ORIGINAL ARTICLE

Quality by Design-based Formulation and Evaluation of Fast Dissolving Tablet of Aspirin

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Abstract

Aim: The focus of the current study was to develop fast dissolving tablet (FDT) of aspirin using quality by design (QbD) approach. QbD was applied for better understanding the process and to enhance design space, using quality target product profile, critical quality attributes, and risk assessment. The aim of the project is to achieve early onset of aspirin by FDT. **Materials and Methods**: FDT of aspirin was developed by 3^2 factorial using Box–Behnken design. In factorial design we have selected two variables povidone and crospovidone at three levels. The response surface plots were generated. Ultraviolet (UV), Fourier-transform infrared, differential scanning calorimeter (DSC), and X-ray diffraction (XRD) analysis have been done for pre-formulation and post-formulation evaluations. The tablets were prepared by direct compression method. **Results and Discussions**: The λ_{max} was confirmed at 275 nm by UV spectroscopy. In compatibility study IR, it was observed that the drug was in pure form and there were no major interactions with other polymers. DSC and XRD studies revealed that the drug was in crystalline form showing sharp peaks. The *in vitro* dissolution study revealed that the batch F7 is best among nine batches been prepared. It was stable at 25°C ± 2°C/60% ± 5% RH and 40°C ± 2°C/70% ± 5% RH for 90 days. **Conclusion**: The study indicates that FDT of aspirin using QbD approach was successfully developed.

Key words: Aspirin, design of experiment, direct compression, fast dissolving tablet, optimization, quality by design

INTRODUCTION

Quality by design (QbD) is an intelligent approach to build quality in product and process. This can be achieved by constructive planning and the previous data available. Although it is based on risks, it has its results that it minimizes the end product and increases the chances of regulatory acceptance.[1] The principles of QbD are best explained by ICH Q8, ICH Q9, and ICH Q10 which gives the guidelines on science and risk-based assessment, product's life cycle and its approach and various method designs.[2] There is a great deal in of unpredictability in scaling up a product from research and development to production scale, and reasons for failure are generally not understood. QbD is a comprehensive approach targeting all phases of drug discovery, manufacturing, and delivery.[3-5]

Thus, the aim of the present investigation was to prepare a fast dissolving tablet (FDT) using aspirin and to understand the concept of pharmaceutical QbD and describe how it helps to ensure pharmaceutical quality. It begins by defining the desired product performance and also by defining the product that meets those performance requirements. The characteristics of the desired product are the basis for designing the manufacturing process which needs to be monitored in terms of performance. Fast dissolving drug delivery is rapidly gaining acceptance as not all fast dissolving technologies actually dissolve some use of different disintegration mechanisms such as high levels of disintegrates that cause the dosage form to disintegrate rapidly in the patient's mouth within a minute and can be gulped easily without the need of water. Thus, it offers an increased patient compliance and convenience. Formulation of FDTs possesses a great challenge in the formulation as there are a number of problems in manufacturing and quality control.

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MATERIALS AND METHODS

Materials

Aspirin and lactose were supplied by Loba Chemicals Pvt. Ltd., Mumbai. Povidone and Mg stearate were purchased from DFN Pharma Pvt. Ltd., Mumbai. All other chemicals used were of analytical grade from Research Fine Lab Chemicals, Mumbai.

Method for preparation

Materials such as drug and excipients are used for the tablet preparation using direct compression method. Drugs are rarely administered as pure chemical substances alone and are almost given as formulated preparations. The excipients provide varied and specialized pharmaceutical functions. It is the formulation that solubilizes, preserves, modifies dissolution, and improves drug substances to form various preparations or dosage forms.[6-8]

Experimental study

Pre-formulation studies

Pre-formulation testing is the first step in a balanced development of dosage forms of a drug. It can be defined as an exploration of physical and chemical properties of drug substance, alone and when combined with excipients. A thorough understanding of physicochemical properties may ultimately provide a rational for formulation design or confirm that there are no significant barriers to the compound development.[9]

Solubility

Solvents such as ethanol, phosphate buffer solution pH 4.5, and pH 6.8 were used for solubility determination of aspirin.

Melting point

The melting point was determined by melting point apparatus. The temperature at which drug melted was recorded. The result was mentioned in table.

