1) with the data obtained from six subjects who completed the study. All the formulations were well tolerated, with no major side effects and no relevant differences in safety profile observed between the preparations. The mean pharmacokinetic profile for the dextromethorphan represented at Table 4 and the mean plasma concentration profile as presented in Fig. 3.

Statistical analyses

The statistical parameters for Ln-transformed values of C_{max}, AUC_{0-t} and $AUC_{0-¥}$ like the sum of square, degree of freedom, mean square, F,

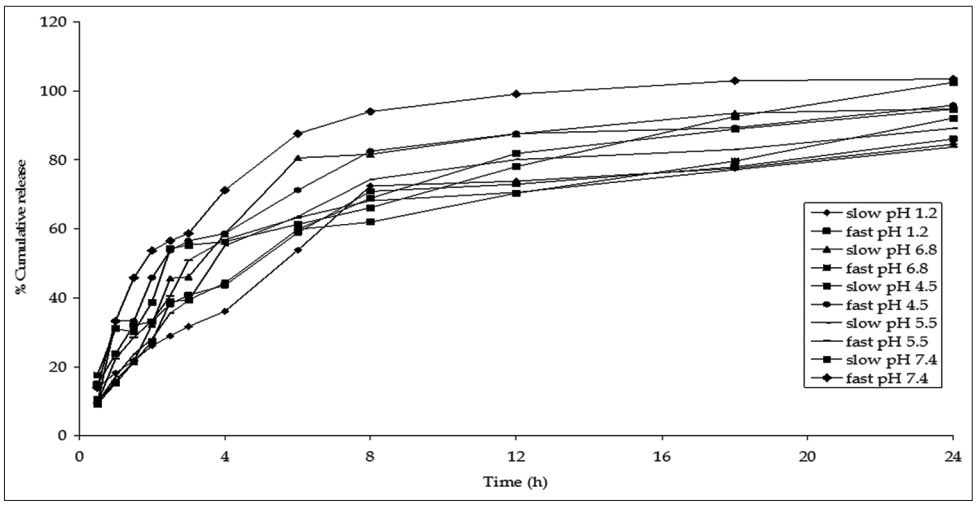

Fig. 1: Percentage of dextromethorphan hydrobromide release versus time profile for slow and fast modified release tablets using 50 rpm

Table 1: Cumulative percentage dissolved at 50 rpm for the dextromethorphan hydrobromide test formulations

Time (hrs)	Square root of time (hrs)	Formulation									
		pH 1.2 buffer		pH 4.5 buffer		pH 6.8 buffer		pH 5.5 buffer		pH 7.4 buffer	
		Slow	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow	Fast
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.50	0.71	13.93	15.01	10.58	9.31	9.84	17.63	9.69	9.54	9.31	13.98
1.00	1.00	18.29	23.73	15.26	33.28	15.96	31.10	17.24	22.37	15.26	33.28
1.50	1.22	21.82	32.01	21.44	33.28	21.49	30.21	23.66	28.54	21.44	45.88
2.00	1.41	26.11	33.10	27.32	45.88	32.39	38.81	28.16	33.41	27.32	53.67
2.50	1.58	28.93	38.19	38.93	53.67	45.67	54.25	35.58	40.55	38.93	56.51
3.00	1.73	31.69	40.79	39.42	56.51	46.09	55.35	39.15	50.88	39.42	58.63
4.00	2.00	36.12	43.66	44.30	58.63	58.57	56.31	55.16	56.86	44.30	71.27
6.00	2.45	53.85	58.87	59.89	71.27	80.55	61.36	63.57	63.26	59.89	87.66
8.00	2.83	72.47	70.95	62.02	82.48	81.65	66.12	74.33	68.16	68.92	94.07
12.00	3.46	73.81	72.97	70.34	87.66	87.53	78.08	80.10	70.58	81.85	99.09
18.00	4.24	77.60	77.94	79.68	89.36	93.54	92.57	82.99	77.13	88.90	102.95
24.00	4.90	84.56	86.10	92.10	95.83	94.85	102.51	89.15	83.74	94.78	103.44

