Section A-Research paper

FORMULATION AND EVALUATION OF ALLOPURINOL AND QUERCETIN PULSATILE TABLET USING CENTRAL COMPOSITE DESIGN

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Abstract: The objective of the study is to formulate and evaluate pulsatile drug delivery containing a combination of allopurinol and quercetin for the treatment of gouty arthritis which is used to deliver the drug at a specified time by the disease's pathophysiological requirements, improving therapeutic effectiveness and patient compliance. Allopurinol was prepared as a core tablet with varying concentrations of superdisintegrants, microcrystalline cellulose, magnesium stearate, and talc, and as an outer shell tablet with quercetin which is formulated with different weight ratios of ethyl cellulose (EC) and different grades of polyox. The methodology calls for the creation of solid dispersion, pulsatile release tablets, and analytical method development to simultaneously estimate combination medications. An oral press-coated tablet was designed via direct compression to create the time-controlled tablet with a distinct specified lag period. Evaluation studies were performed for prepared pulsatile tablets like thickness, hardness, weight variation, friability, and disintegration time. In in vitro release profile of 8 hours study in the first 6 hours, it shows minimum drug release and at the end of eight hours rapid and transient release was observed.

Keywords: Allopurinol, Central composite design**,** Pulsatile delivery, Press coated, Quercetin

Introduction:

The pulsatile drug delivery system is the most fascinating and unique system by the pathophysiological requirements of the condition. A pulsatile drug delivery system has a brief period of no release (lag time), followed by a quick and thorough release of the drug.[1]

Pulsatile systems are achieving a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed based on the circadian rhythm of the body. However, there are certain conditions of drugs in which such a release pattern is not suitable. The rationale for using the proposed system is to deliver the drug at a time when the disease is in the most morbid and mortal state for 24 hours. For diseases that follow circadian variation, control release systems for 12 or 24 hr drug release are not suitable, and in such cases, a time- or pulsatile-based drug delivery system is required.[2] Chronopharmaceutics is an approach to delivering drugs at a time that matches the biological requisite for specified disease treatment or prevention.[3] One of the most prevalent rheumatic disorders is gouty arthritis. The clinical impact of gouty arthritis has long been understood, although gout is frequently misdiagnosed and treated incorrectly. Nonsteroidal anti-inflammatory medicines (NSAIDs), colchicine, corticosteroids, or a combination of two medications should be used to treat acute gouty arthritis. The widely accepted first-line therapy for the prevention of recurrent gout is xanthine oxidase inhibitor medication. Acute gout prophylaxis with NSAIDs, colchicine, or corticosteroids is generally recommended when urate-lowering therapy is initiated to prevent acute gouty arthritis for at least 6 months. Gouty arthritis is the most common inflammatory arthritis in men over the age of 40. Gouty arthritis is commonly the first clinical manifestation of gout and typically presents as acute and episodic, although it can manifest or progress to chronic arthritis.[4] Allopurinol is mainly indicated for the treatment of acute gouty arthritis. The usual dose to relieve or abort an attack is 100 to 300 mg.[5]Allopurinol is rapidly absorbed from the upper gastrointestinal tract and it has a plasma half-life of about 1 to 2 hours. It is relatively insoluble in water and freely soluble in alkaline aqueous solutions.[6,7] Quercetin is an aglycone. It is a yellow colour, bitter taste and is poorly soluble in water, but quite soluble in alcohol and lipids. Many pharmacological activities have been reported to demonstrate the health benefits of quercetin, such as the prevention of cardiovascular and neurodegenerative diseases, anticancer, antidiabetic, antihypertensive, antihyperlipidemic, antibacterial, antiviral, antiallergic, antioxidant, anti-inflammatory, and anti hyperuricemic activities. Interestingly, several of these activities are beneficial for hyperuricemia and gouty arthritis.[8] Aim of the present investigation was focused on combating the early morning hours or night sleep of gouty arthritis. This approach will be achieved through a pulsatile drug delivery system containing a combination of allopurinol and quercetin.

Materials and methods:

Quercetin was procured from Otto Chemie Pvt. Ltd (Mumbai, Maharashtra). Allopurinol was kindly provided by College Chemicals. Cross Carmellose Sodium, ethyl cellulose and Polyox were procured from Analab Fine Chemicals, Mumbai. Microcrystalline Cellulose, Magnesium Stearate, Talc and Polyethylene Glycol- 8000 were procured from the Research lab Fine Chem. Industries, Mumbai respectively.