Ultraviolet (UV) spectroscopy

Determination of λ_{max}

Preparation of stock solution

An accurately weighed 10 mg of aspirin was transferred in 100 ml volumetric flask. The volume was made up to 100 ml phosphate buffer pH 6.8 to get a concentration of 100 µg/ml and scanned in the range of 400–200 nm^{-1}cm cell, against a resultant solvent as a blank and spectra were recorded.

Standard calibration curve of aspirin

Standard calibration curve of aspirin was developed in 0.1N HCl, UV-spectrophotometer was used with matched quartz cells of 1 cm in width. Absorbance of solution was measured at λ_{max} of 275 nm. Calibration curve was plotted as absorbance v/s concentration.

Fourier-transform infrared (FTIR)

An FTIR spectrum of pure aspirin was recorded on Agilent FTIR spectrophotometer. The instrument was operated under dry air purge and the scans were collected with resolution of 4 cm^{-1} over the region 4000–650 cm^{-1}.

Differential scanning calorimeter (DSC)

DSC experiment was carried out to evaluate thermal properties and to illustrate the state of drug in pure form. The DSC studies of the pure drug and drug with mixture were carried out using DSC (SDT Q 600 V20.9 build 20).

X-ray diffraction (XRD)

XRD was performed using X-ray fluorescence spectrophotometer with a line as the source of radiation. Standard runs were carried out using a voltage of 56 kv, a current of 182 mA, and scanning rate of 2°min^{-1} over a 2 θ range of 5–90°C.

QbD tools

Quality target product profile (QTPP)

The pharmaceutical development of aspirin as a FDT begins with the identification of desired dosage form and performance attributes through the target product profile. The pharmaceutical target profile for aspirin is safe FDT that facilitates patient compliance and promotes onset of action. The manufacturing process for the tablet should result as a product that meets the appropriate drug product critical quality attributes which includes dosage form, strength, route of administration, hardness, disintegration time, and dissolution.

From the target product profile, the initial critical quality attributes (CQAs) that were used are identified concerning the quality that is satisfactory.

Risk assessment to identify variables potentially impacting product quality

From the perspective, it was investigated that the CQAs of the drug product have a high potential to be impacted by the formulation and its process.

- Hardness
- Disintegration
- Dissolution.

Risk assessment analysis

All the formulation and process parameters are evaluated for the risk. Based on the physicochemical properties of the drug substance, the initial risk assessment of drug substance attributes on the drug product the CQAs are classified as low, medium, and high.

Preparation of FDT of aspirin

Nine batches of different formulation were prepared, each batch including aspirin (API), lactose, and povidone weighed equally in each batch formulation. Then, different superdisintegrants such as sodium starch glycolate, croscarmellose sodium, and crospovidone were mixed with the previous mixture in different ratios, and then, the magnesium stearate as a lubricant was added finally to all the formulation batches. The resultant powder blend was then compressed under constant pressure using KBR press each tablet containing 325 mg of aspirin.

Pre-compression evaluation parameters[10]

Evaluation of powder blend

Powder blend was evaluated for flow properties as follows:

Bulk density

Bulk density is the mass of the powder divided by the bulk volume and is expressed as g/cm^{-1}. Accurately weighed 10 g of blended powder from each formulation was taken and initial volume of blended powder was poured in the measuring cylinder was noted. It was calculated by formula,

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume}}$$

Tapped density

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder blend for about 100 times. The tapped density was calculated using the following formula:

$$\text{Tapped density} = \frac{\text{Mass of powder}}{\text{Tapped volume}}$$

The mean ± standard deviation values of angle of repose were calculated. The results were determined and mentioned.

Angle of repose

The angle of repose of powder blend was determined using funnel. 10 g of accurately weighed powders was placed into the funnel. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation:

$\Theta = \tan^{-1}$ (h/r)

Initial wt of tablet − Final wt of tablet

Initial wt of table − t X 100

Where, h=height and r=radius

Hausner's ratio

It is expressed by ratio of tapped density to the bulk density. It is given by formula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Carr's index (compressibility ratio)

It is the ratio of bulk density and tapped density and is given by formula,

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ X } 100$$

Post-compression evaluation parameters of prepared FDT[11]

Thickness and diameter

Thickness and diameter of tablets were measured with the screw gauge micrometer that had a scale of 0–25 mm and were capable of differentiating up to 0.01.

Hardness test

Hardness of the tablet was measured using the Pfizer hardness tester. The indicator remains at the reading where the tablet breaks and returns back to zero by releasing the press button to reset.

