ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Development of bio-relevant dissolution method for prognosis of In-vivo performance of Dipyridamole from modified release capsules

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

[1]Department of Pharmacy, Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, India, 608002
[2]Malla Reddy Pharmacy College, Maisammaguda, Hyderabad, India, 500014

Article History:

Received on: 20 Mar 2020
Revised on: 15 Apr 2020
Accepted on: 22 Apr 2020

Keywords:

Dipyridamole, biorelavant, deconvolution, pre-prandial

ABSTRACT

In-vitro biorelevant dissolution test method was developed for Dipyridamole in modified release multiparticulate dosage form, to simulate the product drug release after oral administration to human. The Dipyridamole concentration in blood plasma achieved after oral administration under pre-prandial(fasting) condition were used for deriving the target dissolution profile by deconvoluting the plasma concentration using numerical deconvolution technique. The fraction of drug absorbed was considered as the target dissolution profile. The drug product was tested by using the dissolution method recommended by office of generic drugs, and the dissolution results observed are not comparable with the target dissolution profile. Dissolution method was developed using reciprocating cylinder, Bio-Dis (apparatus -3 as per USP), by simulating the pre-prandial conditions. A full factorial design of experiment was carried out to achieve the target dissolution profile. Media volume and dips per minute (DPM) are considered as main factors, in design of experiment. The dissolution results achieved with media volume 250ml and 10DPM were found to be comparable with target dissolution profile and observed with the F_2 value (similarity factor) of 92%. The developed dissolution method demonstrates a very good in-vitro/in-vivo correlation under pre-prandial condition, and shall be used as a predictive in-vitro tool for evaluation Dipyridamole extended release capsules.

*Corresponding Author

Name: Devi Thamizhanban
Phone: +919840946681
Email: devrajmphd@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i2.2211

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Dipyridamole(DPM) is a nucleoside transport inhibitor and antiplatelet agent. Chemical name is 2,2',2",2"'-[(4,8- Dipiperidinopyrimido [5,4d] pyrimidine-2,6-diyl) dinitrilo] -tetraethanol. Dipyridamole is intensely yellow, crystalline powder or needles. Very soluble in methanol, in alcohol, and in chloroform, slightly soluble in water, very slightly soluble in acetone and in ethyl acetate. The antiplatelet mechanism of action involves by inhibiting the uptake of adenosine into platelets, endothelial cells and erythrocytes. The rate of inhibition occurs in a dose dependent manner at therapeutic concentrations (0.5-1.9 μg/mL) (Dipyridamole, 2008; Zhang *et al.*, 1997). Aggrenox capsules is the combination of Dipyridamole in a multi particulate extended release form and Aspirin in immediate release tablet form filled in a hard gelatin capsule. The present study is aimed to develop the dissolution method for Dipyridamole

Table 1: Segmentof human GI tract and pre- prandial residence time

GI tract Segment	pH & Media		Residence time (min)
	Biorelevant medium	pH	
Stomach	FaSSGF	1.6	60
Duodenum/Jejunum	New-FaSSIF	6.5	45
Jejunum/Ileum	Half-FaSSIF	7.0	45
Distal ileum	FaSSIF-sans	7.5	120
Colon	SCoF	5.8	450

Table 2: A Full factor factorial design for dissolution method development

Factors	Levels	Values	Responses			
DPM	4	7, 10, 15, 20	1hr dissolution	4hrs dissolution	8hrs dissolution	12hrs dissolution
Volume	2	100, 250				

Table 3: Dissolution media composition simulating the conditions in the GI tract

Medium	SCoF	FaSSGF	New-FaSSIF	Half-FaSSIF	FaSSIF-sans
Sodium tauro-cholate	-	80μM	3.0 mM	1.5 mM	-
Lecithin	-	20μM	0.2 mM	0.2 mM	-
Pepsin	-	0.1mg/mL	-	-	-
pH	5.8	1.6	6.5	7.0	7.5
Osmolality (mOsm/kg)	295	120.7	180	270	270
Buffer capacity (mEq $L-1$ $\Delta pH-1$)	29		10	10	10

Table 4: Physical parameters of Aggrenox capsules

S. No.	Parameter	Observations
1	Product brand name	Aggrenox(R)
2	Batch/Lot No	007395
3	Exp. date	May 2020
4	Average weight of capsule	712.0mg
5	Average fill weight	615.0mg
6	Average weight of filled pellets	504.0mg
7	Average weight of filled tablet	110mg
8	Thickness of tablet	3.50mm
9	Capsule shell size and lock length	23.30mm (size ”0EL”)

