Original Article

QBD Approach to Predict the *in-vivo* Performance Based on *in-vitro* Results using *Mucuna pruriens* Seed Mucilage as a Novel Tablet Dosage Form Excipient and Dicofenac Sodium as Model drug Candidate

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ABSTRACT

Background: Aim of the present study was to put forth certain modifications in Quality by design approach to predict the *in-vivo* performance of dosage form based on *in-vivo* performance parameter simulation using *in-vitro* experimentations. **Materials and Methods:** One factor design was used with prime focus on impact of *Mucuna pruriens* seed mucilage as excipient on dosage form functionality and applicability. During product development stage, apart from manufacturing variables other impacting parameters considered were GI pH, alterations in body temperature and GI motility. Factors considered were simulated pH, Temperature and RPM (Rotations per minutes) variations. Process flow worksheet was developed. QTPP (Quality target product profile) and CQA (Critical Quality Attributes) data was generated. **Results:** Risk assessment and Ishikawa diagram (Cause and effect analysis) were found to be helpful to generate the results predicting *in vivo* performance of dosage from. The process capability indices helped for judging product/process performance. The study design could be helpful to analyze the alterations in *in-vivo* performance based on excipient behavior in simulated conditions tested *in-vitro*. **Conclusion:** The present research work has successfully used Quality by design approach to predict the *in-vivo* performance of Tablet dosage form based on *in-vitro* data simulation. It can be concluded that study design with more number of simulating variables could be helpful pattern to come up with *in-vivo* performance predictions.

Key words: *Mucuna pruriens*, Seed polymer, Excipient, QbD perspective, Process capability study, Ishikawa diagram, QTPP, CQA.

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INTRODUCTION

Quality by Design (QbD)

Quality by design is a system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of new and in-process materials and processes, with the goal of ensuring final product safety. The Principle of QbD is science and risk based product development, risk assessment, lifecycle approach and method design are explained in the quality guidelines of international conference on harmonization that is ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, ICH Q10 Pharmaceutical Quality System, ICH Q11 Development and Manufacture of Drug Substances. Key elements in quality by design are quality target profile, critical quality

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attributes, design space, control strategy and risk assessment.[1-3]

Mucuna pruriens (Velvet beans)

M. pruriens is a tropical twining herb commonly known as Velvet bean belongs to the family Fabeaceae. *M. pruriens* is very well known for its medicinal utility. In Ayurveda *Mucuna pruriens* has been well documented for its therapeutic potentials as well as keen interest in phytochemical and Ayurvedic research due to its excellent medicinal values From the ancient times Cowhage has been used in Ayurvedic medicine for the treatment of Parkinson's disease associated with progressive degeneration of dopaminergic neurons in specific areas in the brain which is a common age-related neurodegenerative disorder The beans of the *M. pruriens* are known to produce the unusual non protein amino acid L-dopa, a potent neurotransmitter. it is also used in many other diseases such as for treating arthritis, anxiety, cancer, cough, diarrhoea, dysentery, diabetes, dysmenorrhea, delirium, gonorrhoea, gout, impotence, muscular pain, parasitic infections, rheumatic disorders, as analgesic and antipyretic, to induce vomiting, to treat snakebite (anti-venom activity) and scorpion stings, sexual debility, sterility, tuberculosis and its direct application on skin can help to stimulate surface blood flow in conditions that involve paralysis.[4,5]

Discreet data is available describing the utilization of mucilage isolated from Mucuna seeds as pharmaceutical excipient in dosage for design and development. Numbers of general methods are reported in the literature for the isolation of seed mucilage.[6-9]

The objective of the present research work was to focus on Quality by design perspectives to generate data on the functionality and applicability of dosage form designed using *Mucuna pruriens* seed polymer as novel tablet dosage form excipient. Predicting the *in-vivo* behavior of polymer/excipient and ultimately dosage form based on *in-vitro* simulated testing formed the basis for the present research work.

MATERIALS AND METHODS

Mucuna pruriens seeds were procured from local market and authentified from western regional centre, Ministry of environment Forestry and climate change, Botanical survey of India, Koregaon Road Pune. Drug used in the study was Diclofenac sodium. All other required chemicals used were of appropriate grades purchased from authentic chemical supplier of the institute.

Methodology

Isolation of Mucilage component) (*Mucuna* Seed Mucilage: MSM)

1. Seeds were grinded in and passed through sieve no. 60. Refer Figure 1 for seeds and seed powder image.
2. Grinded seed powder of 40 gram was weighed and dissolved in a beaker containing 400 ml water.
3. Powder was allowed to soak for 24 hr. After 24 hr the soaked powder with water was allowed to boil for half hour and then cooled.
4. Above material was squeezed from muslin cloth and filtrate was collected in beaker. To the filtrate 190 ml of acetone was added and precipitate was obtained.
5. Precipitate was collected in Petri dish and dried in hot air oven at 40°C. After drying material was collected and ground to obtain isolated component.
6. Obtained mucilage component was stored in desiccators to protect it from moisture which was taken for further characterization study.