Weight variation test

The United State Pharmacopeia (USP) weight variation test was performed by weighing 20 tablets individually calculating the average weight and comparing the individual tablet weight to the average weight.

$$\text{Deviation (\%)} = \frac{\text{Average wt of tablet} - \text{Individual wt of tablet}}{\text{Average wt of tablet}} \text{ X } 100$$

Friability

A total of 20 tablets were weighed and placed in the Roche friabilator test apparatus; the tablets were exposed to the

rolling and free falls within the apparatus at 100 revolutions in 25 rpm. The friability test determines the percentage loss % in weight of tablets.

$$\text{Friability (\%)} = \frac{\text{Initial wt of tablet} - \text{Final wt of tablet}}{\text{Initial wt of tablet}} \text{X } 100$$

Wetting time

This method is followed to measure tablet wetting time. A piece of circular tissue paper was placed (10 cm diameter) folded twice was placed in each small petri dish containing freshly prepared phosphate buffer 6.8 pH about 10ml in each petri dish. Few drops of crystal violet solution were added to each petri dish. Each tablet is placed carefully on the surface of the tissue paper. The time required for the solution to reach the upper surface is noted as wetting time.

Disintegration time

To note the disintegration time, a single tablet was placed in each tube of the USP disintegration apparatus. The device is used to move the basket assembly containing of tablet up and down through a distance of 25–32 cycles per minute.[13]

Drug content

The tablets from each formulation were weighed individually and crushed and powdered. The powder equivalent to 100 mg of aspirin was weighed and dissolved in 100 ml of ethanol or freshly prepared buffer solution by stirring for few minutes. Absorbance of solution was measured spectrophotometrically at 275 nm using ethanol or buffer solution as blank.

In vitro dissolution test

The in vitro dissolution of batches (samples) was performed using united state Pharmacopoeia dissolution apparatus Type II paddle rotation method. Each batch sample (tablet) was placed in the dissolution vessel containing 900 ml of suitable buffer solution.[14,15] The samples were filtered through 0.45 µm pore size membrane filter (Whatman filter paper), and the concentration of drug of each batch was determined analyzing spectrometrically at 275 nm.

Design of experiment (DOE)

Formal DOE is defined as a structured analysis wherein inputs are changed and differences or variations in outputs are measured to determine the magnitude of the effect of each of the inputs or combination of inputs. Factorial designs allow for the simultaneous study of the effects that several factors such as concentration of disintegrants and diluents concentration may have on the physical characteristics of the tablets.[12]

Effect of variables

To study the effect of variables on the FDT formulation, 3^2 factorial designs were adopted. Binder, disintegrant, and lubricant were considered as three independent variables, whereas disintegration time and hardness were considered as dependent variables.

Stability study

Stability of selected optimized batch formulation was carried out as per ICH guideline. Effects of temperature and RH on the dissolution rate and hardness for optimized batch were studied. The drug dissolution, hardness, and disintegration time were studied during stability period.

RESULTS AND DISCUSSIONS

Pre-formulation study

Pure aspirin was identified by organoleptic properties, odor, taste, color, and melting point. The results were shown in Table 1.

Determination of λ_{max}

For scanning of maximum absorbance 10 µg/ml solution of aspirin in 0.1 N HCL was scanned from 200 to 400 nm against a reagent blank and maximum absorbance was determined at 275 nm as shown in Figure 1.

Table 1: Characterization for identification of drug

Tests	Result
Odor	Odorless
Taste	Bitter
Color	White
Melting point	136°C

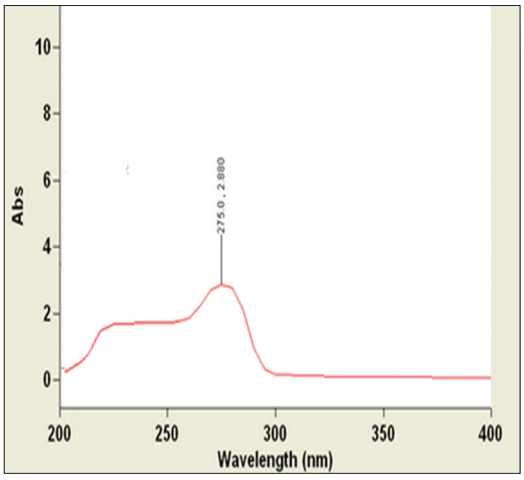

Figure 1: λ_{max} of aspirin

FTIR spectra of aspirin

The IR spectrum of pure aspirin sample was recorded by FTIR spectrometer. The FTIR Spectra was shown in Figure 2.

