ORIGINAL ARTICLE

Quality by Design enabled Development and Optimization of Gastroretentive Floating Matrix Tablets of Dipyridamole

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Abstract

Introduction: This research focuses on development and optimization of dipyridamole (DPM) gastroretentive (GR) floating matrix tablets through risk-based approach using combination of rate controlling hydrophilic polymers. **Materials and Methods:** A 3^2 full factorial design was deployed to optimize ratio of polymers and polymer concentration in the formulation. Dissolution studies, Buoyancy studies, swelling index studies, kinetic modelling, drug content, and differential scanning calorimetry studies were performed to effectively assess developed gastroretentive dosage form. Estimation of related substances was also done for optimized formulations to check the stability of dosage form during shelf life. **Results and Discussion:** Buoyancy studies suggested that concentration of PanExcea™ GR polymer should be at least 25% w/w or more to get better floating and swelling capabilities if used alone as rate controlling polymer. Selection of optimum batches was done using constraint-based graphical optimization technique. The optimum batches exhibited desired extended drug dissolution profile, minimal floating lag time, and total floating time of >12 h. Thermal characterization studies also preclude any drug polymer interaction and change in polymorphic form of drug during manufacturing process. Stability studies indicated optimized formulations are stable under selected packaging configurations. **Conclusion:** The present research exemplifies successful application of quality by design approach in designing gastroretentive dosage form of DPM. From the present study, it can be concluded that selection of appropriate ratio and concentration of hydrophilic polymers play a pivotal role in matrix integrity, buoyancy, swelling potential as well as drug release profile of GRDDS.

Key words: Quality by design (QbD) , dipyridamole, gastroretentive drug delivery system (GRDDS), floating, failure mode effect analysis (FMEA), polymer, controlled release

INTRODUCTION

Oral drug delivery systems are considered as most favorable drug delivery system due to ease of administration, good shelf life, and patient compliance. Among them, there is a consistent interest increasing toward developing controlled release (CR) drug delivery systems to decrease dosing frequency, decrease fluctuations in plasma concentrations, and thereby to improve patient compliance. However, during the development of such dosage forms, one might face challenges such as (i) difficulty to retain dosage form in stomach for sufficient period when required and (ii) incomplete drug absorption resulting in therapeutic variability. Hence, there is a tremendous interest in developing gastroretentive (GR) dosage form with various approaches[1] such as floating dosage forms, bioadhesive dosage forms, raft forming systems, swelling, and expanding systems. Among them, floating dosage forms remain buoyant in the stomach and provide extended drug release along with better control over plasma drug level fluctuations.[2]

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Stroke is a serious, common, age-related health problem[3] that accounts for 1 of every 20 deaths in the US and was the second major cause of mortality behind heart disease in 2013, considered for 11.8% of total deaths worldwide.[4] Dipyridamole (DPM) is indicated for post-operative thromboembolic complications of cardiac valve replacement in combination with coumarin anticoagulants[5] and also to reduce the risk of stroke in patients.[6] Recommended dose is 75-100 mg 4 times a day with coumarin anticoagulants (warfarin) or aspirin.[6] Hence, there is a considerable interest to develop extended release formulation of DPM to reduce dosing frequency with easily scalable, simple and cost-effective technology.

DPM is having pKa value of 6.4.[7] It is having aqueous solubility of 5 µg/ml at neutral pH (pH 7.0) which rises up to 29 mg/ml at pH 2.5.[8] Russell *et al*.[9] reported that gastric pH appeared to be primary determinant in DPM absorption in elderly. Therefore, sufficient gastric acidity is a prerequisite for adequate dissolution and subsequent absorption of the drug *in vivo*.[10] Hence, several efforts reported in literature to provide extended release DPM in stomach using several gastro-retentive approaches, *viz*., floating tablets prepared using blend of xanthan gum and guar gum,[11] different grades of hydroxypropyl methylcellulose,[12] polyethylene oxide,[13] floating alginate beads,[14] gastro-floating pellets using Eudragit NE 30D,[15] and floating osmotic pump.[16]

Development of GR systems involves multiple factors such as selection of system, selection of release rate retarding polymer, optimum concentration of polymers, selection of suitable manufacturing method, and physicochemical characterization. Optimizing such systems using one factor at a time (OFAT) approach is a strenuous effort which demands great deal of money, time and energy.[2,17] Hence, in the present investigation, attempts were made to develop gastroretentive (GR) floating effervescent tablets of DPM using unique combination of two different polymers using quality by design (QbD) approach. As described in literature, use of polymer blends is a more suitable approach to modulate drug release profile for hydrophilic matrix tablets.[18] In the present study, release rate modulating effect of novel biopolymer PanExcea™ GR was investigated in combination with Methocel™ K4M Premium CR (hypromellose 2208). PanExcea™ GR is a biopolymer isolated as a purified fiber rich fraction from fenugreek (*Trigonella foenum graceum*) husk with a proprietary technology.[19,20] PanExcea™ GR polymer is reported to have viscosity in the range of 6000-12000 cps for 1% solution and bulk density in the range of 0.05-0.25 g/ml. Sample lot of the same polymer is having bulk density of 0.09 g/ml, Carr's index of 29.412% and Hausner's ratio of 1.417 indicating poor flow characteristics of the material as per USP General Chapter <1174> Powder flow. To improve flow properties of the blend, it was decided to go with slugging of the blend followed by milling, lubrication and compression approach for tablet preparation.

The major aims of present investigation were (i) determination of quality target product profile (QTPP) and quality risk assessment using failure mode effect analysis (FMEA), (ii) formulation optimization using full factorial design and characterization of dosage form, (iii) risk mitigation and control strategy for moderate to high risk factors identified initially. In addition, stability study of optimized formulations was also performed.

MATERIALS AND METHODS

Materials

DPM was obtained as gratis from Emcure Pharmaceuticals Ltd. PanExcea™ GR (PGR) (Avantor Performance Materials Inc.), hydroxypropyl methylcellulose (K4M) (Methocel™ K4M Premium CR, Dow Chemicals), crospovidone (Polyplasdone XL, Ashland), lactose monohydrate (Supertab 30 GR, DFE), sodium bicarbonate (Church & Dwight Inc.), and magnesium stearate (Ligamed MF-2-V, Peter Greven) were utilized as excipients for formulation development. All other chemicals and reagents were of analytical grade and utilized as received.

Methods

QTPP of DPM gastroretentive floating tablets

QTPP can be served as a basis for the systematic development of patient-oriented dosage form. As defined in ICH Q8 (Pharmaceutical Development),[21-23] QTPP should be defined to meet patients' needs and the intended product performance. QTPP for the DPM gastroretentive floating tablets is defined in Table 1.

