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

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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 F₂ 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.

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 multiparticulate 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 part.
Table 1: Segment of human GI tract and pre-prandial residence time

| GI tract Segment | pH & Media Biorelevant medium | pH | Residence time (min) |
|------------------|-------------------------------|----|----------------------|
| 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 |
| Volume  | 2      | 100, 250 |

1hr dissolution 4hrs dissolution 8hrs dissolution 12hrs dissolution

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

| Medium    | SCoF | FaSSGF | New-FaSSIF | Half-FaSSIF | FaSSIF-sans |
|-----------|------|--------|------------|-------------|-------------|
| Sodium taurocholate | - | 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 ΔpH⁻¹) | 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) | Mean drug plasma concentration in human (pre-prandial) Cp (μg/mL) | In-vivo data | Fraction Absorbed (Numerical Deconvolution by Wagner nelson method) | %Absorbed (Target profile) |
|-----------|-------------------------------------------------|--------------|-------------------------------------------------|---------------------------|
| 0         | 0                                               | 0.00         | 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 0.1M pH 5.5 phosphate buffer for 7 hrs

| Batch number | 079358 | Acceptance Criteria | 75 RPM | 100 RPM | 125 RPM | Target profile (from plasma profile) |
|--------------|--------|---------------------|--------|---------|---------|-------------------------------------|
| Time         |        |                     |        |         |         |                                    |
| 1hr          |        |                     | 23.0 ± 0.2 | 20.1 ± 0.2 | 22.9 ± 0.5 | 13                                  |
| 2 hrs        |        | 46.2 ± 0.4          | 42.8 ± 0.3 | 42.9 ± 0.2 |         | 23                                  |
| 3 hrs        |        | 50-70%              | 62.1 ± 0.5 | 61.1 ± 0.4 | 62.5 ± 0.4 | 34                                  |
| 6 hrs        |        | 76.2 ± 0.4          | 76.4 ± 0.5 | 75.3 ± 0.4 |         | 57                                  |
| 8 hrs        | NLT80% | 89.8 ± 0.3          | 89.6 ± 0.2 | 89.1 ± 0.5 |         | 73                                  |
| F2 (Against target) | 35 | 36 | 35 | | |
| F2 (Against 100 RPM) | 82 | - | 87 | | |

Note: mean ± SD, n=3

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 gastrointestinal conditions. Several dissolution media were developed by simulating human gastrointestinal system, like fasted state simulated intestinal
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

Fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF). (Galia et al., 1998; Jantratid et al., 2008, 2009). The dissolution system can serve as 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 gastrointestinal 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-disintegrating single units (e.g. tablets), and multi-
### Table 9: ANOVA results for Design of Experiment

| Source         | DF | Adj SS 1hr | Adj MS 1hr | Adj SS 4hrs | Adj MS 4hrs | Adj SS 8hrs | Adj MS 8hrs | Adj SS 12hrs | Adj MS 12hrs |
|----------------|----|------------|------------|-------------|-------------|-------------|-------------|--------------|--------------|
| 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  | 1.87       | 0.62       | 17.79       | 5.93        | 86.91       | 28.97       | 78.82        | 26.27        |
| Total          | 7  | 81.29      | 224.01     | 799.12      | 975.89      |             |             |              |              |
| Model summary  |    | 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 |

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)

ple 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 gastrointestinal 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 \textsuperscript{(R)} was procured from United states 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), Glycerol monooleate (Danisco Specialities), Maleic acid (Sigma-Aldrich), Sodium oleate (Riedel-de Haén), Sodium taurocholate (Prodiotti 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.

METHODS: 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 \textsuperscript{®} software to determine the fraction of drug absorbed. Fraction of drug absorbed has been fixed as a target profile to select the suitable biorelevant 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 \textit{et al.}, 2018).

Biorelevant testing: A biorelevant 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 dissolution 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 vol-
Figure 3: Main effect of DPM and media volume on dissolution profile and interaction effect
ume 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 Fasted 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, pH 7.0 & pH 7.5: 3.3 g sodium taurocholate was dissolved in 100ml of methylene chloride by mixing to the achieve the concentration on 100 mg/ml. 11.8 mL of a Methylene chloride solution containing 100 mg/mL lecithin was added to blank 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 up to 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.
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 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 (F2) values observed also below 50%. Hence, it was decided to develop a biopredictive 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) (Kortejärvi et al.,2002; Paul et al., 2008;) 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 biorelevance 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 (F2) 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 R2 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 F2 value with target dissolution profile deconvoluted from in-vivo was observed below 50. A suitable bio-relevant dissolution media was developed, and the developed dissolution media has achieved the level -A IVIVC, with the R2 value of 0.999, which meets USFDA and EMA requirements.
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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. 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, 11:573–580.

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 A in vitro-in vivo correlations 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 intraluminal 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.