DSC

The DSC spectrum of pure drug was obtained and shown in the Figure. Drug shows a sharp melting point peak endotherm at 139.7°C which corresponds to the melting point of drug.

Hence, it concludes that the drug is in pure form as there was a sharp peak in the thermogram; it concludes that the drug was crystalline in nature. The DSC Spectrum was shown in Figure 3.

XRD of pure drug of aspirin

For the confirmation of crystalline nature of aspirin in batches, XRD analysis was performed.

As there was a sharp peak in XRD, hence, it can be concluded that the API form is crystalline in nature. XRD graph was shown in Figure 4.

QbD tools

QTPP

The pharmaceutical development of aspirin as a FDT begins with the identification of desired dosage form and performance attributes through the target product profile. FDT of Aspirin QTPP elements target and conclusion were given in Table 2. The manufacturing process for the tablet should result as a product that meets the appropriate drug product critical quality attributes.

CQAs

Critical quality attributes of FDT was decided and its justification was given in Table 3.

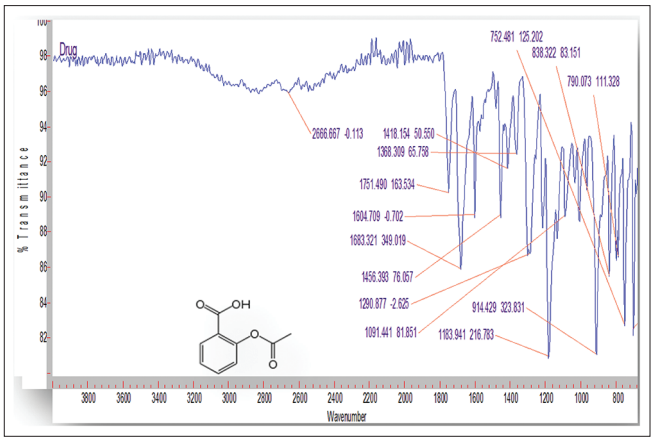

Figure 2: Fourier-transform infrared spectra of aspirin

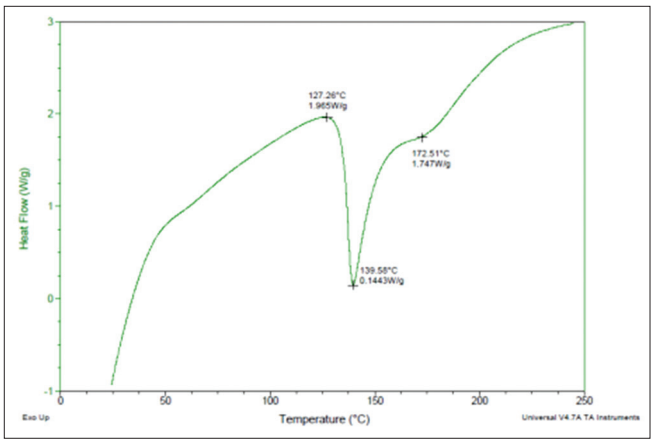

Figure 3: Differential scanning calorimeter thermogram of aspirin

Table 2: QTPP elements target and conclusion

QTPP Elements	Target	Conclusion
Dosage form	FDT	FDT
Dosage strength	325 mg	Dose
Route of administration	Oral	Oral
Palatability	Minimum bitter taste intensity and duration, absence of gritty texture desirable	Grittiness absent
Impurities	Not more than 1.0%	NMT 1%
Content uniformity	Must meet IP criteria	Meets IP
Hardness	NMT 6 kg/cm^2	4.5 kg/cm^2
Friability	NMT 1%	NMT 1%
Disintegration	NMT 30 s	30 s
Dissolution	80–100% drug release as per the marketed product	99.63%
Indications and usage	For the treatment of pain, fever, inflammation	Useful

QTPP: Quality target product profile, FDT: Fast dissolving tablet, NMT: Not more than