Identification of critical quality attributes (CQAs) and quality risk assessment using FMEA

CQAs of the product are the characteristics which should be within appropriate limit or range to ensure desired product quality (ICH Q8).[21] For solid oral dosage forms, they are the aspects which can affect product purity, strength, drug release, and stability. Potential CQAs can be ascertained based on product knowledge and process understanding. For present dosage form, assay, drug dissolution, floating lag time, and total floating time were determined as drug product CQAs.

A quality risk assessment of formulation components was executed using FMEA approach using which failure modes can be prioritized based on their seriousness of consequences, frequency and ease of detection.[24-26] The results of FMEA are represented in Table 2 in the form of risk priority numbers (RPNs) which can be used to rank the risk. It is calculated as mentioned below:

$$RPN = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} O \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} S \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} D \quad (1)$$

Table 1: QTPP of DPM gastroretentive floating tablets

QTPP element	Target	Justification
Dosage form	Controlled release gastroretentive floating tablets	Tablet because of ease of administration and patient compliance Gastroretentive floating because of higher solubility of DPM at acidic pH and therefore better bioavailability after administration and minimizing dosing frequency
Route of administration	Oral	Dosage form designed to be administered orally
Dosage strength	150 mg	Commonly acceptable strength and other market formulation available for similar strength*
Stability	Short term stability of accelerated condition at 40°C/75% RH and long-term condition (24 months) at 25°C/60% RH	Minimum time period (3M and 6M) decided to study stability of optimum formulation
Container closure system	Suitable container closure system to achieve the target shelf-life and to ensure tablet integrity during shipping	HDPE bottles with CR (child resistant) caps and PVC-Alu Blisters are selected to ensure quality up to target shelf life

*Persantin® PL 150 mg (SR capsules), Pytazen® SR 150 mg (SR tablets). QTPP: Quality target product profile, DPM: Dipyridamole

Table 2: Risk assessment by FMEA analysis and RPN scores for various factors affecting CQAs

Formulation component/ parameter	Potential failure mode	Potential effect(s) of failure	S	Potential causes or root of failure	O	Detectability method or control	D	RPN	CQAs affected
Weight variation	Less weight or overweight tablets	Variation in therapeutic dose	5	Machine failure, operator's error	3	Weighing balance, weight check at regular interval	1	15	Assay, Uniformity of dosage units
Hardness	Inadequate hardness	Drug release and higher friability	5	Machine failure, operator's error, selection of excipients	3	Hardness testing, friability testing	1	15	Drug dissolution
Powder flow	Inadequate flow	Weight variation, hardness variation	5	Inappropriate selection of process and excipients	1	Carr's index, Hausner's ratio	1	5	Assay of tablets, Uniformity of dosage units
Amount of release rate controlling polymer(s)	Improper concentraton	Drug release	5	Improper concentration	5	Dissolution	2	50	Dissolution, total floating time
Ratio of rate controlling polymer(s)	Improper concentration	Drug release	5	Improper concentration	5	Dissolution	2	50	Dissolution, total floating time
Packaging configuration	Inappropriate to protect drug product from environmental and transportational variables	Stability	5	Improper selection of packaging material	3	Assay, dissolution, hardness	2	30	Assay, dissolution

RPN: ≥40- high risk, ≥20-<40- medium risk, <20- low risk. RPNs: Risk priority mumbers, CQAs: Critical quality attributes

Where O is the occurrence probability ranked as 5 (frequent), 4 (probable), 3 (50% chance of occurrence), 2 (remote), 1 (unlikely to occur); S is the severity of effect which a given failure mode can cause – ranked as 5 (severe), 4 (critical), 3 (moderate), 2 (minor) and 1 (no effect); D is the detectability which is ranked as 5 (hard to detect), 4 (remotely detectable), 3 (moderately detectable), 2 (highly detectable), and 1 (easily detectable).

Preparation of DPM gastroretentive floating tablets

DPM (30% w/w) was mixed with required quantity and type of polymer (as per design), sodium bicarbonate (7% w/w), crospovidone (polyplasdone XL) (10% w/w), and filler (Lactose monohydrate) co-sifted through 30 mesh sieve (ASTM). Co-sifted material was further mixed in laboratory blender for 15 min. The resultant blend was further lubricated with 60 mesh (ASTM) passed magnesium stearate (0.5% w/w) in laboratory blender for 5 min. The lubricated blend was slugged using 21 × 11 mm capsule shaped punches on 17 station compression machine (Cadmach CMB 4-MT). The slugs were further milled using 1.2 mm sieve using multimill at medium speed, knives forward setting. Milled material was again lubricated with 60 mesh (ASTM) passed magnesium stearate (0.5% w/w) in laboratory blender for 5 min. The resultant blend was free flowing and further compressed using 12 mm round standard concave punch sets at 500 mg target weight. In the present formulation, sodium bicarbonate was used to generate carbon dioxide to increase buoyancy and crospovidone as swelling agent[27] as well as to increase hydration capacity[28] of tablets. The levels of sodium bicarbonate and crospovidone were fixed at 7% w/w and 10% w/w respectively.

Full factorial design

A 3^2 full factorial design was selected in optimization of the formulation. In the present investigation, ratio of PGR and K4M (X1) and total content of both rate controlling polymers (%w/w) (X2) were selected as independent variables. The assay, floating lag time, % drug release at 1 h (Q1), 4 h (Q4), 8 h (Q8), and 12 h (Q12) were selected as dependent variables to define design space. Additional responses measured were total floating time and swelling index. The experimental design with corresponding compositions is outlined in Tables 3 and 4. Ratio of PGR:K4M was studied at 0:1 (−1), 0.5:0.5 (0) and 1:0 (+1) while total content of single or both polymers (as per design) was studied at 20% w/w (−1), 30% w/w (0) and 40% w/w (+1) of total tablet weight. In case of two independent variables, first order model in terms of coded variables[29] is described as:

$$Y=b_0+b_1X1+b_2X2 \quad (2)$$

Where Y is the dependent variable, b_0 is the intercept whereas b_1 and b_2 are the estimated coefficients for the factors X1 and X2, respectively. The main effect (X1 and X2) represents the average result of changing OFAT from its low to high value. Experiment sequence was generated and randomized using Design Expert® Ver.9.0.0.7 (Stat-Ease Inc., Minneapolis, MN 55413) software to avoid any bias. Table 5 lists studied responses and their constraints.

Statistical analysis

The statistical analysis of factorial design batches was performed by Design Expert® Ver.9.0.0.7 (Stat-Ease Inc., Minneapolis, MN 55413) software. All statistical analyses regarding DOE (Design of Experiment) batches were performed using the same software. Response surface plots, overlaid contour plots were generated using the same software.

