Ars Pharmaceutica
https://revistaseug.ugr.es/index.php/ars
E-ISSN: 2340-9894 ISSN: 0004-2927

doi: 10.30827/ars.v66i2.31527
Artículos originales

Formulation, Development, and Evaluation of Flubiprofen Sustained Release Tablets Using a Quality-by-Design Approach

Formulación, desarrollo y evaluación de comprimidos de liberación sostenida de flubiprofeno mediante un enfoque de calidad por diseño

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Received: 08.09.2024
Accepted: 14.12.2024
Published: 18.03.2025

Funding

Not applicable

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

The authors would like to thank the Principal and Secretary of Shreeshakti Shaikshanik Sanstha's Divine College of Pharmacy, Satana, Nashik, India.

Resumen

Introducción: El flurbiprofeno actúa bloqueando las enzimas ciclooxigenasa (COX) del organismo para que no realicen su función normal. El estudio produjo comprimidos de flubiprofeno de larga duración mediante compresión directa con polímeros carbopol, HPMC K100M y HPMC K4M. El flubiprofeno es un antiinflamatorio no esteroide.

Método: La investigación formula y desarrolla comprimidos de liberación sostenida de flubiprofeno por compresión directa con polímeros carbopol, HPMC K100M, y HPMC K4M. La mayor concentración de flubiprofeno en etanol, según las pruebas de preformulación, fue de 215 nm.

Resultados: Se examinó el grosor, el diámetro, el contenido de medicamento y la friabilidad de la tableta comprimible. Todos los exámenes fueron buenos. El índice de compresibilidad, la densidad aparente, el ángulo de reposo y la densidad roscada mostraron buenos resultados para la mezcla de comprimidos. Se realizaron pruebas de liberación in vitro utilizando un dispositivo USP tipo II a 50 RPM, HCl 0,1 N en el medio de disolución durante dos horas, y tampón fosfato pH 6,8 durante seis horas a 37 +0,5°C. Un espectrofotómetro UV-visible con un ajuste de 215 nm evaluó la liberación del fármaco en diferentes periodos. Esta investigación sobre la formulación indicó una liberación del 99,25% del fármaco a partir de F2.

Conclusiones: Una de las ventajas de la forma farmacéutica de liberación sostenida es que permite administrar un medicamento de forma gradual durante un periodo de tiempo prolongado para mantener constante el nivel de concentración en sangre. Esto puede mejorar el cumplimiento del paciente y aumentar la producción de fármacos.

Palabras clave: Flubiprofeno, Liberación sostenida, Disolución, Polímero, DOE, Calidad por diseño.

Abstract

Introduction: Flurbiprofen acts by blocking the cyclooxygenase (COX) enzymes in your body from carrying out their normal function. The study made flubiprofen tablets that last a long time by directly compressing them with carbopol, HPMC K100M, and HPMC K4M polymers. An anti-inflammatory non-steroid is flubiprofen.

Method: The research formulates and develops sustained-release flubiprofen tablets by direct compression with carbopol, HPMC K100M, and HPMC K4M polymers. The highest flubiprofen concentration in ethanol, according to pre-formulation tests, was 215 nm.

Results: The compressibility tablet was tested for thickness, diameter, medication content, and friability. Every exam was good. The compressibility index, bulk density, angle of repose, and tapped density showed good results for the tablet mix. In-vitro release tests were performed utilizing a USP device type II at 50 RPM, 0.1 N HCl in the dissolving media for two hours, and phosphate buffer pH 6.8 for six hours at 37 +0.5°C. A UV-visible spectrophotometer with a 215 nm setting assessed drug release at different periods. This formulation research indicated 99.25 % drug release from F2.

Conclusions: One benefit of the sustained release dosage form is that it allows a medication to be administered gradually over an extended period in order to keep the blood level of concentration constant. This may improve patient compliance and increase drug output.