Hygroscopicity of Isolated Mucilage

Excess amount of dried silica powder was placed in the well of desiccator. Samples of each material (100-300 mg) were weighed (60 mesh and 100 mesh at 40°C and 37°C) in open and tarred glass Petri-plates which then placed into a desiccator which were labelled and maintained at room temperature. After 24 hr of storage, samples were removed from desiccator and final mass of each samples were determined with the aid of calibrated analytical balance.

Formula:

$$\% \text{ increase in mass} = \frac{M3 - M2}{M2 - M1} \times 100$$

Where, M_1= Mass of empty Petri-plate

M_2= Mass of Petri-plate and sample (Initial)

M_3= Mass of Petri-plate and sample (After 24 hr)

Figure 1: *Mucuna pruriens* seeds with isolated seed mucilage powder.

Formulation recommendation and dosage form composition

Formulation recommendation was performed on the basis of results obtained on pre formulation study carried out on *Mucuna* Seed Mucilage (MSM) component/ Excipient. All other excipient like talc, magnesium stearate, lactose were selected as per the general tablet formulation composition requirements

Generation of Product development work flow sheet

During generation of product development work flow sheet both *in-vitro* and *in-vivo* parameters responsible for product performance are kept in mind and accordingly QTPP, CQA, Risk assessment, Cause and effect analysis were performed.[1] During product development only manufacturing variables were not the focus. Other parameters which may have impact on product performance like GI conditions Eg. pH, disease conditions and alterations in physiological parameters, alterations in body temperature, alterations in GI motility were also considered during *in-vitro* product development process and *in-vitro* testing. Where ever possible the parameters were simulated during product evaluation steps itself.

Protocol for product development is shown in the form of formulation, development, optimization and validation work flow sheet as shown in Figure 2.

Quality target product profile (QTPP) generation for tablet dosage form (using QbD guidelines)

QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. Diclofenac sodium was considered as drug of choice to be incorporated into tablet dosage form with dose of 50 mg which is reported the conventional dose of drug. QTPP were decided as per the pharmaceutical equivalence study requirement, product quality attributes considered were assay, content uniformity and % release.[2,3] The generated QTPP as required to generate critical quality attributes is shown in Table 1.

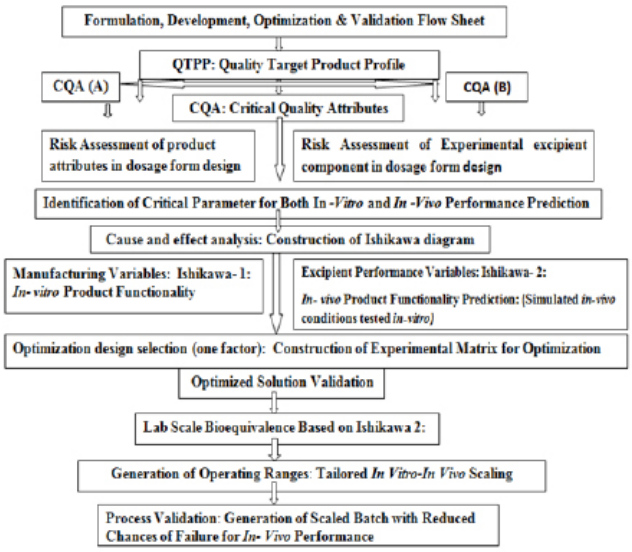

Figure 2: Protocol for Product development (Work Flow Sheet).

CQA data generation

CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.[2,3] QTPP was considered as a guideline to develop CQAs as mentioned in Table 2.

Risk assessment of *Mucuna* Seed Mucilage (MSM) Component/Excipient attributes in dosage form design

The relative risk that polymer component attribute in present work was ranked as high, medium, or low. The same relative risk ranking system was used throughout the pharmaceutical development and is summarized in Table 3 for each risk assessment performed, the rationale for the risk assessment tool selection and the details of the risk identification, analysis and evaluation is also mentioned in the Table 3. The two primary principles that should be considered when implementing quality risk management: The evaluation of the risk to quality

Table 1: Quality target product profile generation for tablet dosage form.

QTPP elements	Target	Justification
Dosage form	Tablet	Pharmaceutical equivalence requirement: same dosage form
Rout of administration	Oral	Pharmaceutical equivalence requirement: same rout of administration
Dosage strength	50mg	Pharmaceutical equivalence requirement: same strength
Drug product quality attributes	Physical attributes Identification Assay Content Uniformity Drug Release etc	Pharmaceutical equivalence requirement: Meeting the Same compendia! or other applicable (quality) standards (i.e., identity, assay, purity and quality).

should be based on scientific knowledge and ultimately link to the protection of the patient;

Generation of Ishikawa diagram for dosage form design and product performance *in vitro*

Ishikawa Diagram/Fishbone diagram (Cause and effect analysis) is designed taking into consideration both *in vitro* as well as *in-vivo* variable responsible for deciding the product performance that is product functionality and applicability.

Ishikawa diagram for product performance prediction both at *in-vitro* variables and *in-vivo* simulated variables is highlighted in Figure 3.