Table 3: Formulation variables and their levels for 32 full factorial design

Batch code#	X1 (PGR:K4M ratio)	X2 (% polymer content)*
OB 1	0	0
OB 2	1	1
OB 3	0	0
OB 4	0	−1
OB 5	−1	1
OB 6	1	0
OB 7	−1	−1
OB 8	−1	0
OB 9	0	1
OB 10	1	−1

#Each batch also contains 30% w/w dipyridamole, 10% w/w crospovidone, 7% w/w sodium bicarbonate, 1% w/w magnesium stearate and quantity sufficient of filler (lactose monohydrate) to make tablet weight 500 mg. *% polymer content includes total content (% w/w) of single or both polymers (PGR and K4M) of total tablet weight. PGR: PanExcea™ GR

Table 4: Translation of coded levels into actual values of independent variables

Coded levels	Actual values	
	X1 (PGR:K4M ratio)	X2 (% polymer content)
−1	0:1	20
0	0.5:0.5	30
1	1:0	40

PGR: PanExcea™ GR

Physical characterization of the tablets

The prepared tablets were tested for appearance, weight variation, thickness, hardness, and % friability. Weight variation was performed on 20 tablets of each batch using Mettler Toledo electronic balance. Tablet thickness and hardness were performed using Mitutoyo vernier calliper and Erweka hardness tester, respectively. % friability was measured on total 14 tablets of each batch using Inweka friability tester for 100 revolutions at 25 rpm.

In vitro buoyancy study

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using USP

Table 5: Studied responses and their constraints

Responses (Dependent variables)	Constraints (Goal)	Remarks
Q1 (% drug released at 1 h)	<25%	Responses used to define design space
Q4 (% drug released at 4 h)	Between 40% and 60%	
Q8 (% drug released at 8 h)	Between 60% and 80%	
Q12 (% drug released at 12 h)	≥80%	
Assay	95-105%	
Floating lag time (sec)	As minimum as possible	
Swelling index (Sw)	For information	Additional responses to be studied
Total floating time (hr)	At least 12 h or more	

type II Paddle apparatus using 900 ml of 0.1N HCl at paddle rotation of 50 RPM at 37±0.5°C. The time required for tablet to rise to surface of dissolution medium after drop into flask and duration of time the tablet constantly float on dissolution medium were noted as floating lag time and total floating time, respectively (n = 6).

Assay of tablets

Preparation of standard solution

Transfer accurately weighed quantity of about 28 mg of DPM working standard to a 50 mL volumetric flask. Add about 40 ml of 0.1N HCl and sonicate to dissolve. Cool to room temperature. Make volume up to the mark with 0.1N HCl and mix to prepare stock solution of working standard. Pipette out 4 ml of stock solution into another 50 ml volumetric flask and make volume up to the mark with 0.1N HCl. Measure absorbance at 405 nm using 10 mm cell, against 0.1N HCl as a blank on double beam ultraviolet visible (UV/VIS) spectrophotometer (Shimadzu UV-1800).

Preparation of sample solution

Find out average weight of 20 tablets and crush to make fine powder. Mix the powder and transfer accurately weighed quantity of powder equivalent to 750 mg DPM into 250 ml volumetric flask. Add about 170 ml 0.1N HCl into a volumetric flask and sonicate for 30 min with intermittent shaking. Dilute up to mark with 0.1N HCl. Centrifuge resultant suspension at 3000 rpm for 10 min. Then, pipette out 3 ml supernatant solution into 200 ml volumetric flask and dilute up to the mark with 0.1N HCl. Measure absorbance at 405 nm using 10 mm cell, against 0.1N HCl as a blank on double beam UV/VIS spectrophotometer (Shimadzu UV-1800).

Assay of tablets can be calculated using formula mentioned in equation (3):

$$\%\,\text{Assay of DPM tablets} = \frac{AT}{AS}\times\frac{SW}{50}\times\frac{4}{50}\times\frac{250}{TW}\times\frac{200}{3}\times\frac{\text{Potency}}{100}\times\frac{AW}{LC}\times 100 \quad (3)$$

Where:
AT = Absorbance of test sample
AS = Absorbance of standard
SW = Weight of standard
TW = Weight of test sample
AW = Average weight of 20 tablets
LC = Label claim.
Potency= %purity of working standard (on as is basis).

In vitro drug release study

The *in vitro* drug release study was performed using USP Type II (Paddle type) dissolution apparatus (Electrolab) using 900 ml 0.1N HCl at paddle rotation of 50 rpm at 37±0.5°C. The aliquots were autosampled at predetermined time intervals for up to 12 h and replaced with fresh medium. The samples were filtered through 0.45 µ Millipore Millex HV PVDF filter, suitably diluted and analyzed at 405 nm using 10 mm cell, against 0.1N HCl as a blank on double beam UV/VIS spectrophotometer (Shimadzu UV-1800).

Determination of Swelling index (Sw)

Swelling studies were conducted using Electrolab dissolution apparatus (USP II Paddle). 50 rpm rotation was applied. Preweighed tablets were immersed in 900 ml of 0.1N HCl and maintained for 12 h at 37.0 ± 0.5°C. At predetermined time intervals (2,4,8 and 12 hr), the swollen tablets were removed from the media, gently wiped with a tissue paper to remove excess surface droplets and weighed. The swelling index (Sw) was calculated according to the following equation:

$$\text{Swelling index}\,(Sw) = \frac{Wt - W0}{W0} \quad (4)$$

Where W0 is the initial weight of the dry tablet and Wt is the weight of swollen tablet at time t.

Kinetics of drug release

To study drug release mechanism from tablets, various kinetic parameters were obtained by fitting dissolution data

into zero order model, Higuchi model, Korsmeyer-Peppas model, Weibull model, and Peppas-Sahlin model using DD-solver add-in available for Microsoft Excel which uses nonlinear least-squares curve fitting technique for fitting dissolution models to non-transformed data.[30] For Korsmeyer-Peppas model, data were fitted for first 60% drug release. Goodness of fit of each model was evaluated using adjusted R^2 (Correlation coefficient) values because R^2 will always increase as more parameters are included, whereas R^2 adjusted may decrease when overfitting has occurred.[24,30]

Akaike information criterion (AIC)

AIC has been used for years in selecting optimal models. The AIC is dependent on the magnitude of the data as well as the number of data points. It is defined as mentioned below:[30]

$$AIC = n*\ln(WSS)+2*p \quad (5)$$

Where n is the number of data points, WSS is the weighted sum of squares, and p is the number of parameters in the model. Model with lower AIC value can be considered a better model when comparing two different models with different number of parameters.

Thermal characterization (differential scanning calorimetry [DSC] studies)

To investigate thermal behavior of pure drug and combination of drug with different ratio of polymers along with other excipients in tablets, DSC of samples was performed using DSC instrument (Pyris 6 DSC, Perkin Elmer). Indium was used as a standard for calibration. Samples including about 2.0 mg pure API, powder of compressed tablets of different batches were placed in hermetically sealed alum pans and scanned at 10°C/min from 30°C to 300°C under nitrogen purge (30 ml/min).