Table 5: Target dissolution profile deconvoluted from *In-vivo* data

Time (hrs)	In-vivo data		
	Mean drug plasma concentration in human (pre-prandial) Cp (μg/mL)	Fraction Absorbed (Numerical Deconvolution by Wagner nelson method)	%Absorbed (Target profile)
0	0	0.00	0.00
0.5	0.135	0.01	0.93
1	1.875	0.13	13.15
1.5	2.175	0.19	18.67
2	2.245	0.23	23.17
2.5	2.435	0.29	28.61
3	2.527	0.34	33.73
4	2.243	0.41	40.84
5	2.187	0.49	48.67
6	2.232	0.57	57.09
8	2.198	0.73	73.22
10	1.897	0.87	86.53
12	0.854	0.90	90.46
18	0.234	0.99	98.80
24	0.0002	1.00	100.00
36	0	1.00	100.00

Table 6: Dissolution profile of Aggrenox at different RPM, in 0.1N HCl for 1hr followed by 0.1MpH 5.5 phosphate buffer for 7 hrs

Batch number		079358			Target profile (from plasma profile)
Time	Acceptance Criteria	75 RPM	100 RPM	125 RPM	
1hr	15-32%	23.0 $\pm$ 0.2	20.1 $\pm$ 0.2	22.9 $\pm$ 0.5	13
2 hrs		46.2 $\pm$ 0.4	42.8 $\pm$ 0.3	42.9 $\pm$ 0.2	23
3 hrs	50-70%	62.1 $\pm$ 0.5	61.1 $\pm$ 0.4	62.5 $\pm$ 0.4	34
6 hrs		76.2 $\pm$ 0.4	76.4 $\pm$ 0.5	75.3 $\pm$ 0.4	57
8 hrs	NLT 80%	89.8 $\pm$ 0.3	89.6 $\pm$ 0.2	89.1 $\pm$ 0.5	73
F2 (Against target)		35	36	35	
F2 (Against 100 RPM)		82	-	87	

Note : mean $\pm$ SD, n=3

part.

Dissolution is a measurement criteria to evaluate the rate of drug release from finished product. The rate of dissolution shall be extrapolated to rate of drug absorption into human body to predict the in-vivo performance of medicinal product. The correlation between drug release rate in dissolution media and drug absorption rate in human body is termed as In-vitro/In-vivo Correlation (IVIVC) or In-vitro/In-vivo Relationship (IVIVR) (FDA, 1997). The regulatory guidelines are acknowledging biopharmaceutics based dissolution study results, for waving the bio study for formulation containing multiple strengths. The in-vivo predictive dissolution method requires most of the time the dissolution media and residence time by reflecting gastro intestinal conditions. Several dissolution media were developed by simulating human gastro intesti-

Table 7: Risk assessment for media volume and DPM for the product

Factors	Severity	Probability	Delectability	Risk Number	Justification
Media volume	3	3	3	27	Dissolution media volume is directly related to intrinsic solubility of drug, hence the risk is high.
DPM	3	2	2	12	The agitation speed disrupts the structure to have faster erosion of pellets.

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

Table 8: A Full factorial study and Responses of the factors

Std Order	Run Order	Factors		Responses			
		DPM	Volume	Dissoln 1hr	Dissoln 4hr	Dissoln 8hr	Dissoln 12hr
5	1	15	100	9.2 ± 0.1	33.5 ± 0.3	56.3 ± 0.2	85.5 ± 0.1
6	2	15	250	13.6 ± 0.8	43.6 ± 0.2	76.3 ± 0.2	97.7 ± 1.1
4	3	10	250	13.2 ± 0.3	42.4 ± 0.3	72.1 ± 0.3	91.9 ± 0.7
8	4	20	250	15.1 ± 0.2	44.7 ± 0.56	80.8 ± 0.3	97.5 ± 0.9
2	5	7	250	7.8 ±0.5	33.6 ± 0.5	58.7 ± 0.3	90.1 ± 0.2
7	6	20	100	9.7 ± 0.2	34.5 ± 0.2	58.3 ± 0.2	88.4 ± 0.2
3	7	10	100	8.6 ± 0.2	32.6 ± 0.2	55.6 ± 0.3	70.9 ± 0.3
1	8	7	100	5 ± 0.2	30.5 ± 0.4	53.5 ± 0.3	65.5 ± 0.2

Note: mean ± SD, n=3

nal system, like fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) (Galia *et al.*, 1998; Jantratid *et al.*, 2008, 2009). The dissolution system can serve a strong indicator based on appropriate IVIVC/R.