Formulation of Tablet Dosage Form

Optimization design and Experimentation (One factor response design)

From the Ishikawa diagram constructed in section. Some of the *Mucuna* Seed Mucilage (MSM) component/ Excipient attributes selected was concentration, temperature to treat excipient sample and particle size. So, one factor design with MSM as quantitative factor and rest of the MSM related parameters were selected as qualitative categorical parameters in the study. The levels of these factors were selected on the basis of initial studies and observations. The data was analyzed using Design expert software.

Mucuna Seed Mucilage (MSM) component/Excipient concentration was selected in the range 50 to 200 mg (with respect to tablet weight of 350 mg) i.e. % 14.28 to 57.14 of MSM concentration, particle size of MSM (mesh size of sieve 60 and 100). Temperature for treating MSM was selected 37°C and 40°C. Formulation composition as per one factor design layout, experimental design matrix in actual levels is shown in Table 4 Tablets containing Diclofenac sodium were prepared by wet granulation method using 10 mm biconvex punch on a tablet compression machine. Data interpretation and Formulation optimization is done by experimental matrix data analysis and interpretations thereof.

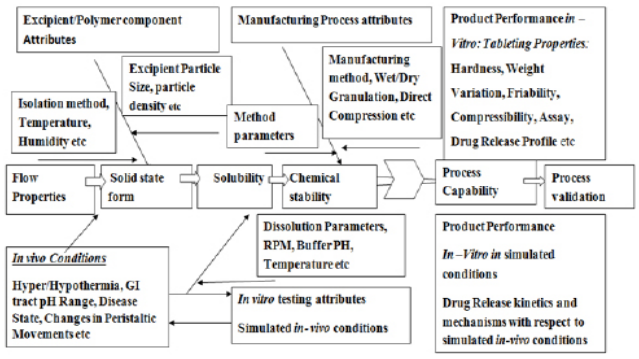

Figure 3: Ishikawa Diagram for product performance prediction both at *in-vitro* variables and *in-vivo* simulated variables.

Pre compression characterization of experimental matrix batches

Characterization of granule blend was carried out by determining bulk density, tapped density, Hausner's ratio, Compressibility index and angle of repose.[10]

Post compression characterization of experimental matrix batches

Post compression parameters like Tablet thickness, Hardness, Friability, Weight Variation, Uniformity of drug content,[10] *in-vitro* drug release study were performed. Study was performed in 1.2 pH 0.1 N HCl for 1st 2 hr and 6.8 pH phosphate buffer for next study at 50 RPM speed and 37 ±0.5°C using USP type II dissolution apparatus. Dissolution data was treated for release

Table 2: Critical Quality Attributes (CQAs) of Tablet Dosage form.

Critical Quality Attributes (CQAs) of the drug product	Target	Is it CQA? (YES/No)
***In-vitro* Variable**		
1-Physical attributes	Appearance	No
	Odor	No
2-Dosage form Factors/Manufacturing variable		
Excipient Particle Size	Pre compression parameter	Yes
Excipient Concentration	Post compression parameter	Yes
Method of Manufacturing	Hardness	Yes
Temperature (may have impact on Excipient moisture content, solid state form etc)	Thickness	No (if within limit)
	% drug release	Yes
	Content uniformity	Yes
	Friability	Yes
	Drug content	Yes
***In-vivo* Variable**		
(Performed *in-vitro* under simulated conditions)		
Gastric Motility changes	Drug Release	Yes
(RPM- *in-vitro*) GI pH Variations	(Based on Excipient behavior and pH Partition Hypothesis)	Yes
(Buffers of varying pH) Body Temperature variations (Dissolution study Temperature variations)		Yes

Table 3: Justification for Risk assessment of *Mucuna* Seed Mucilage (MSM) - Excipient component attributes in dosage form design.

Excipient Attributes	Justification
Particle size distribution(PSD)/ Bulk density **CQA's :** Physical Attributes, Assay, Content Uniformity, Drug release	Particle size and flow properties may have effect on physical attributes like hardness, friability etc. Flow properties if poor may not give tablets with edge finishing, may not be able to compress etc. Ultimately, other CQA's may also be affected. MSM sample sieved through 60 and 100 mesh could be used for comparative evaluation and check the effect of particle size on dosage form behavior. Therefore, the risk of PSD and bulk density to impact the drug product CQA's could be high.
Solid state form **CQA's** : Physical Attributes, Assay, Content Uniformity, Drug release	Solid state form transformation may occur during the compression process with the aid of heat generation. This transformation may impact drug release. Furthermore, the MSM powder is having amorphous nature that may get converted into crystalline form during the storage of the finished product; the drug release profile may change. The risk of solid state form to impact drug release from the tablets could be high.
Hygroscopicity **CQA's** : Physical Attributes, Assay, Content Uniformity, Drug release.	Because the MSM powder is hygroscopic, the risk of sorbed water to impact tablet physical attributes (micromeritics), assay, content uniformity (CU) or drug release could be high.
Solubility **CQA's** : Physical Attributes, Assay, Content Uniformity, Drug release	MSM solubility has no impact on tablet physical attributes (size and splitability), assay, content uniformity (CU). The risk could be low in dosage form design but risk could be high in pharmacokinetic and pharmacodynamic dosage form behaviour in the body and therapeutic response may alter. The MSM powder has moderate dissolution rate and good solubility. It potentially impact the drug release profile. The risk could be high. Analysis of pH dependent solubility could help in deciding site targeting of dosage form. pH dependent solubility may show different ionization potential and different release pattern.
Chemical stability **CQA's** :Physical Attributes	Stability of MSM has no impact on tablet physical attributes (size and splitability). Assay and content uniformity (CU) may have high impact with change in stability.