Solubility Enhancement:

Solid dispersion method:

Solid dispersions of Allopurinol and Quercetin with different polymers (PEG- 6000, PEG-8000, Mannitol, Poloxamer 188) at weight ratios of 1:1, 1:2 was prepared by melting method. After the polymer or carrier was completely melted on a thermostatically controlled hot plate, allopurinol and quercetin were added and then solidified by pouring them on a glass petri dish stored in an ice bath. After cooling the solid, it was kept in a desiccator under vacuum at room temperature for 48 h. The mass was then pulverized with a mortar and pestle and was sieved into defined particle size fractions (200-150 μm).[9] The solid mass was dissolved in 1ml of water and finally absorbance was taken at UV spectroscopy.

Experimental Design of Formulation by Central Composite Design:

The Central composite (CCD) was used for the experimental design. CCD helps you efficiently to study the relationship between two factors (independent variables) and three responses (dependent variables) in your experimental design. The design consists of three types of experimental points: factorial points, axial points, and centre points. By conducting experiments at these defined points and collecting data on the three responses, you can create regression models that describe the relationship between the factors and responses. These models enable you to optimize the software design and make informed decisions based on the obtained results. Statistical analysis techniques, such as analysis of variance (ANOVA) and regression analysis, are commonly employed to interpret the data and determine the significance of the factors and their interactions.[10] Here, for the optimization of the pulsatile release tablet, 2 independent variables i.e., Factors and three dependent variables i.e., Responses are selected which are given in Table1 and Table 2 and the dose of the drug Allopurinol is constant i.e., 100 mg for all batches.

Table no. 1: Independent variables selected for optimization studies include:

Independent Variables	**Parameters**	**Levels**	
		-1	**+1**
X1	Conc of Super disintegrant	12.5	17.5
X2	Conc of diluent	97.5	112.5

Table no.2: Dependent variables selected for optimization studies include:

Y1	% Drug release	Response 1
Y2	% Friability	Response 2
Y3	Hardness	Response 3

Formulation and Evaluation of Rapid Release Core Tablet (RRCT):

The inner core tablets were prepared by using the direct compression method. Different preliminary batches of core tablets were taken in to fix the concentration of Superdisintegrant in the tablet. Powder mixtures of Allopurinol, Cross Carmellose, Microcrystalline Cellulose, and Talc were dry blended for 20 mins followed by the addition of magnesium stearate. The mixtures were then further blended for 10 min, and 250 mg of the resultant powder blend was compressed using rotary tableting machine with a 7mm punch and die to obtain the core tablet (Table 3)

Table no.3: Composition of Rapid Release Core Tablet

Batch	**Allopurinol**	**Cross Carmellose**	**MCC**	**Magnesium Stearate**	**Talc**
F1	100	18.5	105	7.5	19
F2	100	17.5	97.5	7.5	27.5
F3	100	11.4	105	7.5	26.04
F4	100	15	105	7.5	22.5
F5	100	15	94.3	7.5	33.11
F6	100	15	105	7.5	22.5
F7	100	15	105	7.5	22.5
F8	100	12.5	97.5	7.5	32.5

F9	100	15	115.6	7.5	11.9
F10	100	15	105	7.5	22.5
F11	100	17.5	112.5	7.5	12.5
F12	100	12.5	112.5	7.5	17.5
F13	100	15	105	7.5	22.5

Coating of core tablet:

In this method, Quercetin was used. The optimized core tablets were coated with Coating ingredients like ethyl cellulose, and a combination of different grades of polyox to select the best one. A precisely weighed amount of barrier material was now introduced into the 10mm nozzle, then the tablet core was manually placed in the centre. The remaining barrier layer material was added to the die and pressed. Tablets were compressed in a rotary tablet press. The tablet properties of each set of tablets produced were evaluated (Table 4).