While developing the dissolution method to simulate the in-vivo performance of drug product, the dissolution media selection for the particular period of time should match with the environment of gastro intestinal track, to maintain sink condition. Segment of human gastro intestinal track and time at each pH condition is presented in Table 1.

In general the pharmacopoeial dissolution specification are having the limit for maximum extent of drug release, and the dissolution media recommended do not represent the gastrointestinal (GI) tract environment in a comprehensive manner. For development of bio-relevant dissolution method, bio-relevant dissolution media plays a crucial role, which was developed by closely representing pre-prandial condition and post prandial condition (Klein, 2010; Vertzoni *et al.*, 2004).

USP Apparatus 3 - Reciprocating cylinder is used for solid dosage form drug products, mostly non-

Table 9: ANOVA results for Design of Experiment

		Dissolution at 1 hr		Dissolution at 4 hrs		Dissolution at 8 hrs		Dissolution at 12 hrs	
Source	DF	Adj SS	Adj MS	Adj SS	Adj MS	Adj SS	Adj MS	Adj SS	Adj MS
Model	7	81.29	11.61	224.01	32.00	799.12	114.16	975.89	139.41
Linear	4	79.42	19.86	206.22	51.56	712.21	178.05	897.07	224.27
DPM	3	42.30	14.10	67.61	22.54	198.08	66.03	337.62	112.54
Volume	1	37.12	37.12	138.61	138.61	514.14	514.14	559.45	559.45
2-Way Interactions	3	1.87	0.62	17.79	5.93	86.91	28.97	78.82	26.27
DPM*Volume	3	1.87	0.62	17.79	5.93	86.91	28.97	78.82	26.27
Error	0								
Total	7	81.29		224.01		799.12		975.89	
Model summary (R^2)		100%		100%		100%		100%	

Table 10: Target and ranges recommended for the dissolution study

Response	Goal	Lower	Target	Upper
Dissoln 12hr	Target	66	90	98
Dissoln 8hr	Target	53	73	81
Dissoln 4hr	Target	30	41	45
Dissoln 1hr	Target	5	13	15

Table 11: A comparative *In-vitro* and *In-vivo* dissolution

Dissolution media and time	Cumulative time	Cumulative % drug Release	Target profile
FaSSGF pH 1.6 for 60 mins	1 hr	13.2 ± 0.3	13
pH 6.5 FASSIF for 45 mins and pH 7.0 Half-FaSSIF for 15 mins	2hrs	24.2 ± 0.4	23
pH 7.0 Half-FaSSIF for 30 mins & pH 7.5 FaSSIF-sans for 30 min	3 hrs	34.7 ± 0.2	34
90 mins	4 hrs	42.4 ± 0.3	41
pH 5.8 SCoF for 90mins	6hrs	56.5 ± 0.3	57
210 mins	8 hrs	72.1 ± 0.3	73
330 mins	10 hrs	82.3 ± 0.4	87
450 mins	12 hrs	91.9 ± 0.7	90
F_2		92	