Table 4: Formulations as per one factor design layout, experimental design matrix in actual levels.

Excipient (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
(P, T)	(60,	(60,	(60,	(60,	(100,	(100,	(100,	(100,
	37)	37)	40)	40)	37)	37)	40)	40)
Diclofenac sodium	50	50	50	50	50	50	50	50
MSM (mg)	50	200	50	200	50	200	50	200
Lactose	235	85	235	85	235	85	235	85
Talc (2.28 %)	8	8	8	8	8	8	8	8
Magnesium stearate (2%)	7	7	7	7	7	7	7	7
Total weight of tablet (mg)	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Where, P= particle size of polymer (mesh), T= Temperature (oC) to treat MSM sample

kinetics and mechanism predictions. Data profiling was done to predict the changes in dosage form performance at the simulated *in-vivo* condition performed *in-vitro*.

Experiment matrix data analysis, Optimized solution generation and Validation

Experimental Matrix data was analyzed and factors having significant impact on the expected response were identified for optimized solution generation. Response surface methodology (RSM) is widely practiced approach in the development and optimization of drug delivery devices. Based on the principle of design of experiments (DoE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to determine the optimum formulation. Statistical validity of the polynomials was established on the basis of analysis of variance (ANOVA) provision include in the Design Expert Software. Optimized solution generated was formulated and evaluated for parameters like content uniformity, hardness, thickness, dissolution performance, % drug release etc.

Performance Scale up Trials on Optimized Solutions

In-vivo biowaiver using *in-vitro* simulating conditions (RPM, pH, Temperature)

Optimized solutions generated were further taken for performance scale up trials. Critical parameters/Causes responsible for the expected effects are identified as shown in Figure 2, like acidic (1.2 pH, 0.1 N HCl) and basic (6.8 pH, Phosphate Buffers-PBS) conditions for any change in acidic and basic pH condition at the site of administration and in turn site of action. RPM conditions like 50 RPM and 100 RPM to represent the change in peristaltic movement of digestive tract. Temperature conditions like (32°C and 37°C) to represent altered temperature conditions of body. One *in-vitro* parameter considered was change in dissolution media (acidic and basic), paddle and baskets were also taken for comparative scale up trial. Study carried out would help to generate process capability index in terms of behavior in altered body conditions compared to normal physiological conditions. The comparative dissolution data profiling was performed considering the above selected parameters and physiological process performance and process potential was interpreted along with dissolution profiling study.

Dissolution data profiling (Model independent approach-Similarity and dissimilarity factor calculation)

Optimized formulation was evaluated on the basis of different dissolution conditions for the determination of similarity and dissimilarity factor. The dissolution conditions considered were paddle, basket, HCl (1.2) pH, PBS (6.8 pH), PBS (8 pH) temperature conditions as 32°C and 37°C. [11,12]

Generation of process capability indices

Process capability analysis using normal assumption often leads to erroneous interpretations of the process performance. Profile monitoring is a relatively new set of techniques in quality control that is used in situations where the state of product or process is represented by a function of two or more quality characteristics.[13] Here normal assumption means we can say conventional pattern of risk analysis like manufacturing process variables. We in the present research work have considered not only the manufacturing process variables but also the *in-vivo* conditions simulated *in-vitro* to predict the product performance that is functionality and applicability. Profile monitoring at manufacturing level considering both *in-vivo* and *in-vitro* product performance variables can generate very important information which can be helpful to predict results of exhibit batch taken for clinical performance check. A capability index relates engineering specification to the observed behavior of process. The capability of process is defined as the ratio of the distance from the process center to the nearest specification limit divided by measure process variability.[14,15] Results obtained generates very useful information regarding the dosage form development and dosage form performance.

Risk predictions and Conclusion

On the basis of data generated from experiment data analysis, process scale up trials, process capability indices, the impact of variables on formulation components were studied on drug product critical quality attributes and high or low risk components were identified for expected response of % drug release.

RESULTS AND DISCUSSION

Hygroscopicity of Isolated Mucilage

Along with other pre-formulation parameter, Hygroscopicity was considered as the important parameter in decision making to consider the mucilage for the study as tablet dosage form excipients. Hygroscopicity values reported for 60 mesh Powder at 40 Degree celcius and 37 degree celcius were 0.98±1.056 and 0±0.022 respectively and for 100 mesh Powder40 Degree celcius and 37 degree celcius were -6.55±0.056 and 0.38±0.0965 respectively. Hygroscopicity values of 0 to 1.5 ranges indicates that powder could be fruitfully utilized for tablet dosage form design. It shows no impact of environmental humidity which could make it good candidate in dosage form design.