Table 3: CQA profile and its justification

CQA profile	Is this CQA?	Justification
Physical attributes Color, odor, appearance	No	Physical attributes of the formulation are not directly linked to the efficacy and safety
Hardness	Yes	Hardness will affect friability, disintegration, and dissolution that can impact the bioavailability. Both formulation and process variables affect the hardness
Disintegration	Yes	Disintegration will affect dissolution and can impact the bioavailability. Thus, both formulation and process variables affect disintegration
Impurities	Yes	The degradation products can affect the safety and efficacy, and it must be controlled based on the ICH requirements
Assay and content uniformity	Yes	Variability in assay and content uniformity will affect the safety and efficacy. It impacts both formulation and process variables
Dissolution	Yes	Failure to meet the dissolution specification can impact bioavailability as both the formulation and process variables affect dissolution profile
Palatability	Yes	Palatability influences the patient compliance, and it should be appropriate for the target

CQA: Critical quality attribute

Table 4: Pre-compression evaluation parameters

Batch	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (°)	Hausner's ratio	Carr's index
F1	0.60±0.4	0.72±0.21	32.10±0.3	1.25±0.2	16.6±2.17
F2	0.63±0.33	0.72±0.23	29.74±0.2	1.14±0.4	12.5±2.02
F3	0.62±0.34	0.73±0.41	30.46±0.45	1.16±0.5	15.06±2.03
F4	0.60±0.41	0.70±0.6	29.05±0.11	1.16±0.3	14.28±2.06
F5	0.63±0.2	0.73±0.41	28.39±0.23	1.15±0.1	13.69±2.07
F6	0.64±0.6	0.72±0.21	29.15±0.8	1.15±0.1	11.11±2.17
F7	0.68±0.1	0.75±0.28	25.46±0.11	1.10±0.2	9.33±1.03
F8	0.79±0.40	0.88±0.1	28.78±0.10	1.13±0.1	10.22±1.14
F9	0.73±0.12	0.82±0.11	28.29±0.110	1.13±0.2	10.77±2.08

The bulk density of all the batches was found to be in the range of 0.60±0.2 to 0.79±0.40, similarly tapped density (0.70±0.6–0.88±0.1), angle of repose (29.15±0.8–32.10±0.3), Hausner's ratio (1.10±0.2–1.25±0.2), and Carr's index (9.33±1.03–16.6±2.17)

Table 5: Post-compression evaluation parameters

Batch	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Dis. time (s)	Drug content (%)	Wetting time (s)
F1	6.1±1.0	3.5±0.2	1.2±0.10	60±0.6	98.79±0.8	65.40±0.2
F2	6.32±1.12	3.1±0.3	1.02±0.1	35±0.5	97.88±0.65	51.45±0.5
F3	6.31±1.2	3.3±0.4	0.91±0.25	34±0.8	98.36±0.89	46.9±0.1
F4	6.37±1.1	4.0±0.8	0.73±0.33	37±0.6	98.73±0.4	55.01±0.30
F5	6.30±1.02	3.7±0.6	0.91±0.2	62±0.4	98.12±0.10	69.3±0.33
F6	6.35±1.0.1	4.2±0.4	0.71±0.45	84±0.7	97.14±0.6	89.35±0.4
F7	6.30±1.4	4.8±0.7	0.55±0.05	31±0.5	99.14±0.92	36.3±0.1
F8	6.30±1.23	4.0±0.6	0.93±0.8	44±0.3	98.79±0.83	54.9±0.41
F9	6.32±1.22	3.9±0.6	0.91±0.33	39±0.7	98.18±0.82	45.31±0.5

Ranges of all the batches for every parameter were found to be as thickness (6.1±1.0–6.37±1.1 mm), hardness (3.1±0.3–4.8±0.7 kg/ cm²), friability (0.55±0.05–1.2±0.10%), disintegration time (31±0.5 to 84±0.7 s), drug content (97.14±0.6 to 99.14±0.92%), and wetting time (36.3±0.1 to 89.35±0.4 s). Hardness of tablet increases when the concentration of binder is increased simultaneously the disintegration time increases with the increase of disintegrant level

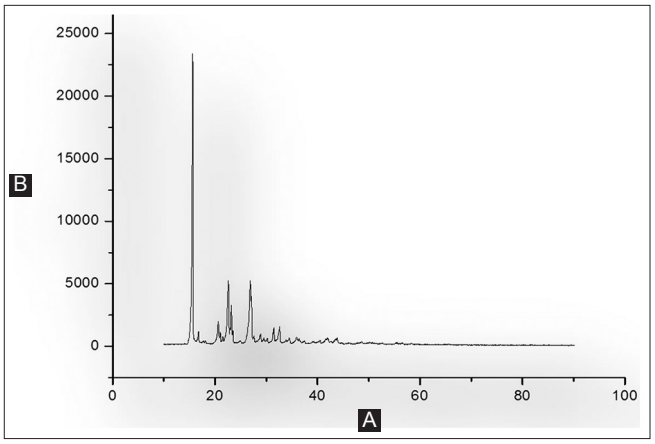

Figure 4: X-ray diffraction of pure drug aspirin. A = 2Ø Angle, B = Relative intensity