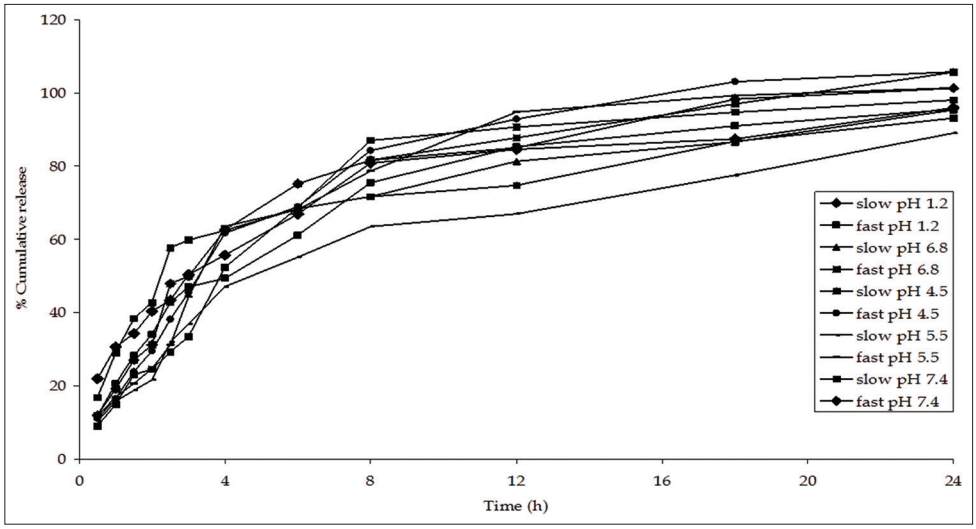

Fig. 2: Percentage of dextromethorphan hydrobromide release versus time profile for slow and fast modified release tablets using 75 rpm

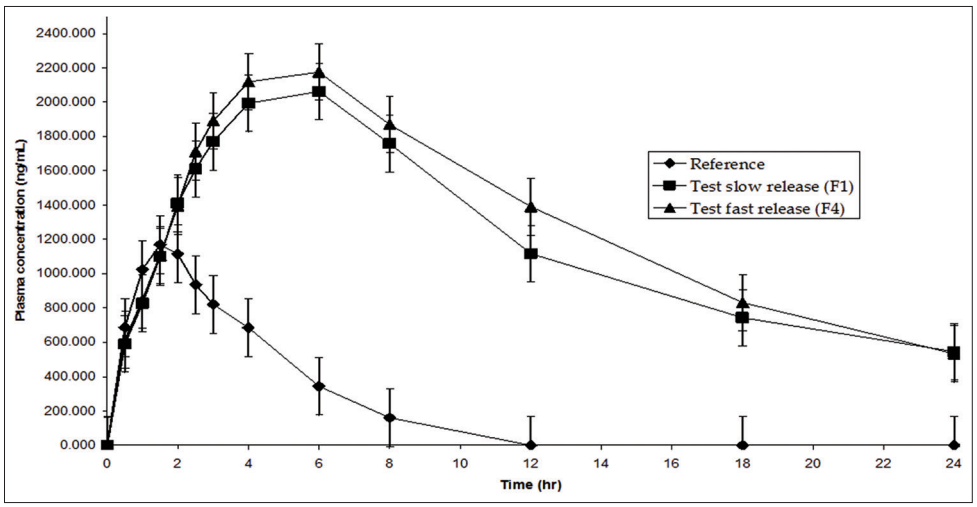

Fig. 3: Mean plasma concentration-time profile of dextromethorphan hydrobromide from developed sustained release tablets (test) and marketed immediate release tablet (reference)

Table 2: Cumulative percentage dissolved at 75 rpm for the dextromethorphan hydrobromide test formulations

Time (hrs)	Square root of time (hrs)	Formulation									
		pH 1.2 buffer		pH 4.5 buffer		pH 6.8 buffer		pH 5.5 buffer		pH 7.4 buffer	
		Slow	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow	Fast
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.50	0.71	21.93	11.79	9.04	11.04	16.83	11.89	10.31	11.88	16.83	11.89
1.00	1.00	30.57	20.52	14.94	16.49	29.06	19.18	15.71	16.91	29.06	19.18
1.50	1.22	34.27	28.25	23.08	23.89	38.42	26.98	18.73	20.64	38.42	26.98
2.00	1.41	40.29	34.11	24.47	29.54	42.72	31.16	21.60	24.65	42.72	31.16
2.50	1.58	43.36	42.77	29.24	38.10	57.67	47.85	31.89	31.19	57.67	47.85
3.00	1.73	50.34	46.96	33.46	45.45	59.83	49.90	36.84	44.32	59.83	49.90
4.00	2.00	55.67	49.35	52.34	61.65	62.40	62.54	47.09	63.56	62.40	62.54
6.00	2.45	66.89	61.12	68.64	68.92	68.34	75.15	55.06	68.10	68.34	75.15
8.00	2.83	80.79	75.47	87.01	84.23	71.63	81.61	63.48	78.58	71.63	81.61
12.00	3.46	84.56	85.24	90.66	92.81	81.27	87.71	66.91	94.75	74.74	84.98
18.00	4.24	87.41	90.92	94.70	103.02	86.53	96.98	77.49	99.26	86.73	98.28
24.00	4.90	95.87	95.51	98.05	105.76	95.31	105.62	89.03	101.36	93.02	101.30