Table no.4: Coating of core tablet

Batch	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**
Quercetin	150	150	150	150	150	150
Ethylcellulose	30	30	30	30	30	30
Polyox 303	35	35	35	-	-	-
Polyox 301	35	-	-	35	35	-
Polyox 205	-	35	-	35	-	35
Polyox 1105	-	-	35	-	35	35

Post-compression parameters:

Hardness: Hardness indicates the tablet's ability to withstand mechanical shocks while handling. The hardness of the tablet was determined using a Monsanto hardness tester. It was expressed in kg/cm. 10 tablets were randomly selected and the hardness of the same tablets of each formulation was determined. Mean values and standard deviation are also calculated.[11]

Thickness and Diameter: The thickness and diameter test permits accurate measurement and provides information on the variation between tablets. 10 tablets were taken and the thickness and diameter were measured using a digital Vernier calliper. The tablet thickness and diameter should be controlled within a ±5 % variation of the standard value.[12]

Friability: Tablet friability was determined using a Roche Friabilator. It was expressed in %. Initially, 10 tablets were weighed and transferred to the friabilator. The friabilator was operated at 25 rpm for 4 mins or runs up to 100 revolutions. The tablets were weighed again (W final). The friability test was calculated.

$$\text{Friability (\%)} = \frac{\text{Initial Weight (W1)} - \text{Final Weight (W2)}}{\text{Initial Weight (W1)}} \times 100$$

% Friability of tablets less than 1% was acceptable.[13]

Weight Variation: 10 tablets from each formulation were randomly selected and weighed individually to check the weight variation. The US Pharmacopoeia allows for a small amount of variance in tablet weight.[14]

Disintegration Time: The process of a tablet disintegrating is crucial to the drug's absorption. The USP disintegration test apparatus at Electro Lab was used to conduct the disintegration test. One tablet was placed in each tube and the basket rack was placed in a 1L beaker filled with pH 1.2 Buffer solution at 37°C 1°C to test the disintegration time of tablets. Tablets disintegrate slowly enough to keep the tablet 2.5 cm below the liquid's surface. The time taken for the complete disintegration of the tablets was noted.[15]

Drug Content uniformity: 10 tablets were randomly selected and crushed. These tablets were then dissolved in a small amount of methanol, and 100 ml of phosphate buffer with a pH of 6.8 was added to the mixture to make it full. The solution was then filtered and the absorbance was measured at 2 nm and 252nm and 372nm respectively using phosphate buffer as a blank. The test results were interpreted with the limits of British Pharmacopoeia.[16]

In vitro dissolution test: The in vitro drug release from was carried out using USP type II dissolution apparatus at 50 rpm and 37 ^{0}C ± 0.5 ^{0}C. 0.1N hydrochloric acid was used as the dissolution medium for 2 h and the tablet was then transferred to PBS ph 6.8 for the remaining 6 h. 10 ml of dissolution medium was withdrawn at predetermined time intervals and fresh dissolution medium was replaced. The samples were withdrawn at regular intervals and analysed by UV spectrophotometer at 252nm and 372nm for the presence of the drug.[17]

Precompression Parameters of Pulsatile Release Tablet:

1. **Angle of Repose:** This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane

$$\text{Tan } \theta = h/r$$

$$\Theta = \text{Tan } -1\ h/r$$

Where, h = height of granules

r = radius of granules

The angle of repose was determined by measuring the height, and radius of the heap of powder blend. A funnel was fixed to stand and the bottom of the funnel was fixed at a height of 2 cm from the plane. The powder mixture was placed in a funnel and allowed to flow freely.

The height and radius of the heap of powder were measured. Following Tables show limits on which angle of repose should show flow properties.[18]

2. **Bulk density and tapped density:** Both are loose bulk density (LBD) and tapped bulk density (TBD) determined. 2 g of powder from each formulation was placed in a 10 mL measuring cylinder, which was first gently shaken to break any agglomerates formed.

   After observing the initial powder of the process, the cylinder was allowed to fall under its weight from a height of 2.5 cm onto a hard surface in 2 seconds. at intervals. Tapping was continued until no change in volume was observed. LBD and TBD were calculated using the following formulas:

   LBD = weight of sample in gram/ volume occupied by the sample

   TBD = weight of sample in gm/ tapped volume

   The LBD and TBD values were calculated and correlated with standard values.[19]
3. **Carr's index:** Carr's index or compressibility index of the powder blend was determined by Carr's compressibility index.