Formulation of FDT by direct compression

This is an ideal process of manufacturing and its use is limited due to the necessity of raw material mixture requirements related to compressibility, free flow (flow property). Hence, direct compression was a superior choice. Tablets were prepared using direct compression method, all the nine different batches were compressed and the tablets were punched using flat edges punch.

Physical evaluation of tablet

Pre-compression evaluation parameters of DOE batches

The bulk density of all the batches were found to be in the range of 0.60 ± 0.2 to 0.79 ± 0.40, similarly tapped density (0.70 ± 0.6 to 0.88 ± 0.1), angle of repose (29.15 ± 0.8 to 32.10 ± 0.3), Hausner's ratio (1.10 ± 0.2 to 1.25 ± 0.2), Carr's index (9.33 ± 1.03 to 16.6 ± 2.17). The pre compression evaluation results are mentioned in the [Table 4].

Post-compression evaluation parameters of DOE batches

The ranges of all the batches for every parameter were found to be as thickness (6.1±1.0 to 6.37 ± 1.1 mm), hardness (3.1 ± 0.3 to 4.8 ±0.7 kg/cm2), friability (0.55±0.05 to 1.2±0.10 %), disintegration time (31±0.5 to 84± 0.7 sec), drug content (97.14±0.6 to 99.14±0.92 %), wetting time (36.3±0.1 to 89.35±0.4 sec). Hardness of tablet increases when the concentration of binder is increased simultaneously the disintegration time increases with the increase of disintegrant level. The post compression evaluation results are mentioned in the [Table 5].

In vitro dissolution test

The *in vitro* dissolution test for all the batches were performed. Variations were found in all the batches for the purpose of

Table 6: *In vitro* dissolution study of DOE batches

Sr. No.	% Drug release									
Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9	Market product
0	0	0	0	0	0	0	0	0	0	0
1	52.51±0.72	64.16±0.2	64.29±0.12	67.34±0.1	58.60±0.14	53.80±0.10	72.12±0.14	66.75±0.20	67.76±0.12	70.21±0.123
2	67.59±0.45	68.61±0.1	77.32±0.63	71.66±0.12	68.40±0.15	63.35±0.11	87.03±0.2	71.4±0.15	75.30±0.5	86.41±0.20
3	71.56±0.29	74.35±0.32	82.55±0.12	85.81±0.23	76.23±0.33	75.81±0.2	92.9±0.12	76.45±0.12	80.62±0.20	92.5±0.20
4	86.58±0.33	87.69±0.41	88.61±0.41	90.42±0.12	85.62±0.14	79.41±0.14	98.5±0.12	86.51±0.15	88.32±0.14	96.4±0.15
5	91.06±0.31	92.85±0.32	91.23±0.12	95.69±0.20	92.47±0.14	86.30±0.12	99.15±0.4	93.47±0.20	94.21±0.21	97.7±0.15
10	95.54±0.20	98.96±0.1	94.78±0.14	96.77±0.20	95.78±0.20	96.14±0.30	99.80±0.12	95.66±0.30	96.46±0.12	99.35±0.25

DOE: Design of experiment

maximum drug release in minimum time. Also it was then compared with the drug release of marketed product. The results of *in vitro* dissolution DOE batches are mentioned in the [Table 6].

Box–Behnken experimental design

The traditional approach to develop a formulation is to change one variable at a time. By this method, it is difficult to develop an optimized formulation, as the method reveals nothing about the interaction among the variables. Systematic optimization procedure is carried out by selecting an objective function, to find the most important or contributing factor and investigating the relationship between response and factors by the so-called surface response methodology. In the present work, Box–Behnken design was used to optimize the concentrations of the disintegrants, binder for hardness with controlling disintegration time.

Where, X1, X2, X3 = Independent variables and Y1, Y2 = Dependent variables

In the present work, Box–Behnken design was used to optimize the concentrations of the disintegrant, binder for hardness with controlling disintegration time. The result of the batches are discussed in the [Table 7].