Optimization design and Experimentation (One factor design)

In order to determine the drug release time profile, *Mucuna* Seed Mucilage (MSM) component/Excipient was taken as a factor and variation in drug: MSM concentration, particle size of MSM Powder, temperature conditions of MSM Powder were used in order to study the influence of these conditions on the overall drug release and to obtain the optimized formulation by one factor design.

Pre -compression characterization of experimental matrix batches

The bulk density obtained for all formulations in the range of 0.49 to 0.56 (g/ml) and tapped density in the range of 0.45 to 0.68 (g/ml). Angle of repose of granule blend of all the formulations was found to be in the range of 29.36 to 34.96°C which is showing good flow ability,

necessary for proper flow of granule blend into the die cavity. Carr's index of the granule blend of all formulations was found to be in the range of 7.57 to 16.92 % which indicates the blend would not have any problem during compression of mass between the punch tools, powder mass segregation and mass charge development could be avoided with the obtained care's index value. Hausner's ratio was found to be in the range of 1.09 to 1.20. All these results indicated that, the granule blends possess good compression property and good flow of granule blend into the die cavity.

Post compression parameters

The tablets were evaluated for hardness, thickness, % friability and weight variation and content uniformity. The hardness of tablets of all the batches was found in the range 4.10 to 4.55 kg/cm^2. Thickness of all tablets was found to be in the range of 3.121 to 3.186 mm. Tablets showed % friability in the range of 0.404 to 0.774 % which is within limit. All the formulations pass the weight variation test as per the range limit for weight variation. Whereas Tablets from each batch showed uniformity of drug content in the range of 92.52 to 98.11 % which is within pharmacopoeial specifications. All the formulations complies the test for uniformity of drug content as it was found to be within the limit of 90 to 110 %.

In-vitro drug release (Dissolution study)

As depicted from Table 5 for *in-vitro* drug release and Table 6 for dissolution mechanism and release profiling, it is seen that concentration of MSM plays very important role in drug release profile.

1. Batches (F1, F3, F5, F7) with 14.28% concentration could prolong the release of drug for about 12 hrs whereas batches F2,F4,F6,F8 with 57.14% MSM concentration were about 50 % released at the end of 12th hr could show the release for still more 12 hr. The said results focus moreof release retarding behaviour of the MSM Excipient component (Table 5).
2. But the rate of release of drug from all the batches was found to be first order with Maximum *R2* values as compared to *R2* values of Zero order rate predictions which is also supported by sum of squared error/residual error calculations. The reason could be pH sentitive solubility and Ionization of MSM excipient component.
3. Release rate prediction of individual batch:
   Batch F1: First order which is drug concentration dependent.
   Batch F2: Pseudo first order as *R2* values of both rate predicting models are close to each other. Pseudo first order prediction as residual error is less with zero order model.
   Batch F3: First order which is drug concentration dependent.
   Batch F4: First order (but as values are nearer may be mixed order)
   Batch F5: Mixed prediction
   Batch F6: Mixed prediction
   Batch F7: Mixed prediction
   Batch F8: Mixed prediction
4. From the observations for zero order and first order release kinetics predictions, the regression values are very close. So, it can be said that concentration range of MSM may show mixed order pattern of release based on solubility pattern along with other factors like impact of particle size, temperature used to dry the MSM powder etc.
5. Observations among release mechanism predicting models shows the *R2* values on higher side (near to 1) for Higuchi model and Korsemeyer peppas with the residual error values lowest for Higuchi release mecahnism
6. From this observation it can be interpreated that drug diffuses out of MSM strucuture chain. But the component might also be showing time dependent solubility/ionization which may lead to erosion of mucilage chain matrix which is ultimatly shifting the release pattern from Higuchi to Korsemayer Peppas.
7. Observations for N exponent values of Korsemeyer Peppas model indicates that value of N Exponent for the batches between 0.9 to 1.2 predicts super case II transport for the concentration range selected (50 mg and 200 mg) expect batch F3 which is 0.9149 indicates anomalous transport mechanism signifying zero order release which was initially judgemented as pseudo first order release from the regression value for zero order and first order kinetic models.
8. So, the overall conclusion for the observations of readings for dissolution is that concentartion range from 50 to 200 mg (14.28 to 57. 14 %) is responsible to show anomalous transport mechanism involving diffusion as major mechanism along with time dependent solubility of diffusing polymer chains which ultimately takes the eroding release pattern over the time. Time dependent polymer base release patterns makes the mixed order or pseudoorder kinetics as a major rate of reaction.

Table 5: *In-vitro* dissolution data of tablets for formulations F1 to F8.