   Carr's index = Tapped density – Bulk density/ Tapped density X 100

   Compressible index values were calculated and correlated with standard values.[20]
4. **Hausner's ratio:** Hausner's ratio was determined from the ratio of tapped density to bulk density using the formula as follows:

   Hausner's ratio = Tapped density/ bulk density

Results:

Calibration curve of Allopurinol

Development and standard curve of drug using UV- spectrophotometer:

The standard curve of Allopurinol in methanol using a UV- spectrophotometer was estimated. The absorbance was shown at 252nm. The standard plot of absorbance versus concentration was plotted as shown in Figure 1.

Calibration curve of Quercetin

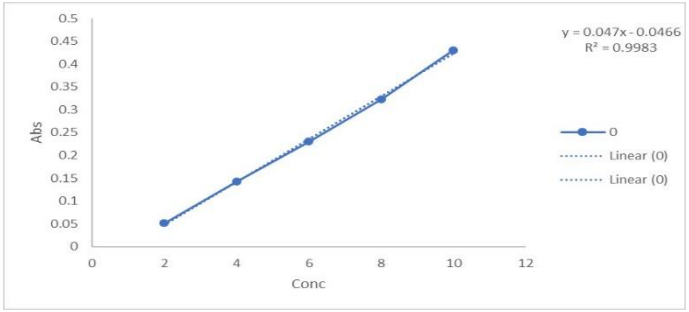

Figure 1: Calibration curve of Allopurinol at 252 nm

Development and standard curve of drug using UV- spectrophotometer:

The standard curve of Quercetin in methanol using a UV- spectrophotometer was estimated. The absorbance was shown at 372nm. The standard plot of absorbance versus concentration was plotted as shown in Figure 2.

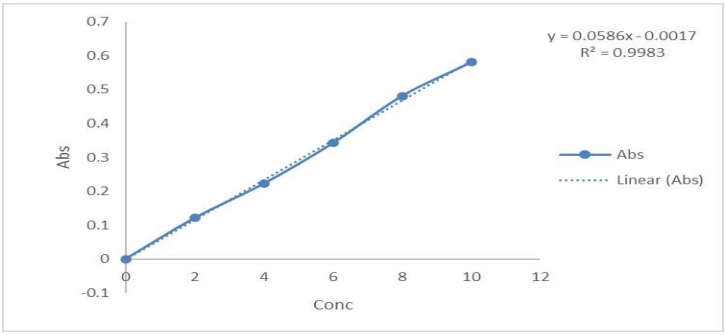

Figure 2: Calibration curve of Quercetin at 372 nm

Pre-compression parameters of the core tablet of allopurinol: Pre-compression parameters were conducted for all formulations blend and were found to be satisfactory. The values are found to be in the range from 26.74 ± 0.13 to 34.07 ± 0.10. 1, 3, 6, 8, 9, and 13 showed excellent flowability exhibiting an angle of repose below 300. 2, 4, 5, 7, 10, 11, and 12 showed good flowability by exhibiting an angle of repose below 36^0. The powder blends of all formulations were evaluated for LBD and TBD. The value of LBD and TBD ranged from 0.600 ± 0.09 and 0.806 ± 0.020 and 0.769 ± 0.019 and 0.961 ± 0.015 respectively. The value for all powder blends of Carr's index ranged from 13.17 ± 0.11 to 19.95 ± 0.18. The compressibility blends for all the powder blends were found to be good to fair as it falls

within the range of 13 – 19. The results for Hausner's ratio were found to be between 1.13 ± 0.016 to 1.23 ± 0.017. The flowability of all blends was found to be good to fair as it falls within the range of 1.15 to 1.24.

Solid dispersion studies:

Different ratios of polymers were taken and from the best of which was PEG – 8000 in a drug carrier ratio of 1:2, which exhibited complete drug release of allopurinol and quercetin in less than 30 mins, hence this ratio was further used for tablet preparation.

Pre-compression parameters of core tablets:

All 13 formulations were compressed by using a 7mm punch in multi-station tablet punching machine. The thickness, hardness, friability, weight change and disintegration time of the obtained tablets were evaluated (Table 5).