significance values for slow, fast release test formulations and reference formulation of dextromethorphan hydrobromide between subject effects, period, sequence and treatment effects are non-significant. The 95% confidence interval for slow, fast test formulations and reference formulation i.e. C_{max} ranges from 0.46175 to 0.59158 and from 0.51723 to 0.63277, respectively, for AUC_{0-t} ranges from 1.74071 to 1.98655 and from 1.86336 to 2.10635, respectively, for $AUC_{0-¥}$ ranges from 1.5558 to 1.8741 and from 1.46819 to 1.66181, respectively, The mean

differences for C_{max} were 0.52667 and 0.57500, for AUC_{0-t} were 1.8633 and 1.9700 and $AUC_{0-¥}$ were 1.5650 and 1.7150, respectively. The mean percentage ratio for C_{max} was 169.32 and 177.71, for AUC_{0-t} were 478.26 and 555.66, for $AUC_{0-¥}$ was 644.51 and 717.06 respectively. The percentage confidence interval for C_{max} ranges from 93.71 to 106.70 and from 94.38 to 105.56, for AUC_{0-t} ranges from 90.77 to 110.16 and from 85.28 to 117.24 and for $AUC_{0-¥}$ ranges from 88.40 to 113.11 and from 87.25 to 114.60 respectively. All statistical analyses were performed on using SAS® 9.1 version software.

Table 3: Similarity factors for dextromethorphan hydrobromide modified release dosage forms in various dissolution conditions

S. no	pH	Conditions	Formulation	Similarity factor (f2)
1	pH 1.2 buffer	50 rpm	Fast versus slow	60.61
2	pH 1.2 buffer	75 rpm	Fast versus slow	61.49
3	pH 4.5 buffer	50 rpm	Fast versus slow	42.06
4	pH 4.5 buffer	75 rpm	Fast versus slow	59.62
5	pH 6.8 buffer	50 rpm	Fast versus slow	48.79
6	pH 6.8 buffer	75 rpm	Fast versus slow	52.02
7	pH 5.5 buffer	50 rpm	Fast versus slow	60.72
8	pH 5.5 buffer	75 rpm	Fast versus slow	43.64
9	pH 7.4 buffer	50 rpm	Fast versus slow	34.44
10	pH 7.4 buffer	75 rpm	Fast versus slow	41.49

Establishment of the IVIVC

Level A IVIVC is the most informative and very useful from a regulatory point of view because it involves a point-to-point comparison between *in vitro* dissolution and the *in vivo* input rate. An IVIVC plot was constructed using a percentage of the drug dissolved at pH 7.4 buffer dissolution media at 50 rpm and 75 rpm versus the percentage of drug absorbed. The slope of the best-fit line was examined using linear regression analysis and the coefficient of determination (r^2), slope and intercept values calculated are presented in Tables 5 and 6 and in Figs. 4 and 5.

The correlation coefficient (r^2) value for pH 7.4 buffer at 50 rpm and 75 rpm was 0.9177 and 0.9604, respectively. A good linear regression relationship was thus observed at pH 7.4 buffer and 75 rpm. Linear regression analysis was applied to the IVIVC plots and the coefficient of correlation (r^2), slope and intercept values calculated are presented in Figs. 6-8. The correlation coefficients (r^2) value was 0.9997.

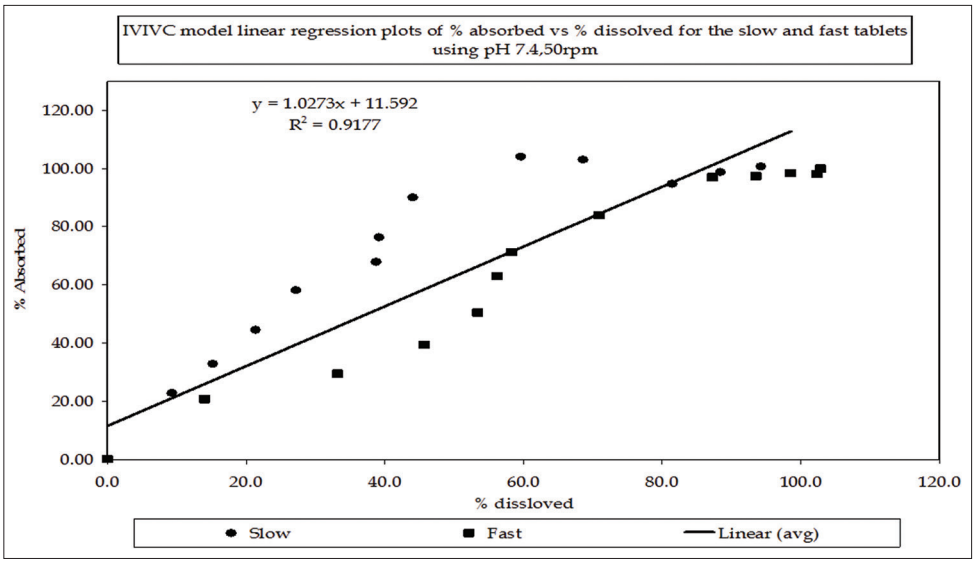

Fig. 4: *In vitro* and in vivo correlation model regression plots of % absorbed versus dissolved for the slow and fast tablets using pH 7.4, 50 rpm