Related substances estimation

Selected optimized batches were tested for related substances using analytical method reported by Vaghela *et al*.[31] as mentioned briefly in Supplementary 1.

Packaging and stability studies

The optimized batch tablets were packed in HDPE (high-density polyethylene) bottle with CR (child resistant) cap and PVC (250 µ)-Alu Blisters. Both packs containing samples were subjected for accelerated (40°C/75% RH) and long term (25°C/60% RH) stability conditions up to 6 months. The samples were withdrawn periodically (0, 90 and 180 days) and evaluated for appearance, hardness, floating lag time, total floating time, assay, and drug dissolution.

RESULTS AND DISCUSSION

QTPP and quality risk assessment by FMEA

QTPP was defined based on type of formulation and process selected for the same. QTPP for DPM gastroretentive dosage form is enlisted in Table 1. Based on QTPP, CQAs were determined (drug dissolution, assay, floating lag time, and total floating time) for the same dosage form. Table 3 depicts the formulation factors and their levels which were considered in the design and development of DPM floating matrices. As discussed in literature, factors having RPN ≥40 were considered as high risk, RPN ≥20 to <40 were considered as medium risk, <20 were considered as low risk.[32] Weight variation, hardness, and powder flow were identified as less risk factors. Ratio of rate controlling polymer and amount of rate controlling polymer were identified as high-risk factors and therefore studied in detail using DOE to identify optimum levels. Packaging configuration was identified as a moderate risk factor and therefore studied in detail in packaging and stability studies section.

Physical characterization of tablets

All physical parameters were found to be satisfactory. The tablets weighed 500 mg ± 2% had an average diameter of 12.00 ± 0.05 mm, thickness of 5.80 ± 0.20 mm, and hardness of 5-6 kP (kiloponds). % Friability was <0.02 for all batches.

Effect of factors on the responses

Table 6 summarizes effect of polymer ratio and polymer content on various measured responses.

Buoyancy studies

As shown in Table 6, studied formulation variables did not have any significant impact on floating lag time since tablets of all batches were having reasonably very good floating lag time of <1 min. Also except for batch no. OB-10, all batches were having very good floating time of >12 h. This indicates very good floating capacity of all matrices except OB-10. Floating lag time and total floating time did not differ between different polymer ratio and total polymer content. This study ensured that both polymers have sufficient swelling and hydrophilic gel formation capacity which entraps bubbles of carbon dioxide inside the swollen matrix for extended period and hence sufficient floatation in media. Less floating time for OB-10 may be attributed to less polymer content of tablet and hence less swelling as well as rapid erosion of tablet matrix in drug release media. This study also emphasized that if only PGR is to be used as rate controlling hydrophilic polymer without any combination, polymer level should be at least 25% w/w or more to ensure sufficient swelling and floating capacity of tablets.

Table 6: Matrix of experiments of 3^2 full factorial design and measured responses

Batch code	X1	X2	Floating lag time (sec)[a]	Total floating time (hr)	Assay	Cumulative % drug release[a]			
						1 h (Q1)	4 h (Q4)	8 h (Q8)	12 h (Q12)
OB 1	0	0	15±0.6	>12	98.9	19.45±0.7	50.27±1.2	68.75±1.7	83.42±2.4
OB 2	1	1	35±0.8	>12	99.2	12.42±0.4	45.62±1.0	64.86±1.8	84.46±2.4
OB 3	0	0	20±0.9	>12	100.2	18.52±0.5	51.31±0.8	66.12±1.6	82.43±2.2
OB 4	0	−1	30±0.8	>12	99.5	30.42±0.4	55.46±1.1	78.52±1.6	90.23±2.2
OB 5	−1	1	25±0.8	>12	98.6	10.19±0.5	28.82±1.2	49.23±2.3	61.20±2.1
OB 6	1	0	15±0.7	>12	99.8	24.52±0.4	59.46±0.9	77.82±1.7	92.45±2.1
OB 7	−1	−1	25±0.7	>12	100.1	22.46±0.5	58.49±1.1	72.74±1.9	84.14±2.3
OB 8	−1	0	15±0.9	>12	99.5	12.54±0.7	45.56±1.3	65.74±1.7	79.54±2.1
OB 9	0	1	25±0.8	>12	100.2	13.83±0.2	32.04±1.2	52.73±1.5	65.72±2.3
OB 10	1	−1	30±0.8	<4	99.8	52.50±0.6	89.45±1.2	98.57±1.3	99.99±2.2

X1: Polymer (PGR:K4M) ratio, X2: Polymer content, [a]Mean±SD (n=6). PGR: PanExcea™ GR

Assay

Results of assay of experimental batches are shown in Table 6. From the data, it can be concluded that neither polymer ratio nor polymer level has any significant impact on assay of tablets. All assay values were found to be well within target range of 95-105%.

In vitro drug release studies

Results of *in vitro* drug release studies are mentioned in Table 6. ANOVA results and regression coefficients of measured responses are given in Table 7.

From the results shown in Table 6 and 3D response surface plots shown in Figure 1, it can be concluded that although quadratic effect is seen in case of floating lag time, practically there was no significant impact because all lag time values were found to be <60 s. Furthermore, there was no significant impact on assay of tablets.

From the response plots and data shown in Table 6, it can be concluded that as % of PGR polymer increased in combination with K4M polymer, drug dissolution increased. One of the plausible reasons to explain this phenomenon is greater porosity of PGR polymer. Dissolution data also uncovered greater degree of hydration capacity of PGR polymer in comparision with K4M polymer. Due to increased hydration of PGR polymer, it rapidly allows media inside the swollen matrix and allows drug release at faster rate. A similar study was reported in the literature with combination of xanthan gum and guar gum for DPM floating matrix tablets.[11] They reported that increased guar gum concentration leads to rapid hydration of matrix and ultimately higher drug release.

Furthermore, it was ascertained that drug dissolution tended to decrease with increased total polymer content. This phenomenon can be appertained to increased swelling and gelation of diffusion matrix with increased polymer level. This ultimately formed highly viscous swollen gel layer around tablet and decreased drug release. Furthermore, it was noteworthy to study the fact that in present dosage form, as content of rate controlling polymer increases, lactose monohydrate concentration decreases to maintain constant tablet weight. This ultimately led to decreased pore formation and therefore decreased penetration of dissolution medium inside swollen floating matrices with increased polymer content.

Results of ANOVA revealed that both the factors X1 and X2 have a significant impact ($P < 0.05$) on all studied time points of drug dissolution. Model was linear with nonsignificant lack of fit at all time points for drug dissolution. The predicted R^2 was in reasonable agreement with adjusted R^2 for all studied time points. Adequate precision values are also >4 which is desirable. Same model can also be utilized to explore the design space. Coefficients of multiple regression analysis as shown in Table 8 revealed that polymer ratio has positive effect (increased drug release) at all dissolution time points, and polymer content has negative effect on drug dissolution.