Note : mean ± SD, n=3

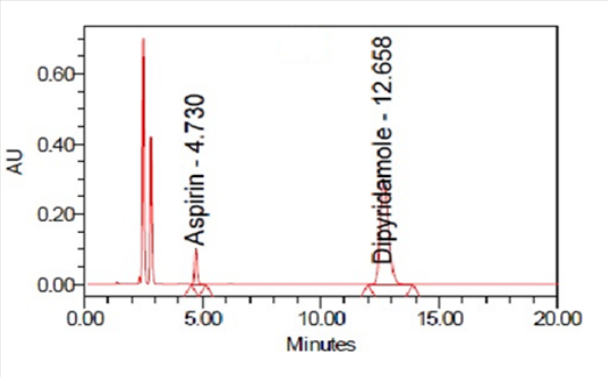

Figure 1: A typical chromatogram of standard for Aspirin and Dipyridamole

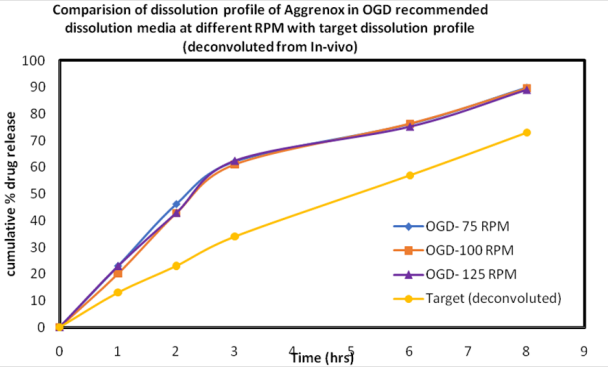

Figure 2: Dissolution profile of Aggrenox in OGD dissolution media at different RPM with target dissolution profile(deconvoluted from *In-vivo*)

disintegrating single units (e.g. tablets), and multiple units (e.g. encapsulated beads). Highly recommended to use for extended release products. USP Apparatus -3 is programmable to run dissolution in various media with different speed at set time intervals. pH changes shall be simulated to gastro intestinal physiology.

A Level-A In-vitro/in-vivo correlation is established by comparing the percentage or fraction of drug dissolved, which was achieved from dissolution results, to the percentage or fraction of drug absorbed, which was achieved by deconvoluting the plasma drug concentration by numerical deconvolution method (Cardot and Davit, 2012).

MATERIALS AND METHODS

Aggrenox$^{(R)}$ was procured from United sates of America. Working standards and impurities for Aspirin was obtained as gift samples from Andhra sugars, for DPM was obtained from Mylan. The finished dosage form Aggrenox was procured from pharmacy.

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 Haën), Sodium taurocholate (Prodotti Chimici), Tetrahydro furan (Merck), Pancreatin powder (Scientific Protein Laboratories LLC)were procured from indigenous vendors and used for evaluation.

Instrumentation

Dissolution was performed using Dissolution apparatus USP-I (Electrolab) and dissolution apparatus USP-III (Vankel 25-1000 BIO-DIS Reciprocating cylinder). The analysis was carried out using Agilent 1200 RP-HPLC system consisting of a pump, an injector, and photodiode array (PDA)/UV-Visible 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 (0.45micron) used for sample filtration were purchased from Rankem, India.

Deconvolution of pharmacokinetic data

The mean plasma concentration data obtained from the study at pre-prandial condition of Dipyridamole from Aggrenox (SBOA) was deconvoluted using WinNonlin ® software to determine the fraction of drug absorbed. Fraction of drug absorbed has been fixed as a target profile to select the suitable biorelavant dissolution media.

Quality control testing

The office of generic drugs recommended finished product release test condition was using USP apparatus-I with 900 mL 0.1N HCl for 1hr, followed by 0.1M pH 5.5 phosphate buffers for 7 hrs as dissolution medium, at 100 rpm, and a temperature of 37°C. The effect of speed on dissolution was evaluated at 75, 100 & 125RPM. 3 units were evaluated for each test condition. The samples were withdrawn at 1 hr, 2 hr, 3hr, 6hr & 8hrs. Sampling was performed through automatic sampling device, fitted with filter. Approximately 5 mL was withdrawn at each sampling interval, the solution was replaced with fresh dissolution media to the vessel. the filtered samples were analysed using HPLC (Anilkumar *et al.*, 2018).

Biorelevant testing

A biorelavant dissolution media used, to simulate the pre-prandial condition, using USP dissolution test apparatus-3 (Reciprocating cylinder) to simulate release of Dipyridamole from Aggrenox in the GI tract. The top and bottom mesh size for the Bio-dis vessel was 405μm (40 mesh). The dissolu-