Pareto chart - ANOVA

The Pareto chart developed by software was used to investigate the standardized effect of the independent variables and their interaction on the dependent variables**.** As disintegration time (Y1) and hardness (Y2) depicts the main effect of the independent variables and interactions with their relative non-significance on Y1 and Y2.

The length of each bar below significance or critical line detonated by blue color in the chart indicates the standardized effect of that factor in the responses. Factor remains inside the reference line indicate that these terms contribute the least in the prediction of responses so form the Pareto chart it is concluded that for linear, interaction, and quadratic effect shows non-significance effect on disintegration time (Y1) and hardness (Y2) which were shown in Figures 5 and 6.

Response surface analysis

It is the impact of input variables at different levels of various responses, the graphical interpretation using two-dimensional (2D) plot, that is a contour plot and a three-dimensional (3D) plot that is response surface plot is performed.

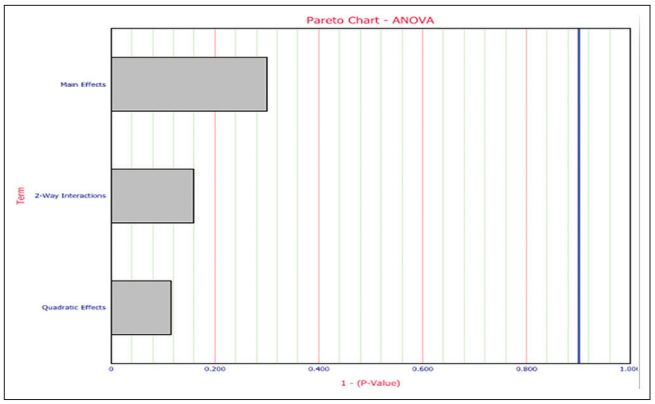

Figure 5: Pareto chart - ANOVA showing effect and interaction on disintegration time

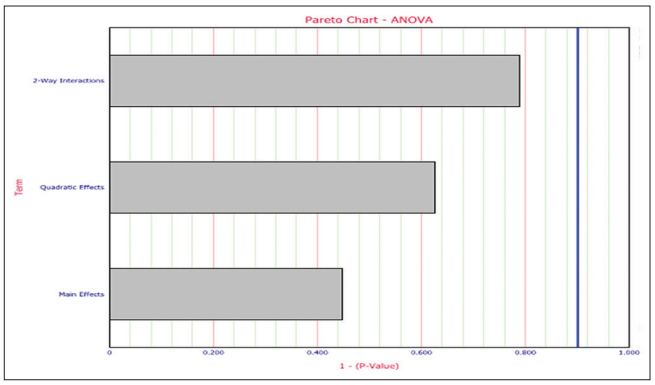

Figure 6: Pareto chart - ANOVA showing effect and interaction on hardness

Contour plot

2D contour plots are presented in Figure below which is very useful to study the interaction effect of the factor on the responses. The plots were found to be linear up to 27.45–31.39% indicating a linear relationship between X1 (binder) and X2 (disintegrant) for disintegration time. Similarly, all the values were reminded dependent variables.

It was determined from the contour plot that an optimum value of disintegration time could be obtained with level range 27.45–31.39% and hardness level range 5.83–4.37%. It is an evident from the contour plot that the higher level favors the formulation.

Response 3D surface plot

Response surface (3D) plot is a graphical illustration of the potential relationship between three variables similar to contour plots, 3D surface plot is useful for establishing the response values but in a more precise manner.

As shown in Figure 7, the disintegration time increases with the increase on binder and disintegrant level. It shows that the hardness increases when the concentration of binder increases,

Table 7: Box–Behnken design for independent and dependent response

Run order	X1 povidone	X2 crospovidone	X3 Mg stearate	Y1 disintegration time (s)	Y2 hardness (kg/cm²)
1	1	0	1	60±0.6	4.2±0.2
2	−1	0	−1	25±0.5	4.1±0.3
3	0	0	0	34±0.8	3.3±0.4
4	−1	0	1	37±0.6	4.0±0.8
5	−1	−1	0	32±0.4	4.8±0.6
6	0	−1	−1	34±0.7	4.6±0.4
7	−1	1	0	29±0.1	4.3±0.7
8	1	0	−1	24±0.3	2.0±0.6
9	0	1	1	39±0.7	5.3±0.6
10	1	1	0	11±0.1	4.5±0.3
11	0	1	−1	36±0.4	3.4±0.2
12	0	0	0	39±0.3	5.3±0.5
13	−1	1	0	41±0.2	4.6±0.4
14	0	−1	1	35±0.6	3.9±0.2
15	1	−1	0	33±0.1	4.2±0.7