Model equations 6-9 for different dissolution time points in terms of coded factors are mentioned below:

$$Q1 = +21.69+7.38X1-11.49X2-6.95X1X2 \text{ (Linear with 2FI)} \quad (6)$$

$$Q4 = +51.65+10.28X1-16.15X2 \text{ (Linear)} \quad (7)$$

$$Q8 = +69.82+8.92X1-13.83X2 \text{ (Linear)} \quad (8)$$

$$Q12 = +82.57+8.67X1-10.50X2 \text{ (Linear)} \quad (9)$$

Above equations can be utilized to predict % drug dissolution at respective time points with different levels of factors within studied range.

Table 7: ANOVA summary output showing effect of independent factors on measured responses

Source	Sum of squares	Df	Mean square	F value	*P* value Prob>F	PRESS	R^2	Adjusted R^2	Predicted R^2	Adequate precision
ANOVA results for Q1										
Model-2FI	1311.81	3	437.27	25.97	0.0008	514.71	0.9285	0.8928	0.6357	14.540
X1	326.34	1	326.34	19.39	0.0046					
X2	792.12	1	792.12	47.05	0.0005					
X1X2	193.35	1	193.35	11.49	0.0147					
Residual	101.01	6	16.83	-	-					
Lack of fit	100.58	5	20.12	46.51	0.1108					
ANOVA results for Q4										
Model-Linear	2199.24	2	1099.62	23.11	0.0008	797.93	0.8685	0.8309	0.6849	13.990
X1	633.66	1	633.66	13.32	0.0082					
X2	1565.58	1	1565.58	32.90	0.0007					
Residual	333.13	7	47.59	-	-					
Lack of fit	332.59	6	55.43	102.50	0.0755					
ANOVA results for Q8										
Model-Linear	1626.20	2	813.10	53.04	<0.0001	254.54	0.9381	0.9204	0.8532	21.224
X1	477.76	1	477.76	31.16	0.0008					
X2	1148.44	1	1148.44	74.91	<0.0001					
Residual	107.31	7	15.33	-	-					
Lack of fit	107.19	6	17.86	142.92	0.0639					
ANOVA results for Q12										
Model-Linear	1112.09	2	556.05	35.95	0.0002	225.69	0.9113	0.8859	0.8151	17.795
X1	451.01	1	451.01	29.16	0.0010	-	-	-	-	-
X2	661.08	1	661.08	42.74	0.0003	-	-	-	-	-
Residual	108.27	7	15.47	-	-	-	-	-	-	-
Lack of fit	107.59	6	17.93	26.20	0.1485	-	-	-	-	-

2FI: 2 factor interaction, Df: Degree of freedom, PRESS: Predicted sum of squares, *P* value<0.05: Significant term

Table 8: Regression coefficients summary

Factors	Q1 coefficient	Q4 coefficient	Q8 coefficient	Q12 coefficient
Intercept	21.69	51.65	69.82	82.57
X1	7.38	10.28	8.92	8.67
X2	−11.49	−16.15	−13.83	−10.50
X1X2	−6.95	*	*	*

*Not applicable

Swelling index study

Swelling index study was performed up to 12 h in 0.1N HCl media. Results are shown in Figure 2. Batch no. OB-5 was found to have very good swelling index of 2.99 (at 12 h) which indicates higher swelling with K4M at concentration of 40% w/w in comparison with swelling index of 2.23 (at 12 h) of PGR at the same concentration (batch no. OB-2). Comparably low swelling index of PGR polymer can also be due to swelling followed by rapid erosion due to rapid polymer chain disentanglement, whereas K4M showed slow polymer chain disentanglement and slow drug release profile. The swelling index data are also in good agreement with dissolution data which exhibits comparable slow drug release profile with OB-5 batch. Swelling index of batch no. OB-10 could not be determined due to loss of matrix integrity after 2 h in 0.1N HCl media. However, dosage form can be manufactured using mixture of both polymers at varying concentrations to achieve optimum swelling as well as desired drug release profile.