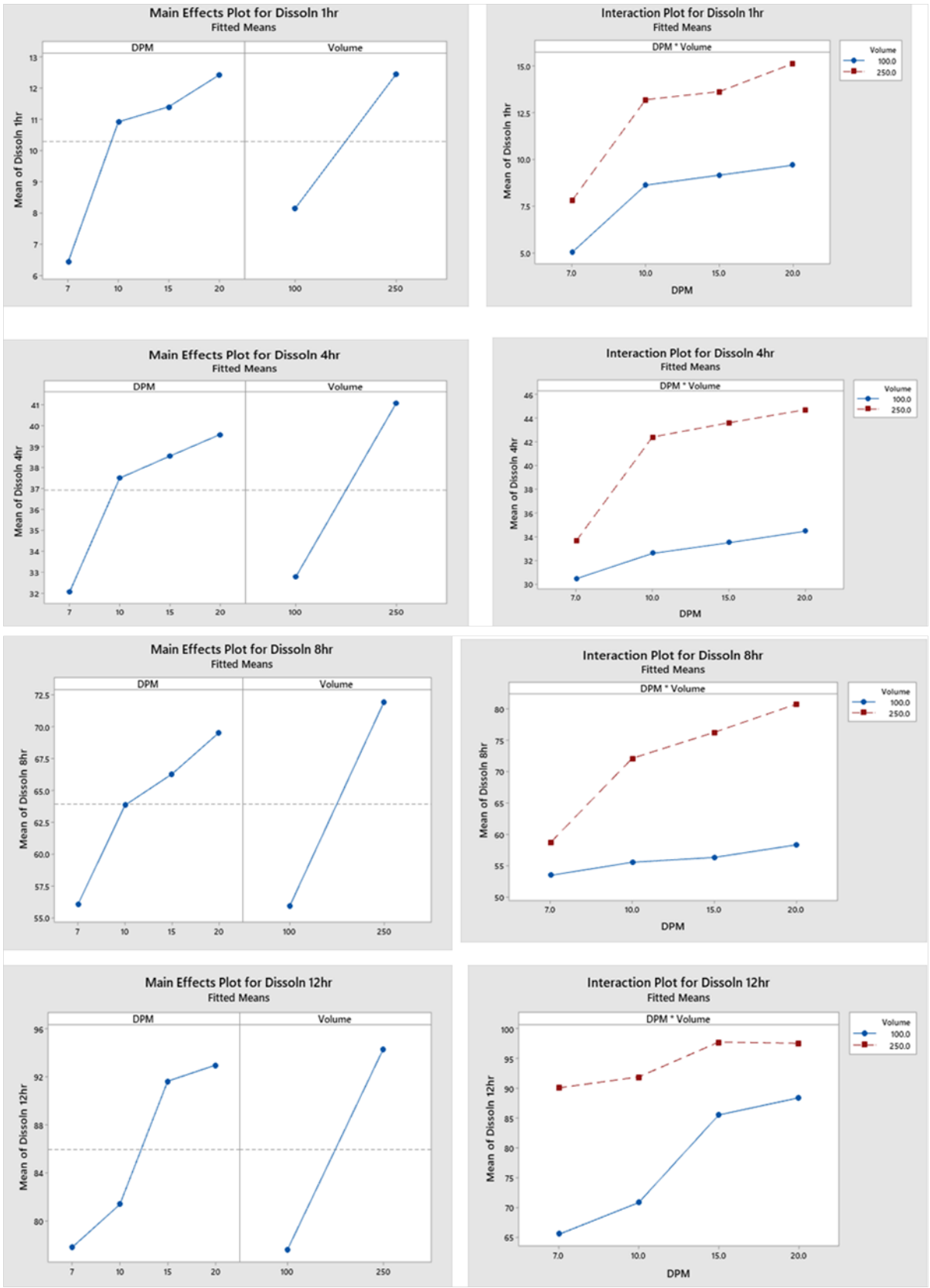

Figure 3: Main effect of DPM and media volume on dissolution profile and interaction effect

tion experimental design was executed using design of experiment (DOE), using minitab software, a full factorial design, with 2 factors of dips per minute (DPM) at 4 levels & Media volume at 2 levels, the response was evaluated at four time points for dissolution. (Wei and Löbenberg, 2006; Jantratid *et al.*, 2009). The factor levels and response to be measured were presented in Table 2 & the detailed compositions has been presented in Table 3.

Preparation of Fated state simulated gastric fluid (FaSSGF) : 0.16 g Lecithin was dissolved in 1.6 ml of Dichloromethane, and added to 5 liters of purified water. 0.42 g of Sodium taurocholate was added to the above solution and stirred for 45 minutes. 1 g Pepsin and 20 g of NaCl was added to the above solution, heated at 40°C, using hot plate under continuous stirring for 30 minutes. The pH was adjusted to 1.6 using 1N HCl. The volume was made up to 10 liters.