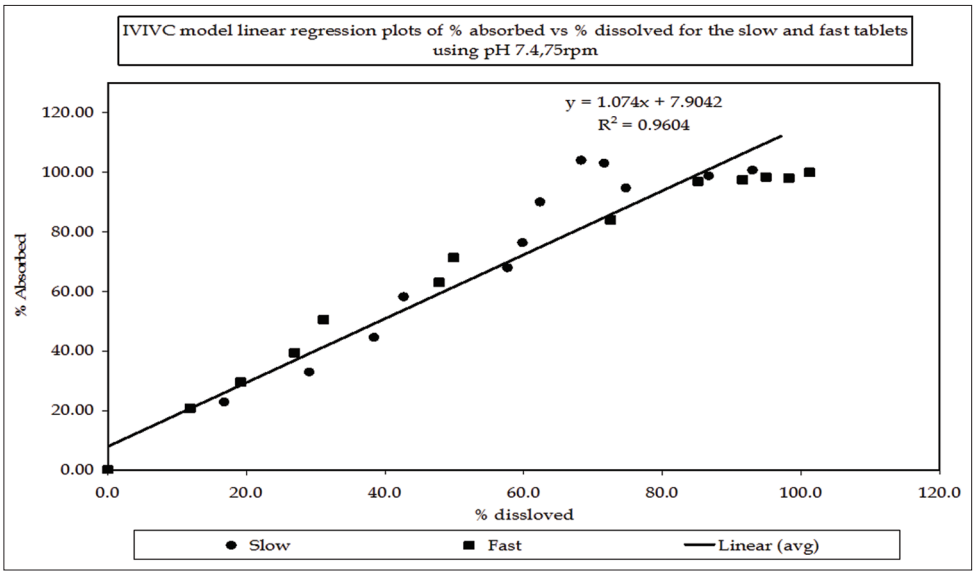

Fig. 5: *In vitro* and *in vivo* correlation model regression plots of % absorbed versus dissolved for the slow and fast tablets using pH 7.4, 50 rpm

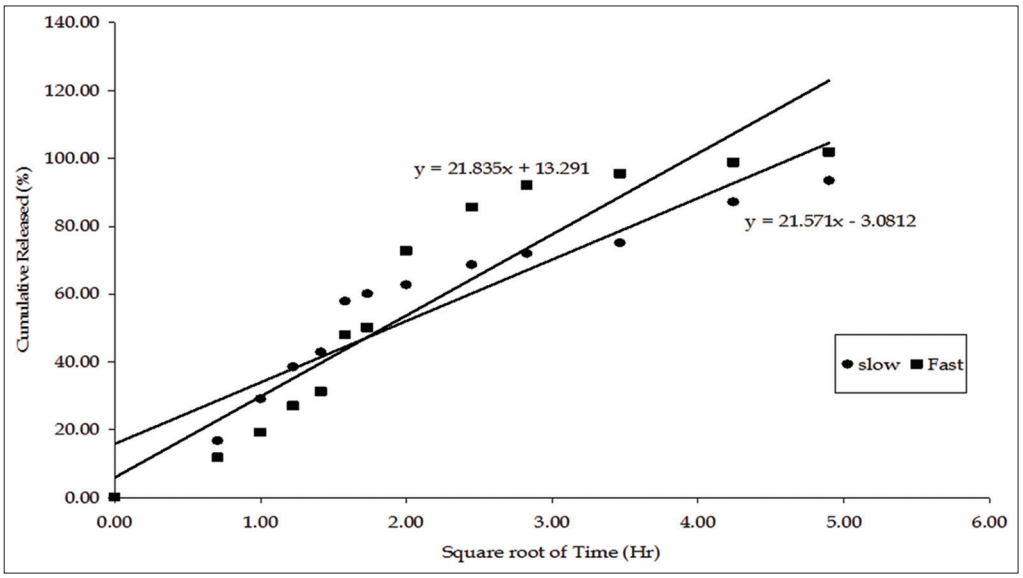

Fig. 6: Cumulative dextromethorphan hydrobromide release versus square root of time profile for slow and fast modified release tablets using pH 7.4, 50 rpm