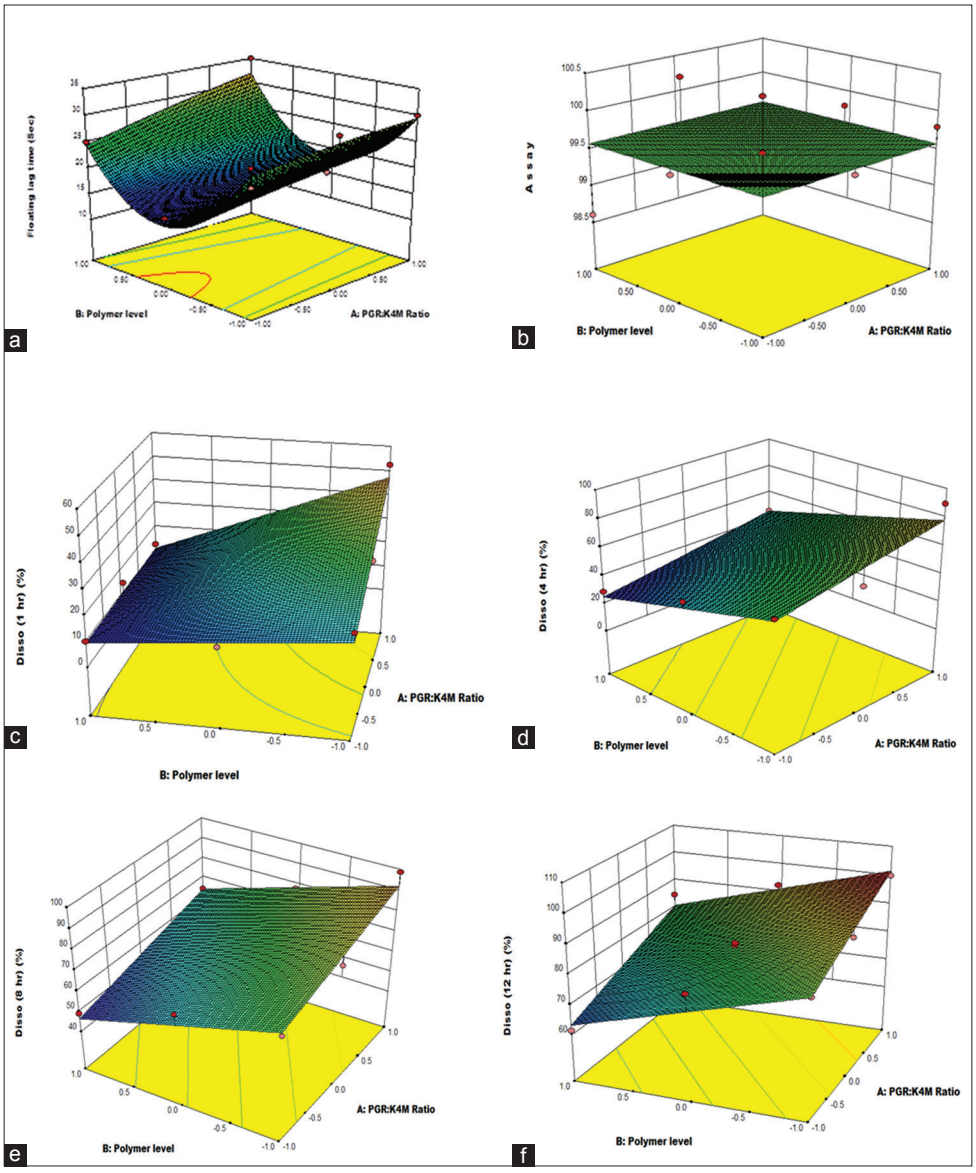

Figure 1: 3D response surface plots for (a) floating lag time (sec), (b) assay of tablets, (c) % drug dissolved at 1 h, (d) % drug dissolved at 4 h, (e) % drug dissolved at 8 h, and (f) % drug dissolved at 12 h

Curve fitting and drug release kinetics

Results of kinetic modelling of drug release data are mentioned in Table 9. Models were compared for individual batch using their adjusted R^2 value and AIC value. Fittest model data (R^2 adjusted and AIC) are shown in bold letters.

Although three models namely Korsmeyer-Peppas power law, Weibull and Peppas-Sahlin model displayed good adjusted R^2 value (>0.99), criteria of AIC was applied to select the fittest model for dissolution data to keep analysis independent of number of parameters between models. Models showing lowest AIC value were termed as fittest. From the data, it can be concluded that drug release data of batches containing only PGR as rate controlling polymer showed a good fit to Weibull model up to 30% w/w concentration, i.e., showing parabolic release pattern ($\beta < 1$, case 3),[30] whereas drug release from batch containing 40%w/w PGR polymer fitted well to Peppas-Sahlin model and showed Fickian diffusion predominantly over Case II relaxational transport through polymer chains.[33] Drug release kinetics of tablets

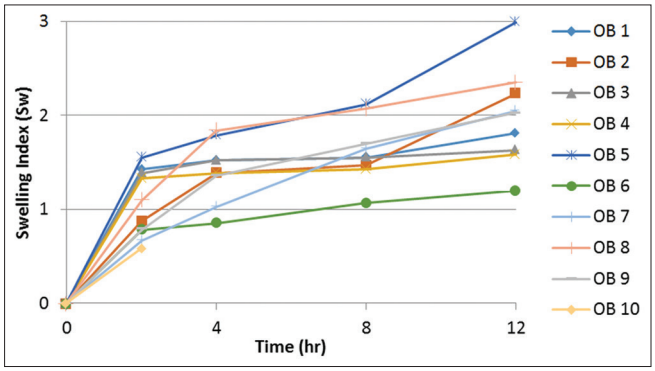

Figure 2: Swelling index data for experimental batches

Table 9: Kinetic modeling of drug release data of different DOE batches

Batch No.		OB 1	OB 2	OB 3	OB 4	OB 5	OB 6	OB 7	OB 8	OB 9	OB 10
Zero order	k0	7.874	7.677	7.968	8.725	5.572	8.864	8.213	7.445	6.011	10.661
	R^2 Adjusted	0.8646	0.9366	0.8697	0.7793	0.9554	0.8171	0.7757	0.9112	0.9356	0.3273
	AIC	34.3239	30.7702	34.3157	37.3613	25.8421	36.843	37.0947	32.071	28.1751	44.4834
Higuchi	kH	24.137	23.188	24.401	27.04	16.763	27.352	25.466	22.605	18.189	34.263
	R^2 Adjusted	0.9945	0.9730	0.9917	0.9945	0.9702	0.9938	0.9833	0.9770	0.9840	0.8458
	AIC	18.3326	26.4945	20.5599	18.8908	23.8128	19.9369	24.1114	25.3267	21.2315	37.1182
Korsmeyer Peppas	kkp	21.597	16.030	21.333	29.730	11.191	27.145	26.181	15.940	13.672	55.585
	n	0.566	0.685	0.578	0.464	0.692	0.517	0.508	0.693	0.636	0.292
	R^2 Adjusted	0.9921	0.9811	0.9872	**0.9991**	0.9965	0.9898	0.9769	0.9838	**0.9984**	0.9853
	AIC	14.8283	18.0620	16.8877	**6.6563**	13.6852	16.8535	19.7351	17.5186	**10.2129**	20.3050
Weibull	α	4.640	7.076	4.761	3.099	9.929	3.629	3.582	6.447	7.862	1.346
	β	0.835	1.008	0.860	0.746	0.905	0.852	0.764	0.940	0.850	0.807
	R^2 Adjusted	**0.9984**	0.9942	**0.9975**	0.9914	**0.9990**	**0.9971**	**0.9954**	0.9976	0.9967	**0.9999**
	AIC	**12.6913**	19.3849	**15.1601**	21.7221	**7.5884**	**16.6979**	**18.1935**	14.6233	13.9517	**–0.3317**
Peppas Sahlin	K1	21.619	–95.004	21.097	31.431	–17.388	27.538	26.265	–232.867	–2.264	62.978
	K2	–1.262	107.715	–1.219	–1.555	27.301	–1.927	–2.056	245.43	15.782	–9.817
	m	0.707	0.143	0.734	0.504	0.249	0.671	0.708	0.078	0.303	0.518
	R^2 Adjusted	0.9976	**0.9966**	0.9953	0.9980	0.9970	0.9967	0.9918	**1.0000**	0.9977	0.9983
	AIC	14.7212	**16.6168**	18.2249	14.2873	12.8144	17.2486	21.0817	**–6.8033**	12.1407	15.2404

k0-Zero order constant, R^2 Adj- Adjusted correlation coefficient, AIC: Akaike information criterion, kkP: Korsemeyer Peppas constant, kH: Higuchi constant, α and β - shape parameter for weibull equation, K1 - constant for Fickian diffusion, K2 - constant for Case II relaxational mechanism, m - Fickian diffusion exponent. DOE: Design of experiment

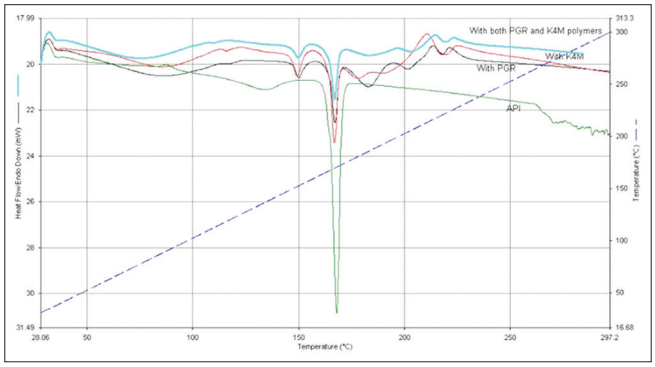

Figure 3: Overlay of differential scanning calorimetry thermograms of pure API and tablets containing API with different rate controlling polymers

containing only K4M as a rate controlling polymer (OB 5 and OB 7) are construed well by Weibull model for 20% and 40%w/w polymer content, respectively. Both batches showed parabolic release pattern (β < 1, case 3). OB 8 (30% w/w K4M) showed case II relaxational release due to positive value of k2.[30,34,35] Batches containing 0.5:0.5 ratio of both polymers at total 30% w/w (OB 1 and OB 3) showed Weibull type drug release, whereas drug release kinetics of batches containing 20% w/w (OB 4) and 40% w/w (OB 9) can be best described by Korsmeyer-Peppas power law equation. Both batches exhibited anomalous or non-Fickian transport.