Preparation of blank Fasted state simulated intestinal fluid (FaSSIF) pH 6.5, pH 7.0 & pH 7.5: 19.77g of sodium dihydrogen phosphate monohydrate, 1.7g of sodium hydroxide pellets and 30.93g of sodium chloride were dissolved in 5L of purified water, by stirring for 30 minutes. The pH was adjusted to exactly pH 6.5 or pH 7.0 or pH 7.5 using 1N sodium hydroxide solution or 1N Hydrochloric acid solution.

Preparation of Fasted state simulated intestinal fluid(FaSSIF) pH 6.5 , pH7.0 & pH 7.5: 3.3 g sodium taurocholate was dissolved in approximately 500 mL of the blank FaSSIF of specifc pH solution. 10g of Lecithin was dissolved in 100ml of methylene chloride by mixing to the achive the concentartion on 100mg/ml. 11.8 mL of a Methylene chloride solution containing 100 mg/mL lecithin was added to balnk FaSSIF, and stirred well for 15 minutes. A milky emulsion obtained. The solution was introduced into rotavapor, and methylene chloride was evaporated by heating at 40 °C, under vaccum with the RPM of 50. The result was a clear, micellar solution having no perceptible odor of Methylene chloride. After cooling to room temperature, the weight of the solution was checked again. The water lost to evaporation was replaced with demineralized water to obtain a total weight. Finally, the volume was made upto 2L using blank FaSSIF.

Preparation of Simulated colonic fluid pH 5.8: 1.44g of dibasic sodium phosphate, 8g of sodium chloride, 0.2g of potassium chloride and 0.24g of monobasic potassium phosphate in were dissolved in 1litre of purified water. pH was adjusted to pH5.8 using 1N sodium hydroxide solution or 1N Hydrochloric acid solution (Marques *et al.*, 2011).

Samples were with withdrawn at the following time interval 60, 105, 120, 150, 180, 240, 360, 480,600 and 720 min, and replaced with fresh dissolution media. The temperature in the vessels were maintained at 37±0.5 ○C. The sample volume withdrawn was approximately 5 mL, and analysed using HPLC.

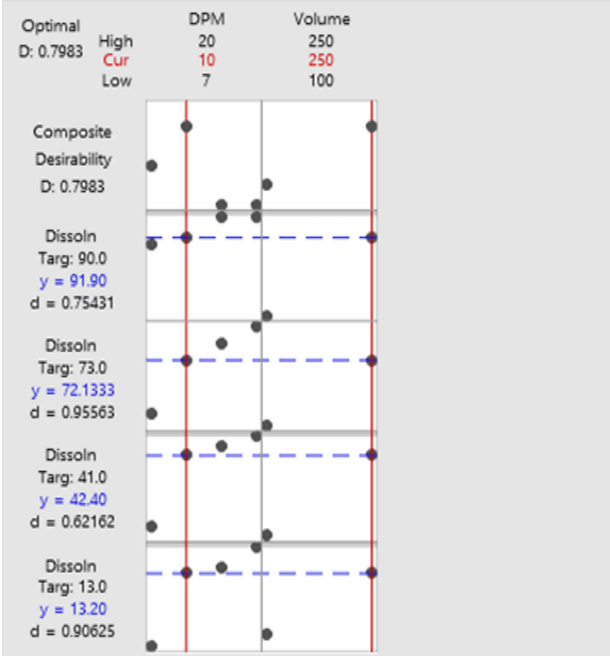

Figure 4: Response optimisation for dissolution at 1hr, 4hrs, 8hrs & 12hrs

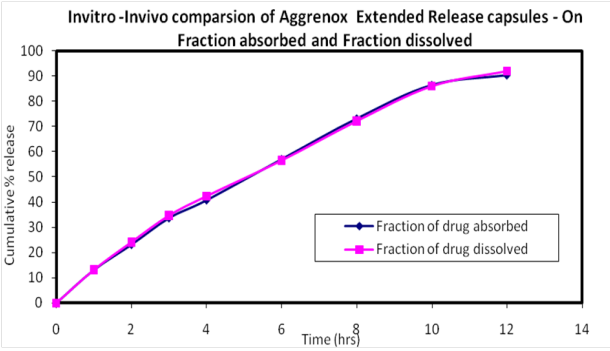

Figure 5: Comparison of Aggrenox Extended Release capsules - On Fraction of drug absorbed and Fraction of drug dissolved

RESULTS AND DISCUSSION

The RLD was checked for physical characterization, and results were presented in Table 4.