Table no. 5: Evaluation of RRCT

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability	Weight variation (mg)	Disintegration time (min)
F1	4.13 ± 0.032	3.2	0.29	249.6 ± 0.48	1.03
F2	4.32 ± 0.034	3	0.3	250.7 ± 0.33	1.27
F3	4.30 ± 0.033	2.8	0.3	250 ± 0.10	1.05
F4	4.31 ± 0.031	2.7	0.2	250.2 ± 0.16	1.21
F5	4.30 ± 0.029	2.9	0.22	249.4 ± 0.78	1.33
F6	4.31 ± 0.031	2.7	0.2	250.2 ± 0.16	1.21
F7	4.31 ± 0.031	2.7	0.2	250.2 ± 0.16	1.21
F8	4.30 ± 0.031	3	0.26	249.7 ± 0.48	1.17
F9	4.32 ± 0.034	3.2	0.24	250.4 ± 0.14	1.25
F10	4.31 ± 0.031	2.7	0.2	250.2 ± 0.16	1.21
F11	4.31 ± 0.032	3.4	0.26	250.6 ± 0.21	1.07
F12	4.30 ± 0.03	2.7	0.31	250.4 ± 0.10	1.52
F13	4.31 ± 0.031	2.7	0.2	250.2 ± 0.16	1.21

Weight variation, thickness, hardness, and friability were found to be within acceptable limits. The friability was below 1% in all formulations, which is an indication of the good mechanical resistance and the core tablet.

Evaluation of Pulsatile Release Tablet:

The thickness of all formulations was found to be between 3.74 ± 0.049 to 3.80 ± 0.06 mm. The Hardness was found between 5.7 ± 0.12 to 6.4 ± 0.31 kg/cm2. The required hardness is produced to ensure good handling characteristics with all the polymers. The friability test was found to be below 1% ensuring that all the batches were mechanically stable. In the weight variation test, the average % deviation of all tablet formulations was found to be within the pharmacopoeia limit, and hence all formulations passed the test for uniformity of weight as per official requirements (Table 6).

Table no. 6: Post compression parameter of press coated pulsatile formulation

Formulation	**Hardness (kg/cm^2)**	**Friability (%)**	**Weight variation (mg)**	**Thickness (mm)**
B1	6.2 ± 0.27	0.46	499.03 ± 0.13	3.79 ± 0.05
B2	5.7 ± 0.12	0.56	500.04 ± 0.28	3.74 ± 0.049
B3	6.0 ± 0.13	0.41	498.06 ± 0.47	3.82 ± 0.07
B4	5.9 ± 0.22	0.48	502.04 ± 0.52	3.73 ± 0.04
B5	6.3 ± 0.29	0.35	500.06 ± 0.21	3.79 ± 0.05
B6	6.4 ± 0.31	0.31	499.04 ± 0.25	3.80 ± 0.06

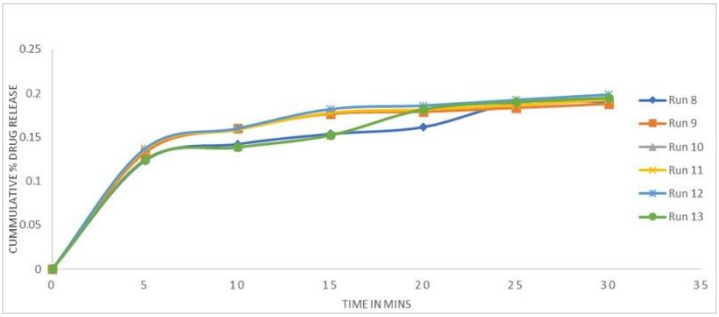

Figure 3: % drug release profile of Allopurinol (Run 1 – Run 7)

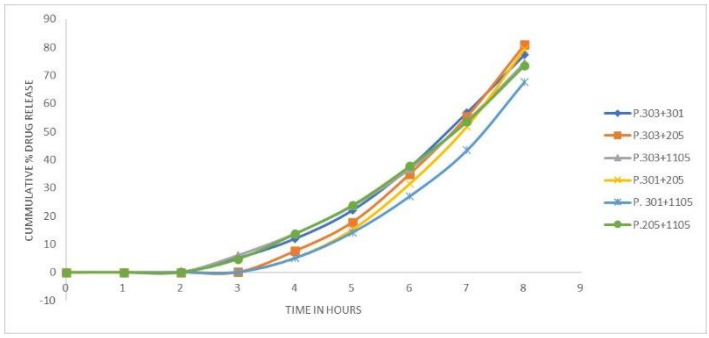

Figure 4: % drug release profile of Allopurinol (Run 8 – Run 13)