Thermal characterizaion using DSC

Figure 3 shows overlay of DSC thermograms of pure API, tablets containing only PGR as rate controlling polymer, tablets containing only K4M as rate controlling polymer and tablets containing both rate controlling polymers. Both the API (DPM) as well as tablets containing different polymers along with DPM exhibited sharp endothermic peak around 168°C which is melting point of DPM. It indicates the absence of any physicochemical incompatibility between drug-polymer and also the absence of change in polymorphic form of drug during manufacturing process. Furthermore, all three tablets exhibited characteristic small sharp endothermic peak around 147°C which is due to dehydration of the monohydrate form of lactose (i.e. loss of crystalline water). This finding was well-anticipated and pretty in-line with DSC studies of different grades of lactose reported in literature.[36]

Graphical optimization of measured responses (overlay plot)

Design Expert® Ver.9.0.0.7 (Stat-Ease Inc., Minneapolis, MN 55413) has in-built option for graphical optimization which frames "design-space" based on given constraints for measured responses. Based on available data for dissolution studies, "overlay plot" as shown in Figure 4 was obtained

through graphical optimization. Design space is shown in yellow color. Independent factors with levels selected within design-space yield desired results within given specifications. From the data, batches OB 2 (PGR:K4M ratio 1:0, polymer content 40% w/w), OB 3 (PGR:K4M ratio 0.5:0.5, polymer content 30% w/w), and OB 7 (PGR:K4M ratio 0:1, polymer content 20% w/w) were found to be optimum batches.

Checkpoint batches and cross-validation of DOE model

Three experiments were performed at varying polymer ratio and content at values other than those used in experimental design to check reliability of the model. The experimental values and predicted values for each response were shown in Table 10. Bias or % relative error was calculated for each response as per following equation;[24,37]

$$\% \text{ Bias} = \left[\frac{\text{Predicted value-Experimental value}}{\text{Predicted value}} * 100 \right] \quad (10)$$

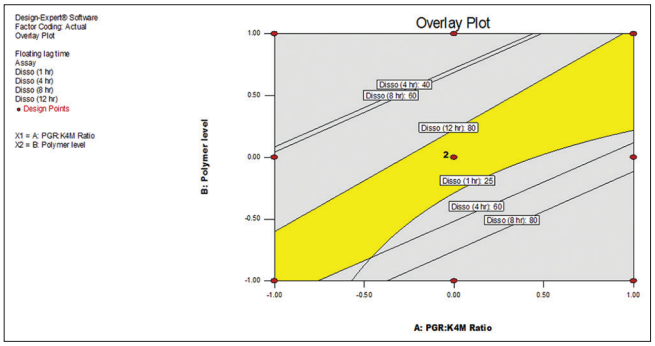

Figure 4: Overlay plot showing design space for dipyridamole gastroretentive floating tablets

From the data, it can be deduced that the equations satisfactorily demonstrate influence of formulation variables on the responses of the study due to fairly good agreement between the predicted and experimental values in all three checkpoint batches and low value of bias. Assay of all checkpoint batches was found to be in the range of 98.5-99.9. Floating lag time was also found to be <30 s for all batches.

Packaging and stability study

The optimized batches exhibited negligible change under stability conditions for parameters such as appearance, hardness, assay, floating lag time, total floating time, related substances, and drug dissolution for both packs (bottles and blisters). Assay of all stability samples was ranged between 98.6% and 99.8%. The similarity factor (f2) was employed for comparison of dissolution profiles of different stability stations with initial samples. It was found to be >80 for all samples. Known impurities and unknown impurity for all optimum batches were also found to be less than limits specified by ICH Q3B (R2)[38] for initial and stability samples. Thus, it can be concluded that selected batches are stable under both packaging configuration and therefore risk is reduced from medium to low.

Risk mitigation and control strategy

3^2 full factorial design was utilized to investigate the effect of high-risk independent variables on dissolution to establish the design space. The design space is a multidimensional combination and interaction of input variables and process parameters where all product CQAs are met.[21] Risk mitigation and control strategy are based on how quality risk can be minimized based on product and process understanding

Table 10: Comparison between experimental and predicted responses (drug dissolution) for checkpoint batches

Responses	Checkpoint batch	Factors (Coded and Actual)		Experimental (observed) values	Predicted values	Bias (%)
		A (PGR:K4M ratio)	B (Polymer level)			
Q1	1	−0.5 (0.25:0.75)	−0.5 (25%w/w)	20.88	21.96	4.92
	2	0 (0.50:0.50)	−0.2 (28%w/w)	23.21	23.98	3.21
	3	0.5 (0.75:0.25)	0.5 (35%w/w)	18.35	17.94	−2.29
Q4	1	−0.5 (0.25:0.75)	−0.5 (25%w/w)	53.85	54.53	1.25
	2	0 (0.50:0.50)	−0.2 (28%w/w)	55.68	54.87	−1.48
	3	0.5 (0.75:0.25)	0.5 (35%w/w)	48.23	48.74	1.05
Q8	1	−0.5 (0.25:0.75)	−0.5 (25%w/w)	72.89	72.23	−0.91
	2	0 (0.50:0.50)	−0.2 (28%w/w)	72.11	72.58	0.65
	3	0.5 (0.75:0.25)	0.5 (35%w/w)	66.92	67.39	0.70
Q12	1	−0.5 (0.25:0.75)	−0.5 (25%w/w)	84.25	83.45	−0.96
	2	0 (0.50:0.50)	−0.2 (28%w/w)	84.25	84.67	0.50
	3	0.5 (0.75:0.25)	0.5 (35%w/w)	81.95	81.67	−0.34

as well as desired product quality can be achieved within studied design space.