Deconvolution of Pre-prandial in-vivo data

The mean plasma drug concentration of Dipyridamole obtained from Aggrenox 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

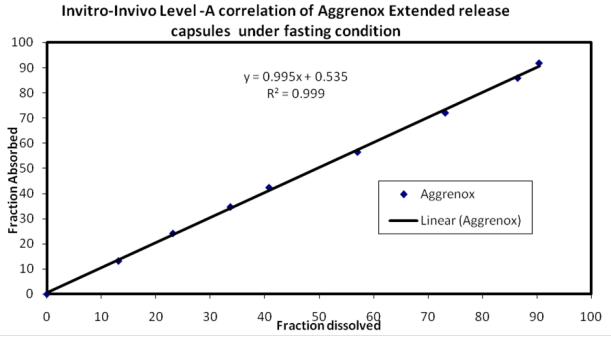

Figure 6: *In-vitro*/*In-vivo* Level -A correlation of Aggrenox under fasting condition

Table 5, (Aggrenox, 1999).

The deconvoluted data indicates that 90% of drug is absorbed in 12 hours, which directs the simulated dissolution to be performed for 12 hrs, using appropriate dissolution sink conditions.

In-vitro dissolution of Aggrenox capsules in OGD recommended dissolution media, and the study on effect of RPM.

Analytical method was developed for evaluation of dissolution, and the standard chromatogram is presented in Figure 1.

A comparative dissolution profile of Aggrenox capsules in OGD recommended dissolution media and target dissolution profile, along with the effect of RPM on dissolution profile are presented in Table 6 and Figure 2 and compared for similarity factor with target dissolution profile.

A comparative dissolution profile of Aggrenox capsules in The office of generic drugs recommended dissolution media was evaluated, for dissolution of Aggrenox capsules. The target profile achieved from deconvoluted data was not comparable with the dissolution profile achieved even by varying the RPM. 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.

Development of bio-relevant dissolution method

The dissolution method was aimed to develop by using QBD approach. The target profile was defined as deconvoluted dissolution profile (Kortejärvi *et al.*, 2002; Suarez-Sharp *et al.*, 2016) Initial risk assessment of CQA (Dissolution profile) on variables are, the residence time, molar concentration and pH of buffer, DPM and media volume, in the biorelavance media dissolution method development. The buffer pH & residence time are fixed based on the research work carried out by (Dressman and Reppas, 2000).

Hence, two factors were evaluated in this study, risk assessment was performed for both parameters, the RPN number was presented in Table 7 and the study design was established using minitab.

A full factorial study was performed, for media volume 2 levels were evaluated and , for DPM 4 levels were evaluated. The response was considered a dissolution with 4 time points of 1 hour, 4hrs, 8hrs & 12 hrs. Significant factors for dissolution 1hr, 4hrs, 8 hrs and 12 hours are presented below the in the Figure 3 and Table 8, on main effects and interaction effects.

For all DOE data analysis, the commonly used alpha of 0.05 was chosen to differentiate between significant and not significant factors. The ANOVA results are presented in Table 9.

The model summary is observed with 100%. The design response was optimised to the target profile using design of experiment study, and the lower, upper level ranges predicted are presented in Table 10. The predicted DPM and media volume required for the product is 10 DPM and 250ml, with the composite desirability of 0.798. The design of target and ranges recommended for the response by minitab was presented below in Table 10, and the response optimisation was presented in Figure 4.

Establishment of the IVIV-R

A comparative dissolution profile using USP apparatus -3 and target profile is presented in Table 11 & in Figures 5 and 6. (Dressman and Reppas, 2000; Suarez-Sharp *et al.*, 2016; Kakhi *et al.*, 2013).

The similarity factor (F_2)observed between the fraction of drug absorbed and fraction of drug dissolved is 92. The level A In-vitro/in-vivo correlation was established for Aggrenox under pre-prandial condition, and the R^2 value observed was 0.999, indicates very good predictive capability of the relationship.

Hence, the dissolution method developed using USP apparatus 3 (reciprocating cylinder) at 10 DPM in 250 mL of change over media simulating pre-prandial condition shall be used as a predictive dissolution method, based on established IVIV-R.