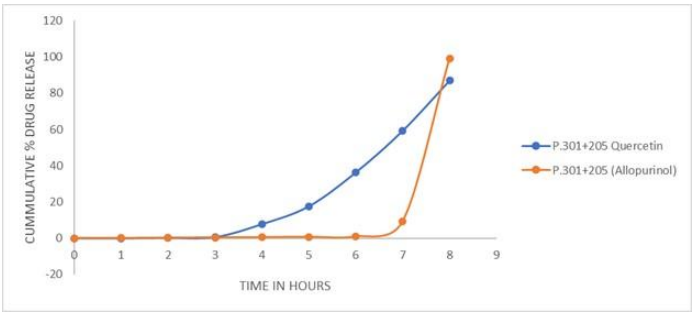

Figure: % drug release profile of Quercetin with different grades of polyox

In vitro release: In vitro, drug release studies were carried out using a USP Type II dissolution apparatus with HCl as the dissolution medium for 2 h and the tablet was then transferred to PBS, pH 6.8, for an additional 6 h at 50 rpm. In vitro, dissolution results elicited that 78% to 99% drug released after lag time was observed in all the formulations. Figures 3 and 4 show the % drug release profile of allopurinol where the total drug is released within 15- 20 mins where nearly 78% to 91% drug release is observed. figure 5 shows the % drug release profile of quercetin with different grades of polyox which shows the lag time of drug release. The drug is released slowly after 7 – 8 hours. The best combination of polyox 303 and polyox 205 is shown where the drug release is seen at 80%. figure 6 shows the best formulation of both drugs in which the release of allopurinol after the lag time is 99% and that of quercetin with combining polyox after the lag time is 86% (Figure 6)

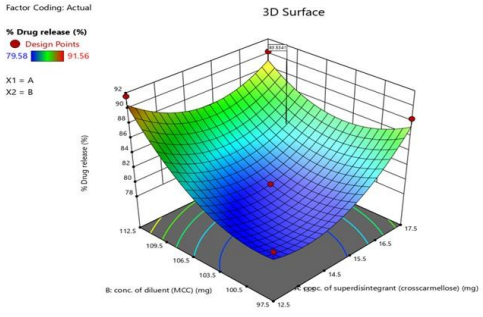

Figure: 3D Surface plot of % drug release

From Figure 7 of % drug release, a 3D surface plot can be used to illustrate the effect of the concentrations of the diluent and Superdisintegrant on drug release. As the concentration of the diluent increases, the drug release decreases initially, as the diluent reduces the porosity of the tablet matrix and slows down the drug release. However, at a certain concentration, further increases in the diluent concentration result in an increase in drug release due to improved tablet disintegration. This occurs due to improved tablet disintegration. Higher concentrations of the diluent can enhance the ability of the tablet to rapidly break apart upon contact with the dissolution medium. This leads to increased surface area exposure and faster drug dissolution. Similarly, an increase in the concentration of the Superdisintegrant initially increases drug release, as the Superdisintegrant promotes rapid tablet disintegration. However, beyond a certain concentration, further increases in the Superdisintegrant concentration result in a decrease in drug release due to the formation of a gel layer that slows down drug release.[21]