From the data, it can be concluded that both the high-risk factors (polymer ratio [X1] and polymer content [X2]) have a significant impact ($P < 0.05$) on all studied dissolution time points (Q1, Q4, Q8 and Q12). For Q1, interaction effect was also observed. As the ratio of PGR:K4M increases from low (−1) to high (+1) level, % drug dissolution increases for the fixed polymer content. Also from the buoyancy studies and overlay plot, it can be inferred that both the polymers should be effectively utilized in optimum ratio and at corresponding optimum level (mentioned as yellow zone in overlay plot) to achieve desired drug release. Hence, working within this range, risk is reduced to low for both the factors. Risk mitigation strategy for the same is to monitor drug dissolution profile, and all the responses (Q1, Q4, Q8 and Q12) must be within constraints range.

For the packaging configuration, identified as moderate risk factor during initial risk assessment, the risk is reduced to low as depicted in respective section (packaging and stability studies). Figure 5 depicts FMEA analysis before and after implementation of control strategy. Furthermore, it is important to note that RPN of all probable moderate to high-risk factors fell below 20 after implementation of control stretegy which put them under low risk. Also further large-scale trials are necessary since currently developed design space was generated based on small scale lab trials which should be justified for use at scale-up and commercial level. In such a way established, design space can be further streamlined and enriched with better product and process understanding gathered throughout the product lifecycle.

CONCLUSION

Although there were tremendous efforts undertaken to develop gastroretentive drug delivery system of DPM to enhance solubility and provide CR over a period, formulation design presented here offers simple, cost-effective, easily adoptable and scalable technology for industry. The present investigation describes overall QbD approach with risk identification and assessment using FMEA, formulation optimization using 3^2 full factorial design, kinetic modelling, risk mitigation, and control strategy. The optimized batches were having floating lag time ranging between 20 and 35 s, total floating time of >12 h and exhibited mean drug dissolution at Q1 between 12.42 and 22.46, Q4 between 45.62 and 58.49, Q8 between 64.86 and 72.74, and Q12 between 84.14 and 84.59. Developed formulation exhibited floating characteristics using both mechanisms CO_2 generation along with significant swelling and expansion capabilities thereby decreasing overall density of dosage form and hence looking to be more promising to exhibit gastroretentive potential *in vivo*. Furthermore, all high-risk failure modes were successfully shifted to low-risk category after establishment of design space and control strategy. The present formulation also serves as exemplar for triumphant paradigm shift in formulation development from conventional design to experimental design using systematic QbD approach. This investigation also extends scope of successful application of PanExcea™ GR polymer in developing extended release floating tablets of DPM in conjunction with methocel K4M premium CR. Although present optimized formulation manifested desired drug release profile *in vitro* and serves as a potential option to switch from immediate-release (IR) tablets to gastroretentive extended-release (ER) tablets, further pharmacokinetic assessments/clinical studies are essential to demonstrate its efficacy *in vivo*. The present formulation strategy can also be extended to develop future CR dosage forms of other molecules which can be benefited in terms of solubility, absorption and ultimately increased bioavailability by stomach targeted drug delivery.

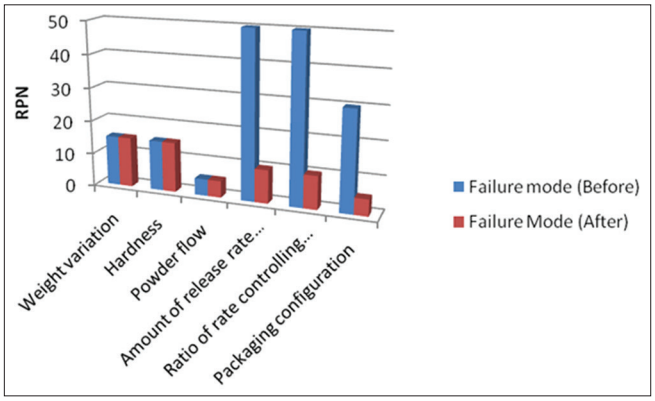

Figure 5: Failure mode effect analysis analysis of formulation factors depicting respective RPN of failure modes before and after application of risk mitigation and control strategy

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SUPPLEMENTARY 1

Related Substances Estimation

Selected optimized batches were tested for related substances using following analytical method reported by Vaghela *et al*.[1] :

Mobile Phase A: 0.007M potassium dihydrogen phosphate buffer, pH adjusted to 7.0 with 5%w/w sodium hydroxide solution.

Mobile Phase B: Methanol

Procedure

Mixture of methanol and 0.01M potassium dihydrogen phosphate buffer, pH adjusted to 3.0 with ortho-phosphoric acid in the ratio of 60:40 v/v was used as diluent. A system suitability solution of Dipyridamole and known impurities was prepared using diluent mixture at concentration of 1.6 mg/ml (1600 ppm) and 3.2 µg/ml (3.2 ppm) respectively. Working standard solution was prepared using Dipyridamole USP and diluent mixture at final concentration of 8 µg/ml (8 ppm).

Find out average weight of 20 tablets and crush to make fine powder. Mix the powder and transfer accurately weighed quantity of powder equivalent to 80 mg Dipyridamole into 50 ml volumetric flask. Dilute suitably using diluent mixture and centrifuge the mixture to get resultant supernatant (sample solution) having Dipyridamole concentration of about 1.6 mg/ml (1600 ppm).

Chromatographic system

Column: Inertsil® ODS-2, symmetry C18 (150 mm x 4.6 mm) 5 µm
UV detector: 295 nm
Flow rate: 1 ml/min
Injection volume: 10 µl
Column temperature: 45˚C
Gradient programme:

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	50	50
4	50	50
25	5	95
28	5	95
30	50	50
35	50	50

Disregard any peak due to placebo and diluent mixture.
Calculate % of known impurity and unknown impurity as per following formula (1) and (2) respectively:
% of known impurity=

$$\frac{AT}{AS}\times\frac{SW}{100}\times\frac{5}{50}\times\frac{5}{50}\times\frac{50}{TW}\times\frac{P}{100}\times\frac{AW}{LC}\times\frac{100}{RRF} \quad (1)$$

% of unknown impurity=

$$\frac{AU}{AS}\times\frac{SW}{100}\times\frac{5}{50}\times\frac{5}{50}\times\frac{50}{TW}\times\frac{P}{100}\times\frac{AW}{LC}\times 100 \quad (2)$$

Where:
AT= known impurity peak area in test sample injection
AU= unknown impurity peak area in test sample injection
AS= Dipyridamole peak area in standard injection
SW= Weight of Dipyridamole for standard preparation in mg
TW= Weight of Dipyridamole tablet powder taken in mg
P= Dipyridamole potency on as is basis
AW= Average weight of 20 tablets
LC= Lable claim
RRF= Relative response factor of each known impurity

% of total impurities = sum of % of all known and unknown impurities

REFERENCE

1. Vaghela BK, Rao SS, Reddy PS. Development and validation of a stability indicating RP-LC method for the estimation of process related impurities and degradation products of dipyridamole retard capsules. Int J Pharm Pharm Sci 2012;4(1):615–22.