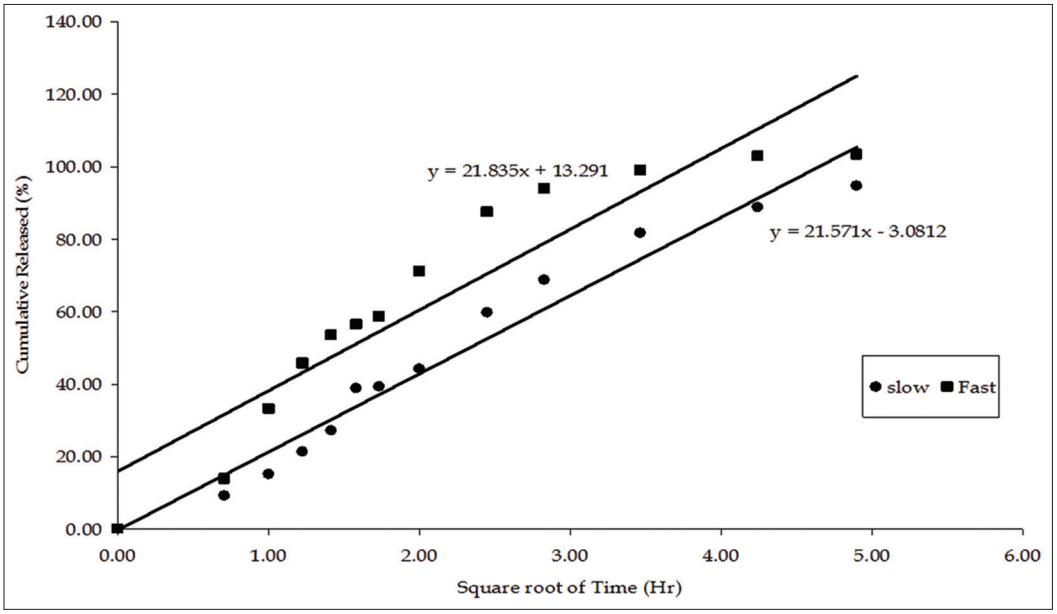

Fig. 7: Cumulative dextromethorphan hydrobromide release versus square root of time profile for slow and fast modified release tablets using pH 7.4, 75 rpm

Table 4: Mean pharmacokinetic profile (n=6)

Dextromethorphan hydrobromide	C_{max}	T_{max}	AUC_{0-t}	$t_{1/2}$	k_{el}	$AUC_{0-\infty}$
Immediate release	1229.608 (59.694)	1.667 (0.258)	5281.061 (518.573)	2.519 (0.207)	0.277 (0.025)	6239.811 (443.451)
Slow release	2086.819 (152.939)	6.333 (0.816)	25132.049 (778.166)	5.507 (0.539)	0.127 (0.012)	40168.688 (3147.203)
Fast release	2191.666 (108.581)	5.333 (1.033)	29329.740 (3183.219)	5.381 (0.495)	0.130 (0.013)	44849.886 (4394.895)

AUC: Area under the plasma concentration

Internal validation

IVIVC predictive performance was carried out by using the mean in vitro dissolution data and mean *in vivo* pharmacokinetics of the selected modified release formulations. To calculate median observed and predicted plasma concentration-time curves for respective formulations were compared. Calculation was done based on percentage prediction error (PE) for AUC and C_{max} for both the formulation.

$$\%PE=\left[\frac{\text{Observed}-\text{Predicted}}{\text{Observed}}\right]\times 100 \quad (2)$$

Percentage PEs for C_{max} and AUC were calculated and are presented in Tables 7 and 8 and in Figs. 9 and 10. The C_{max} PEs for both the slow and fast formulations found to be −6.98 and −8.55 and for AUC was 7.76 and 8.82%, respectively. The PE for C_{max} and AUC were within acceptance