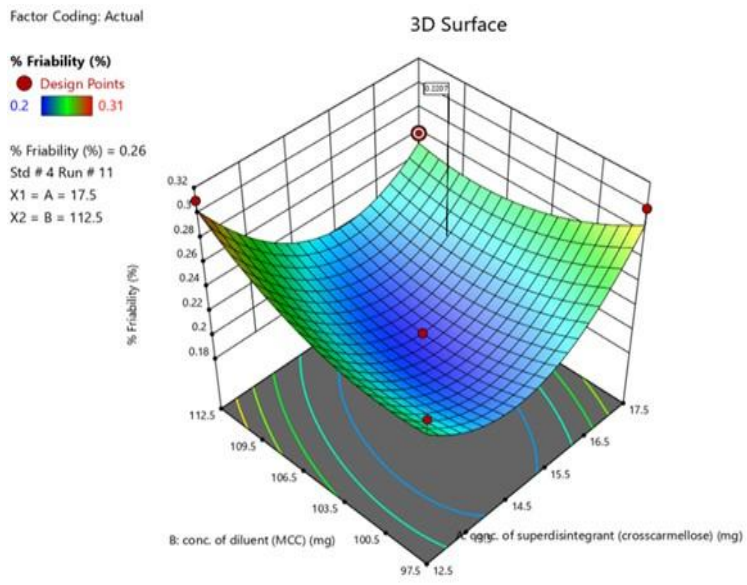

Figure 8: 3D Surface plot of % Friability

From Figure 8 of % friability it was seen that as the concentration of the diluent increases, the friability of the tablet also increases. Friability is a measure of the tablet's ability to withstand mechanical stress and maintain its integrity during handling, packaging, and transportation. If the friability of the tablet is too high, it can lead to the tablet breaking or crumbling, affecting the drug's efficacy and safety. Similarly, as the concentration of the Superdisintegrant increases, the friability of the tablet also increases. This is because the Superdisintegrant enhances the tablet's disintegration, which can lead to the tablet breaking down more easily. Therefore, the concentration of the diluent and Superdisintegrant needs to be carefully

optimized to ensure that the tablet has appropriate friability while also providing effective drug delivery. Other factors, such as the type and concentration of the active ingredients and the tablet's coating, also need to be considered when formulating and evaluating a pulsatile tablet for gouty arthritis. It is crucial to optimize the concentrations of both the diluent and Superdisintegrant to ensure that the tablet achieves the desired balance between effective drug delivery and appropriate friability. This optimization process involves considering other factors, such as the type and concentration of active ingredients and the tablet's coating. The goal was to formulate a tablet that can withstand mechanical stress during handling, packaging, and transportation while maintaining its structural integrity and providing the desired drug release profile.[22]

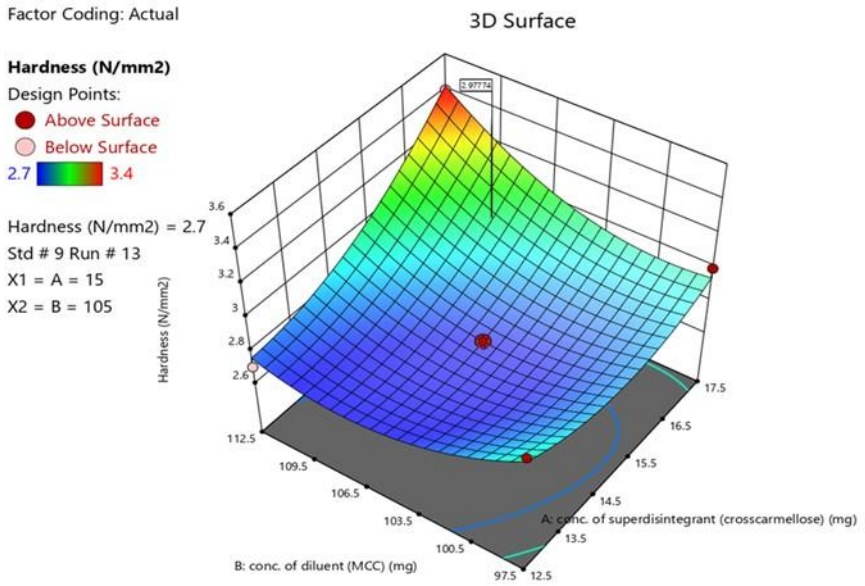

Figure 9: 3D Surface plot of hardness

From Figure 9 of hardness, it was observed that as the concentration of the diluent increases, the hardness of the tablet decreases. This is because the diluent, which is usually an inert material such as microcrystalline cellulose, reduces the concentration of the active ingredients in the tablet. Therefore, the tablet is less compact, and its hardness is reduced. On the other hand, as the concentration of the Superdisintegrant increases, the hardness of the tablet increases. The Superdisintegrant enhances the tablet's disintegration, which can lead to a faster release of the active ingredients. This faster release can cause the tablet to lose its structural integrity, resulting in a reduction in hardness. Therefore, the concentration of the diluent Superdisintegrant needs to be carefully optimized to ensure that the tablet has appropriate hardness while also providing effective drug delivery. To ensure appropriate hardness while providing effective drug delivery, the concentrations of the diluent and