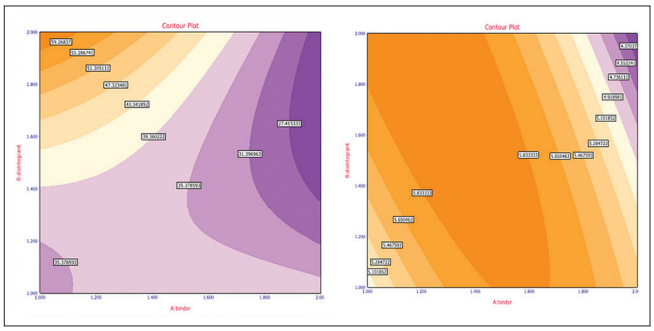

Figure 7: Contour plot showing effect on disintegration time and hardness

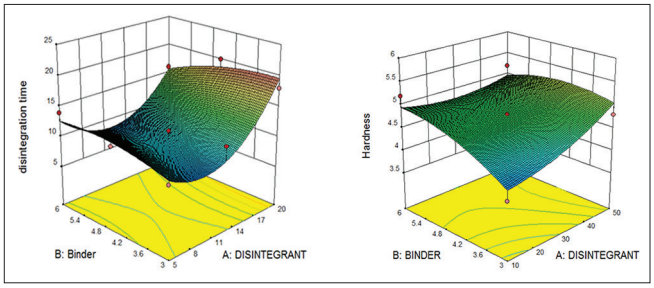

Figure 8: Three-dimensional surface plot showing effect on disintegration time and hardness

while at initial level when the concentration of disintegrant increases it showed increase in the hardness as shown in Figure 8.

Stability

In vitro dissolution study of the optimized batch (F7) was carried out before and after stability and comparison with marketed product.

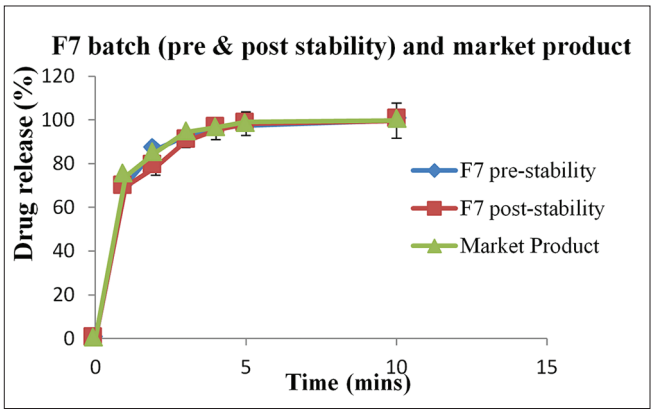

Figure 9: Drug release profile before and after stability, marketed product

In vitro dissolution study for the optimized F7 batch before and after stability showed parallel dissolution pattern as shown in Figure 9.

CONCLUSION

The focus of the current study was to develop FDT of aspirin using QbD approach. QbD was applied for better understanding the process and to enhance design space, using QTPP, CQA, and risk assessment. FDT of aspirin was developed by 3^2 factorial using Box–Behnken design. Two variables povidone and crospovidone at three levels and response surface plots were generated. UV, FTIR, DSC, and XRD analysis have been done for pre-formulation and post-formulation evaluations. The tablets were prepared by direct compression method.

The λ_{max} was confirmed at 275 nm by UV spectroscopy. In compatibility study IR, it was observed that the drug was in pure form and there were no major interactions with other polymers. DSC and XRD studies revealed that the drug was in crystalline form showing sharp peaks. The *in vitro* dissolution study revealed that the batch F7 is best among nine batches been prepared. It was stable at 25°C ± 2°C/60% ± 5% RH and 40°C ± 2°C/70% ± 5% RH for 90 days. Thus, FDT of aspirin using QbD approach was successfully developed. Thus, from the above conclusion, it is summarized that formulation and evaluation of FDT of aspirin by QbD approach was successfully prepared using direct compression method.

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