Time (hr)	% Cumulative drug release			
	F1	**F2**	**F3**	**F4**
1	4.890416+0.23	3.853652±0.25	9.302181±0.21	4.294828±0.26
2	6.32935±0.46	5.838296±0.56	24.00092±0.40	10.38486±0.47
3	61.61596+0.86	20.33156±0.73	36.84532±0.59	19 .50587 ±0 .. 60
4	66.45827+0.98	23.49956±0.90	53.93534±0.76	23.49497±0.76
5	69.92192+ 1.26	25.85884+ 1.11	69.71549±0.90	25.85426±0.93
6	72.70092+ 1.39	32.27638+ 1.34	72.4945+ 1.16	32.2718+1.19
7	78.38314+ 1.69	36.08658+ 1.60	74.04828+ 1.20	36.082+ 1.36
8	81.20481 + 1.86	38.43073+ 1.79	80.97545+ 1.49	41.2747+71.55
9	87.13611 + 1.97	42.06662+ 1.86	91.0352+ 1.85	44.14208+ 1. 70
10	91.73553+2.06	47.9509+2.03	93.18049+ 1.93	54.6204+ 1.89
11	93.88083+2.38	54.81615+2.46	96.16064+2.03	57.14642+2.04
12	94.59034+2.46	57.17681 +2.69	97.91603+2.43	63.27658+2.56
	F5	**F6**	**F7**	**F8**
1	4.44924±0.19	3.412475±0.23	5 .463946±0.20	3.412475±0.22
2	15.69749+0.37	4.512316±0 .. 46	18.20018±0.45	6.409375±0.52
3	32.71688+0.53	15.79028±0.59	32.71688±0.62	14.96459±0.73
4	51.60048+0.86	18.93305±0.78	56.05919±0.86	18.10277±0.88
5	58.12008+0.95	23.33132±0.97	61. 73659±0.90	23.32214±0.98
6	64.13762+ 1.09	26.84519+ 1.08	68.8062+ 1.00	25 .18464+ 1.13
7	70.5996+ 1.38	30.62557+ 1.23	71.9086+ 1.63	30.60723+ 1.56
8	76.68279+ 1.53	33. 76559+ 1.56	79.23715+ 1.82	36.18302+ 1. 70
9	86.7196+ 1.70	37.78909+ 1.75	81.85653+ 1.99	39 .848+ 1.88
10	89.54379+ 1.92	40.34769+ 1.97	88.8642+2.18	50.3038+82.14
11	91.80307+2.00	49.64872+2.11	90.99551 +2.56	51.56844+2.25
12	93.08139+2.56	52.80754+2.43	94.37451 +2.86	58.70089+2.65

Table 6: Dissolution Data modeling for formulations (F1 to F8).									
Product code		**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
(C,P, T)		(50,60,	(200,60	(50,60,	(200,60	(50,100	(200,10	(50,100,	(200,1
		37)	, 40)	40)	,40)	, 37)	0,37)	40)	00,40)
Zero	A	0.7338	0.9725	0.8994	0.9899	0.9151	0.9811	0.8908	0.9896
order	B	117341	12325.	76830.	33958.	156702	1112.92	142684	58208
		5	14	01	69	6		4	3
First	A	0.7587	0.9758	0.9125	0.9908	0.9259	0.9829	0.9041	0.9897
order	B	46634.	106196	11532.	140019	109189	67661.1	105993	97122.
		65	.1	71	.1	5	5	1	1
Higuchi	A	0.7587	0.9758	0.9125	0.9908	0.9259	0.9829	0.9041	0.9897
crowell	B	1.3687	12.267	0.9524	11.360	8.768	11.512	1.376	14.512
Hixon	A	0.5071	0.7580	0.5718	0.8194	0.6217	0.8662	0.6104	0.8836
crowell	B	5957.0	63.558	11.126	1725.5	6814.3	1097.15	5783.79	1496.2
		8			7	5			3
Korsemeyer	A	0.7893	0.9487	0.9487	0.9849	0.9279	0.9535	0.9231	0.9880
Peppas	B	6783.6	3047.4	17620.	4300.2	9007.2	2919.31	10611.3	2798.2
		6	8	28	3				2
N		1.2261	1.101	0.9149	1.0269	1.1621	1.1384	1.08	1.1392
Exponent									

A= R_2 Regression coefficient), B= Sum of square of error (Residual error), C= Concentration of polymer, P= Particle size of polymer, T=

Experiment Matrix Data Analysis, Optimized Solution Generation and Validation

From the above interpretations from one factor lots like effect of MSM component excipient concentration, temperature, particle size and time of drug release we reached to conclusion that for retarding the release up to 24 hr the MSM component excipient concentration required is on higher size i. e. 200 mg (57.14 %). Temperature and particle size has no impact on drug release so MSM powder with no heat treatment can be considered for dosage form design. Particle size of MSM can be kept 60 mesh for optimized batch solution generation. Time of study could be kept 6 hrs and 12 hrs where expected release range can be considered from 50 to 100 % of drug by entring the value acordingly solutions are generated. Among the generated solutions the solution with 200mg(57.14%) concentration with MSM Seived through 60 Mesh Seive and with no heat treatment (Room Temperature conditions considered) and time of drug release upto 12 hr was taken out as optimum solution. The probability of drug release is extension upto 24 hr as the release predicted in 12 hr is around 50 to 60 % only. The optimized solution obtained from the model was formulated and the results are performed in the triplicates for determination of % CDR.