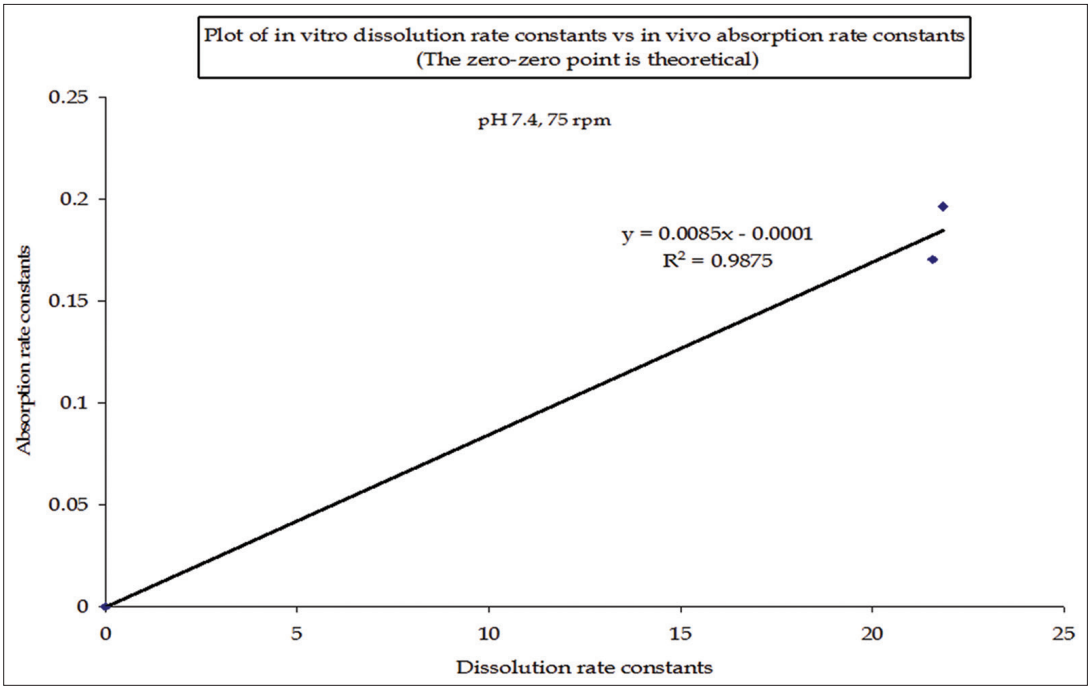

Fig. 8: Plot of *in vitro* dissolution rate constants versus *in vivo* absorption rate constants

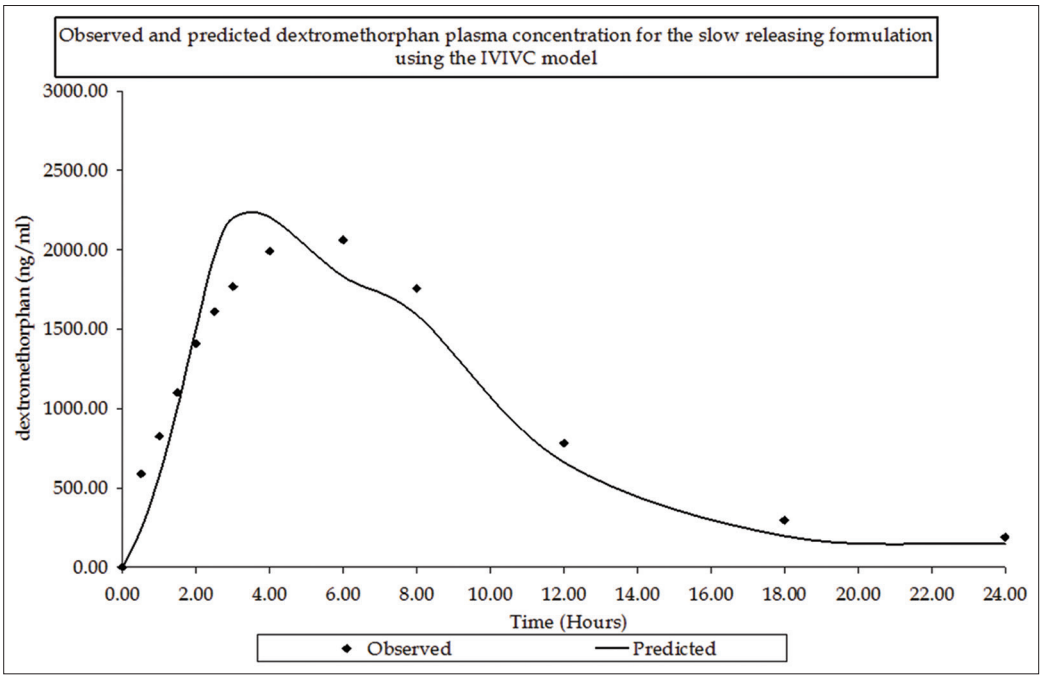

Fig. 9: Observed and predicted dextromethorphan plasma concentration for the slow release formulation using *in vitro* and *in vivo* correlation model

criteria and therefore, established IVIVC was successfully validated and in turn confirm the similarity of *in vitro* and *in vivo* conditions.

CONCLUSION

The validity of the correlation was assessed and determined how well the IVIVC model could predict the rate and extent of absorption as characterized by C_{max} and AUC. The percent PE of £10% for C_{max} and AUC was obtained, which establish the predictability of the developed IVIVC model. IVIVC can be used in the development of new pharmaceuticals product to decrease the number of human studies conducted during formulation development. It supports and/or validates the use of dissolution methods and specification settings. It can be concluded that the developed dissolution methods can surrogate for human bioequivalence studies.

ACKNOWLEDGMENT

The authors would like to thank management for providing facilities to carry out this work.