Superdisintegrant need to be carefully optimized. The goal is to strike a balance between tablet hardness and drug release characteristics. This optimization process involves considering other factors, such as the type and concentration of active ingredients, the presence of other excipients, and the compression force applied during tablet manufacturing. By fine-tuning the concentrations of the diluent and Superdisintegrant, along with the formulation and compression parameters, it is possible to develop tablets with the desired hardness that maintain their structural integrity while ensuring effective drug delivery.[23]

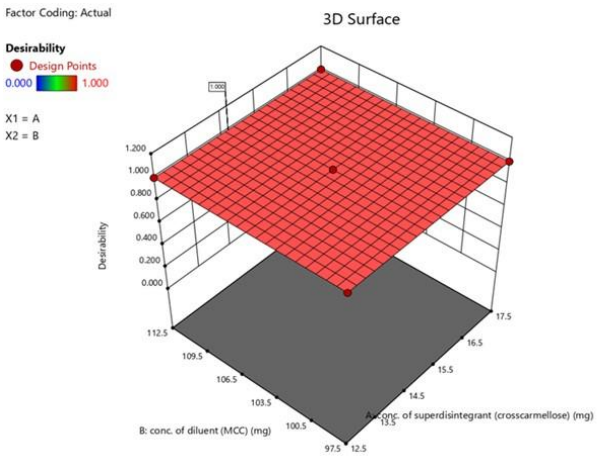

Figure 10: 3D Surface plot for desirability

The desirability plot considers all the responses and generates an overall desirability score that reflects the desired levels of each response (Figure 10). The optimal formulation is the one that has the highest desirability score. In the formulation and evaluation of a pulsatile tablet for gouty arthritis using combination drug therapy, the optimal formulation may have a high level of drug release, a low level of friability, and an intermediate level of hardness. The desirability plot can help determine the concentrations of the diluent and Superdisintegrant that would achieve these desired levels of the responses. By using a desirability plot, the optimal formulation can be obtained, which would have the desired properties in terms of friability, hardness, and drug release, and thus, can provide an effective and safe treatment option for patients with gouty arthritis.

Conclusion:

The objective of the present work was to develop a pulse-type profile of formulation of Allopurinol and Quercetin by using a compression coating technique. The formulation is administered in the evening for the treatment of pain evoked in the morning and it gives relief from the pain by releasing the drug from the formulation in a time-controlled manner. The

calibration curve of Allopurinol and Quercetin was performed with methanol which can be used for drug quantification in dissolution analysis. Solubility study of Allopurinol and Quercetin in different solvents indicates that Allopurinol and Quercetin show the highest solubility in methanol. The solid dispersion of Allopurinol and Quercetin was found to be higher solubility enhancement in PEG- 8000 polymers. The ratio was found to be 1:2 showing the increase in solubility. Formulation of the core tablet was prepared by using optimized and finalized based on solubility enhancement solid dispersion ratio of Allopurinol. Evaluation of immediate release core tablet i.e., Hardness, Thickness and diameter, weight variation, friability, disintegration time and in vitro dissolution studies. Optimization of immediate release core tablet was found to be F4, formulation was better results compared to other formulations. Formulation of press-coated tablet prepared by using Polyox 301, Polyox 205, and Ethyl Cellulose. Evaluation of pre-compression parameters i.e., angle of repose, bulk and tapped density, Carr's index, and Hausner's ratio. Evaluation of press coated tablet i.e., Hardness, Thickness and diameter, weight variation, friability, disintegration time and in vitro dissolution studies. Optimization of press-coated tablet was found to be better with polyox 301 and polyox 205 compared to other grades of polyox. The present study was to overcome the oral side effects of Allopurinol and reduce the dose of Allopurinol to overcome the side effects of Allopurinol Quercetin combined therapy. Thus, formulating a pulsatile drug delivery system containing Allopurinol and Quercetin in combination for local action against gouty arthritis. Hence, it can be concluded that the present study to develop the PDDS of combination drug therapy is a promising approach to overcome the side effect of a single drug i.e., Allopurinol drug therapy and also oral drug delivery.

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