CONCLUSIONS

The finished product is meeting to the acceptance criteria as per OGD recommended dissolution media, and agitation speed is not having any impact on dissolution profile. The F2 value observed was 82 & 87 at 75 RPM & 125RRPM respectively in comparison to 100RPM. However, the F_2 value with target dissolution profile deconvoluted from in-vivo was observed below 50. A suitable bio-relevant dissolu-

tion media was developed, and the developed dissolution media has achieved the level -A IVIVC, with the R^2 value of 0.999, which meets USFDA and EMA requirements.

ACKNOWLEDGEMENT

The authors are thankful to Dr. Reddys laboratories, for providing gift samples and raw materials for testing purpose. The authors are thankful to Malla Reddy pharmacy college, Hyderabad for providing the laboratory facility for the research work.

REFERENCES

Aggrenox 1999. (Aspirin/ Extended-Release Dipyridamole) Capsules, Company. Inc.Application No.:20884, Approval Date: 11/22/1999. *Boehringer Ingelheim Pharmaceuticals*.

Anilkumar, A., Gopala, T. E., Murthy, K. 2018. Avula Prameela Rani, Development of pH Independent Drug Release System for Dipyridamole. *Indian Journal of Pharmaceutical Education and Research*, 52(3):374–380.

Cardot, J. M., Davit, B. M. 2012. In vitro–In Vivo Correlations: Tricks and Traps. *The AAPS Journal*, 14(3):491–499.

Dipyridamole, U. S. P. 2008. United states pharmacopoeia 32-National formulary. 27:2181–2181.

Dressman, J. B., Reppas, C. 2000. In vitro–in vivo correlations for lipophilic, poorly water-soluble drugs. *European Journal of Pharmaceutical Sciences*, 11:S73–S80.

FDA 1997. Extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations. US Department of Health and Human Services,. *Food and Drug Administration, Centre for Drug Evaluation and Research (CDER)*.

Galia, E., Nicolaides, E., Hörter, D., Löbenberg, R., Reppas, C., Dressman, J. B. 1998. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. *Pharm. Res*, 15:698–705.

Jantratid, E., Janssen, N., Reppas, C., Dressman, J. B. 2008. Dissolution Media Simulating Conditions in the Proximal Human Gastrointestinal Tract: An Update. *Pharmaceutical Research*, 25(7):1663–1676.

Jantratid, E., Maio, V. D., Ronda, E., Mattavelli, V., Vertzoni, M., Dressman, J. B. 2009. Application of biorelevant dissolution tests to the prediction of in vivo performance of diclofenac sodium from an oral modified-release pellet dosage form. *European Journal of Pharmaceutical Sciences*, 37(3-4):434–441.

Kakhi, M., Marroum, P., Chittenden, J. 2013. Analysis of level Ain vitro-in vivocorrelations for an extended-release formulation with limited bioavailability. *Biopharmaceutics & Drug Disposition*, 34(5):262–277.

Klein, S. 2010. The Use of Biorelevant Dissolution Media to Forecast the In Vivo Performance of a Drug. *The AAPS Journal*, 12(3):397–406.

Kortejärvi, H., Mikkola, J., Bäckman, M., Antila, S., Marvola, M. 2002. Development of level A, B and C in vitro–in vivo correlations for modified-release levosimendan capsules. *International Journal of Pharmaceutics*, 241(1):87–95.

Marques, M. R. C., Loebenberg, R., Almukainzi, M. 2011. Simulated Biological Fluids with Possible Application in Dissolution Testing. *Dissolution Technologies*, 18(3):15–28.

Suarez-Sharp, S., Li, M., Duan, J., Shah, H., Seo, P. 2016. Regulatory Experience with In Vivo In Vitro Correlations (IVIVC) in New Drug Applications. *The AAPS Journal*, 18(6):1379–1390.

Vertzoni, M., Fotaki, N., Nicolaides, E., Reppas, C., Kostewicz, E., Stippler, E., Leuner, C., Dressman, J. 2004. Dissolution media simulating the intralumenal composition of the small intestine: physiological issues and practical aspects. *Journal of Pharmacy and Pharmacology*, 56(4):453–462.

Wei, H., Löbenberg, R. 2006. Biorelevant dissolution media as a predictive tool for glyburide a class II drug. *European Journal of Pharmaceutical Sciences*, 29(1):45–52.

Zhang, J., Miller, R. B., Jacobus, R. 1997. Development and validation of a stability-indicating HPLC method for the determination of degradation products in dipyridamole injection. *Chromatographia*, 44(5-6):247–252.