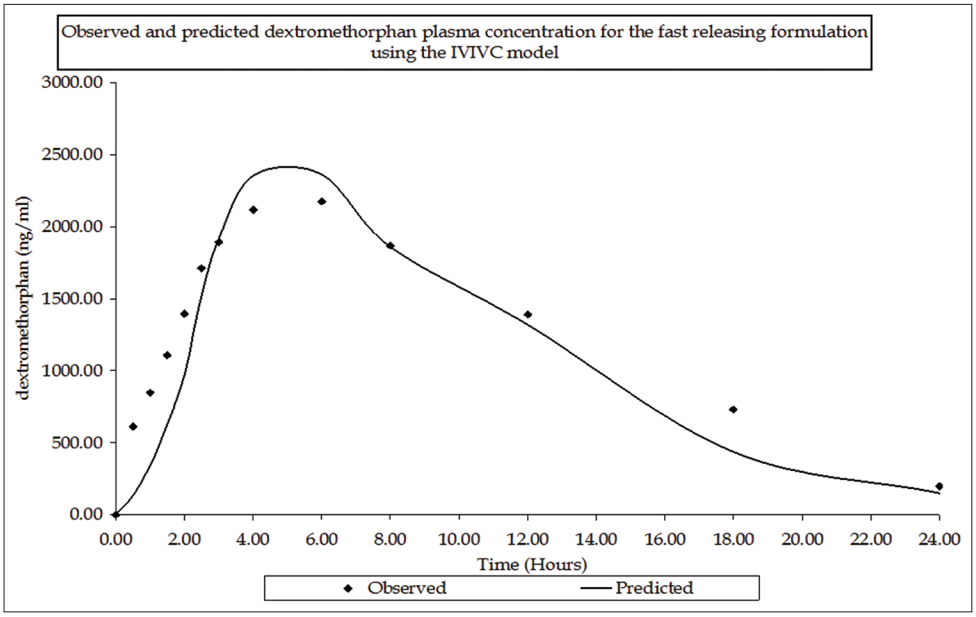

Fig. 10: Observed and predicted dextromethorphan plasma concentration for the fast release formulation using *in vitro* and *in vivo* correlation model

Table 5: IVIVC model linear regression of % absorbed versus % dissolved for dextromethorphan hydrobromide tablets using pH 7.4 at 50 rpm

Time	Percentage dissolved (pH 7.4)		Percentage absorbed	
	Slow	Fast	Slow	Fast
0.0	0.0	0.0	0.00	0.00
0.5	9.31	13.98	22.90	20.74
1	15.21	33.21	32.91	29.44
1.5	21.35	45.70	44.63	39.36
2	27.20	53.42	58.17	50.48
2.5	38.77	56.22	67.97	62.99
3	39.20	58.32	76.36	71.29
4	44.08	70.94	90.13	84.00
6	59.64	87.26	104.06	97.03
8	68.59	93.58	103.10	97.38
12	81.47	98.56	94.73	98.38
18	88.44	102.39	98.82	98.12
24	94.29	102.87	100.76	99.92

IVIVC: *In vitro* and *in vivo* correlation

Table 6: IVIVC model linear regression of % absorbed versus % dissolved for dextromethorphan hydrobromide tablets using pH 7.4 at 75 rpm

Time	Percentage dissolved (pH 7.4)		Percentage absorbed	
	Slow	Fast	Slow	Fast
0.0	0.0	0.0	0.00	0.00
0.5	16.83	11.89	22.90	20.74
1	29.06	19.18	32.91	29.44
1.5	38.42	26.98	44.63	39.36
2	42.72	31.16	58.17	50.48
2.5	57.67	47.85	67.97	62.99
3	59.83	49.90	76.36	71.29
4	62.40	72.54	90.13	84.00
6	68.34	85.15	104.06	97.03
8	71.63	91.61	103.10	97.38
12	74.74	94.98	94.73	98.38
18	86.73	98.28	98.82	98.12
24	93.02	101.30	100.76	99.92

IVIVC: *In vitro* and *in vivo* correlation

Table 7: Observed and IVIVC model predicted C_{max} and AUC values for dextromethorphan hydrobromide dextromethorphan hydrobromide

Time (hrs)	Slow formulation		Fast formulation	
	Fraction observed	Fraction predicted	Fraction observed	Fraction predicted
0.00	0.00	0.00	0.00	0.00
0.50	590.29	238.27	613.667	134.75
1.00	827.11	580.92	847.431	343.92
1.50	1099.56	1008.84	1108.546	623.70
2.00	1409.05	1502.71	1394.795	967.12
2.50	1611.04	1964.67	1711.424	1521.07
3.00	1769.50	2202.29	1891.284	1915.87
4.00	1993.32	2206.11	2118.199	2354.36
6.00	2062.12	1831.54	2175.319	2361.35
00	1757.24	1591.02	1869.885	1860.99
12.00	783.48	661.85	1390.184	1319.40
18.00	296.67	197.09	732.045	437.16
24.00	189.73	148.98	197.520	151.17
AUC	22748.21	20983.45	29329.74	26742.92
C_{max}	2062.12	2206.11	2175.32	2361.35