The optimum solution generated showed % CDR 57.176±1.253. Also test for weight variation passed as per I. P. standard. Thickness of tablet was in the range of 3.57-3.62 mm. Hardness of tablet was in the range of 4-4.5±1.532 kg/cm^2. Percent weight loss in the friability test was found to be less than 0.4 %. Content uniformity was found to be within 100± 1 % of the 350 mg of Diclofenac sodium.

Performance Scale up Trials on Optimized Solutions

In-vivo bio-waiver using *in-vitro* simulating conditions (RPM, pH, Temperature)

From Table 7 it is concluded that all the parameters like change in apparatus, RPM, pH conditions have impact on the dissolution release profile. In correlation with *in-vivo* conditions it can be judged that the MSM shows pH dependent release kinetics. Changes in pH from stomach, small intestine, large intestine may lead to variation in the release profile of the drug based on the pH dependent reponse of the excipient component. Moreover changes in release kinetics/release profile based on RPM can also be correlated with changes in release profile *in-vivo* with respect to changes in the peristaltic movement over the GI tract. Differences in the release profile based on method can be correlated with location of dosage form in body and consumption of acidic or basic food entities may also lead to changes in the release pattern of the dosage form based on changes in the stomach pH. Table 7 Dissolution data profiling-Model independent approach, indicates that all other parameters except Temperature shows impact on the release profiling. Change in the release locations in the body, or changes in gastric motility may have major impact in deciding dosage form performance in terms of functionality and applicability. Decisions on target locations, suitable dosage form modifications can be taken at the development stage itself based on the findings at this step.

Generation of Process Capability Indices

Process capability index, process performance for set parameters

From results mentioned in Table 8 considering the release retardant applications of MSM in the concentration range (14.28-57.14 %) prolonging the release from 12 hr to 24 hr. The Limits for % CDR considered in acidic condition for first 2 hrs of release were 25 to 55% whereas for basic conditions the limits considered

Table 7: Dissolution data profiling- Model independent approach.

Dissolution condition code	Dissolution conditions	50BH37 F2(A)	I 50BW37 F2(B)	I Profile (A)(B)
DI	50PH37	28.370	33.436	(Dissimilar)/ (Dissimilar)
D2	50BH32	76.388	17.853	(Similar)/ (Dissimilar)
D3	100BH37	42.916	23.940	(Dissimilar)/ (Dissimilar)
D4	50PW37	12.467	44.492	(Dissimilar)/ (Dissimilar)
DS	50BW32	16.882	78.199	(Dissimilarj/ (Similar)
D6	100BW37	23.017	47.071	(Dissimilar)/ (Dissimilar)
D7	50BM37	1.499	8.197	(Dissimilar)/ (Dissimilar)

P= Paddle, B= Basket, H= HCl (1.2 pH), W= PBS (6.8 pH), M+ PBS (8 pH), 50= 50 RPM, JOO= JOO RPM, 32= 320 C, 37= 370C.

Table 8: Process capability index, process performance for set parameters.

Sr. No.	Condition	Limit for % CDR		Cp	Cpk	
		Upper limit	Lower limit		Upper limit	Lower limit
1	P 0.1 N I-ICl 37,50	55	25	5.560167	30.28199	35.441805
2	B 0.1 N HCl 32,50	55	25	3.1385	28.42917	4.465039
3	B 0.1 NHCl 37,100	55	25	6.748167	8.348232	5.148101
4	P 6.8 pH 37,50	80	45	9.424333	44.76657	40.89171
5	B 6.8 pH 32,50	80	45	2.849778	55.10867	2.860091
6	B 0.1 N HCl 37,100	80	45	4.830194	2.077444	7.582945

Where, P= paddle, B= basket, 37 and 32= temperature conditions, 50 and 100= RPM conditions

were 45 to 80 %. Variations in RPM and Temperature were also considered simultaneuosly for calculations of process potential and process capability indices. All the values for process potential (Cp) and Process Performance (Cpk) were found to be greater than 2 and greater than 1.33 respectively. The said behaviour indicates that inspite of variable performance of MSM mucilage at acidic and basic conditions but the selected concentration range was well optimized as release retardent dosage form extending the release for about 24 hr. The release process performance of the tablet dosage form was found to be highly capable for the selected range of concentration.

CONCLUSION

The present research work has successfully used Quality by design approach to predict the *in- vivo* performance of Tablet dosage form based on *in-vitro* data simulation. One factor design was used with prime focus on impact of *Mucuna pruriens* seed polymer as excipient on dosage form functionality and applicability. Process flow worksheet was developed. QTPP (Quality target product profile) and CQA (Critical Quality Attributes) data was generated. Risk assessment and Ishikawa diagram (Cause and effect analysis) were found to be helpful to generate the results predicting *in vivo* performance of dosage from. In terms of applicability, *Mucuna* Seed mucilage was found to be release retardant excipient in the concentration range 14.28 to 57.14% (14 to 60 %) The process capability indices and process potential values were found to be above 2 and 1.33 respectively indicating the release performance *in-vivo* as per the required specifications of extended or prolonged release dosage form. Predicted variations in release performance based on dissolution data modeling indicated that, the study design could be helpful to analyze the alterations in *in-vivo* performance based on excipient behavior in simulated conditions tested *in-vitro*. Any component used as excipient in dosage form could be considered at 'High Risk' as it plays very important role in dosage form performance based on its performance in various *in-vivo* variations. Maximum possible *in-vivo* variations under simulated conditions *in-vitro* should also be considered during product development stage to avoid product failure during exhibit batch trials. It can be concluded that study design with more number of simulating variables could be helpful pattern to come up with exhibit batch performance predictor.