IVIVC: *In vitro* and *in vivo* correlation, AUC: Area under the plasma concentration

Table 8: PEs (%) associated with C_{max} and AUC for dextromethorphan hydrobromide

Formulation	C_{max}	AUC
Slow	−6.98	7.76
Fast	−8.55	8.82
Average	−7.765	8.29

AUC: Area under the plasma concentration, PE: Prediction errors

REFERENCES

1. Food and Drug Administration. Guidance for industry: Extended release oral dosage forms: Development, evaluation, and application of *in vitro/in vivo* correlations. Rockville: FDA; 1997.
2. Silvasti M, Karttunen P, Tukiainen H, Kokkonen P, Hänninen U, Nykänen S. Pharmacokinetics of dextromethorphan and dextrorphan: a single dose comparison of three preparations in human volunteers. Int J Clin Pharmacol Ther Toxicol 1987;25(9):493-7.
3. Meyyanathan SN, Rajan S, Muralidaharan S, Siddaiah MK, Krishnaraj K, Suresh B. Formulation and evaluation of dextromethorphan hydrobromide sustained release tablets. Drug Deliv 2008;15(7):429-35.
4. Takka S, Sakr A, Goldberg A. Development and validation of an *in vitro-in vivo* correlation for buspirone hydrochloride extended release tablets. J Control Release 2003;88(1):147-57.
5. Eddington ND, Marroum P, Uppoor R, Hussain A, Augsburger L. Development and internal validation of an *in vitro-in vivo* correlation for a hydrophilic metoprolol tartrate extended release tablet formulation. Pharm Res 1998;15(3):466-73.
6. Mirza T, Bykadi SA, Ellison CD, Yang Y, Davit BM, Khan MA. Use of *in vitro-in vivo* correlation to predict the pharmacokinetics of several products containing a BCS class 1 drug in extended release matrices. Pharm Res 2013;30(1):179-90.
7. Galia E, Nicolaides E, Hörter D, Löbenberg R, Reppas C, Dressman JB. Evaluation of various dissolution media for predicting *in vivo* performance of class I and II drugs. Pharm Res 1998;15(5):698-705.
8. Hayes S, Dunne A, Smart T, Davis J. Interpretation and optimization of the dissolution specifications for a modified release product with an *in vivo-in vitro* correlation (IVIVC). J Pharm Sci 2004;93(3):571-81.
9. Fujisaki Y, Tsukune T, Funyû M, Okumura M, Ukigaya T, Sugibayashi K. Development of sustained-release tablets containing sodium valproate: *in vitro* and *in vivo* correlation. Drug Dev Ind Pharm 2006;32(2):207-17.
10. Balan G, Timmins P, Greene DS, Marathe PH. *In vitro-in vivo* correlation (IVIVC) models for metformin after administration of modified-release (MR) oral dosage forms to healthy human volunteers. J Pharm Sci 2001;90(8):1176-85.
11. Sorasucharti W, Ayres JW. Preliminary bioequivalence testing of two nicardipine hcl sustained-release formulations with *in vitro/in vivo* correlations. European J Drug Metab Pharmacokinet 2001;26(1-2):I-7.
12. Meyer MC, Straughn AB, Mhatre RM, Shah VP, Williams RL, Lesko LJ. The relative bioavailability and *in vivo-in vitro* correlations for four marketed carbamazepine tablets. Pharm Res 1998;15(11):1787-91.
13. Szakács T, Veres Z, Vereczkey L. *In vitro-in vivo* correlation of the pharmacokinetics of vinpocetine. Pol J Pharmacol 2001;53(6):623-8.
14. Qiu Y, Garren J, Samara E, Cao G, Abraham C, Cheskin HS, *et al.* Once-a-day controlled-release dosage form of divalproex sodium II: development of a predictive *in vitro* drug release method. J Pharm Sci 2003;92(11):2317-25.
15. Sirisuth N. Systematic method for the development and validation of an IVIVC metoprolol and naproxen drug examples. Int J Gen Drug 2002;3:250-8.
16. Eddington ND. *In vitro in vivo* correlation with metoprolol extended release tablets using two different releasing formulations: An internal validation evaluation. Int J Gen Drug: 417-29.
17. Lootvoet G, Beyssac E, Shiu, G.K, Aiache JM, Ritschel WA. Study on the release of indomethacin from suppositories: *In vitro-in vivo* correlation. Int J Pharm 1992;85(1-3):113-20. Available from: http://www.dx.doi.org/10.1016/0378-5173(92)90140-W.
18. Dressman JB, Reppas C. *In vitro-in vivo* correlations for lipophilic, poorly water-soluble drugs. Eur J Pharm Sci 2000;11 Suppl 2:S73-80.