Note: As per revised USP official monograph for Diclofenac Extended release dosage form the dissolution media recommended is 0.05 M phosphate buffer, pH 7.5.[16-18] But in the present study the aim was to check the release profile and release mechanism of drug with respect to the behavior of new experimental excipient candidate. Moreover the major objective was to check how the *in-vivo* parameters like dosage form target location, pH, temperature, motility etc play role in deciding the excipients behavior and in turn the performance of dosage form. So the method involved the use of both the acidic and basic pH conditions to check the dissolution release mechanism and data profiling. Ultimately we could predict the process capability indices and certain conclusions were drawn on the basis of these variables.

Drug was taken as model drug for the said study on novel excipients. The present study target was to justify the behavior of dosage form in relation to the characteristics of new excipients and response of excipients to the *in-vivo* body conditions. We wanted to study how excipients behavior with respect to body conditions decides the release mechanism and release profiling. In this stage it was not the target to prove the dosage form better in comparison to marketed dosage form. So comparison of release profile with marketed dosage form was not considered.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

MSM: Mucuna Seed Mucilage; **QbD:** Quality by design; **CQA:** Critical Quality Attributes; **QTPP:** Quality Target Product Profile; **Cp:** Process potential; **Cpk:** Process Performance; **RPM:** Rotations Per Minuite; **NDA:** New drug Approval Appication.

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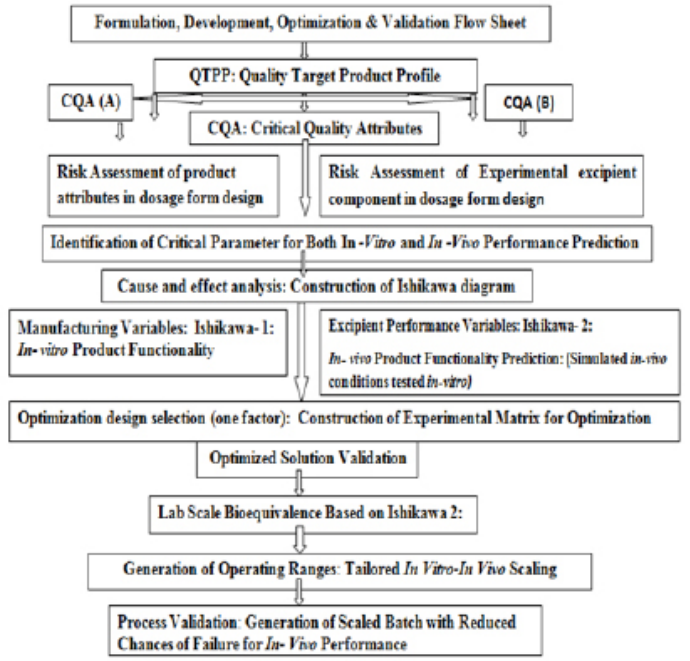
SUMMARY

There is no independent approval process for novel excipients. They are approved as part of an NDA and then only if the drug is approved and only for that particular route of administration and the level of use approved for the NDA. For pharmaceutical companies, it is risky to use a novel excipient because doing so complicates the regulatory issues, because any problem with the new excipient could hold up the approval of the drug product. If the drug fails, the excipient does not receive approval, even if the failure was not related to the excipient and the clinical trial data are not usable, even as a reference."As a result of these combined issues, the regulatory framework for the approval of new excipients creates a dilemma for the manufacturers and users of novel ingredients. Moreover the Novel Excipients Working Group and a similar group formed within IPEC-Americas are currently exploring the development of joint best practices for preclinical safety (testing and specification requirements) and creating a process for designing a well-defined pre-clinical data package for novel excipients. With IPEC-Americas, the group is assessing current challenges to excipient review and approval, and possible next steps to alleviate these challenges.

Considering this dilemma present research work would like to contribute in this process. Formulation development, optimization and validation flow has been proposed on trial basis using Quality by design (QbD) approach. During development stage Critical Quality Attributes (CQA) could be identified based on product parameters and excipient component parameters expected as QTPP (Quality Target product Profile). Critical parameters could be based on both *in-vitro* and *in-vivo* product performance expected as QTPP. Accordingly Cause and Effect analysis at two levels could be planned considering both product functionality and simulated *in-vivo* excipient performance variables tested *in-vitro*. This could be considered as Lab Scale Bioequivalence Based on Ishikawa 2, with generation of operating ranges which could be called as, tailored *in vitro-in vivo* Scaling. If planned appropriately, this would definitely help in generation of scaled batch with reduced chances of failure for *in-vivo* performance.

PICTORIAL ABSTRACT



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