Keywords: Flubiprofen, Sustained release, Dissolution, Polymer, DOE, Quality by Design

Highlights

In this study, the flurbiprofen tablet was formulated by using the direct compression method which includes carbopol, HPMC K100M, and HPMC K4M polymers.

SR formulations were developed to improve drug function by lengthening half-lives, decreasing frequency of administration, minimizing side effects, lowering dose, and delivering the medication in the shortest time using the least amount through the most effective route.

This study aims to maximize yield percentage and flow quality while reducing moisture. The factorial design used statistics to find the best formulation parameters and looked at how the spray dryer's process parameters affected the co-excipient's moisture content, percentage yield, and compressibility index. It also looked at the effects of these parameters on each other and on a quadratic scale. Quadratic and linear response surfaces were examined utilizing Design Expert's 3-factor, 3-level design.

The study found that in vitro dissolution was successful. Batch F2 had the highest drug release rate of 99.25%, according to the formulation. So batch F2 is optimized.

Introduction

Painful disorders like migraines, sprains and strains, menstruation pain, and arthritis can all be treated with flurbiprofen. It is also recommended to reduce discomfort following surgery[1].

The way that flurbiprofen functions is by preventing your body's cyclo-oxygenase (COX) enzymes from doing their job. These enzymes aid in the body's production of prostaglandins, another type of molecule. At the locations of damage or injury, some prostaglandins are created, which results in pain and inflammation. Pain and inflammation are reduced because fewer prostaglandins are generated when COX enzymes are blocked[2].

Additionally, flurbiprofen is sold as throat lozenges and eye drops. Two different medication pamphlets named Flurbiprofen eye drops and Flurbiprofen lozenges have more information about these[3].

Most non-steroidal anti-inflammatory drugs (NSAIDs) block cyclooxygenase in a non-selective manner, thereby inhibiting the enzymes COX-1 and COX-2. Flubiprofen is part of a class of medications known as propionic acid derivatives. This prescription is a suitable candidate for a controlled or sustained-release medicine because it requires three to six daily doses and has a plasmatic half-life of one to two hours, potentially limiting drug release in the upper GI tract. The kind and amount of polymer utilized in the preparations has a big impact on how quickly the medication releases from the dosage form[4].

We developed a sustained-release formulation specifically for patients who required reasonably consistent blood levels over an extended period, thereby eliminating the need for multiple dosage schedules[5].The sustained release drug delivery system (SRDDS) seeks to minimize side effects while releasing medication at a predetermined rate. The main goal of developing SR formulations was to improve the way drugs functioned by lengthening their half-lives, decreasing the frequency of administration, minimizing side effects, lowering the required dose, and delivering the medication in the shortest amount of time using the least amount through the most effective route[6-8]. Therefore, the current work aims to develop flubiprofen tablets that gradually release medication through a variety of hydrophilic polymers. We employ the hydrophilic polymers of HPMC K100M, HPMC K4M, and Carbopol 940 for tablet formulation, and add relevant additives using the direct compression process[9].

Methods

Materials[10-15]

Flubiprofen, magnesium stearate, and talc are procured from a research lab chem industry in Mumbai, and HPMC K 100 m, HPMC K 4M, carbopol, avicel, and lactose are the other excipients; they were collected from the Modern Industry C-74, MIDC Malegaon, India.

Pre-formulation study

Characterization of drug

The organoleptic properties of flubiprofen: The organoleptic characteristics of the Flubiprofen drug sample, such as color and odor.

Melting point determination: The capillary technique was used to determine the drug's melting point.

Solubility determination: Different solvents, including water, alcohol (ethanol/ ethyl alcohol), ether, acetone, and chloroform, were used to test the drug's solubility.

UV spectra (λ max): Flubiprofen 100 mg was weighed, transferred into a 100 ml volumetric flask, and then mixed with alcohol to make 100 ml. It contained 10 mg/ml of the normal stock solution of flubiprofen. Dilutions were made from this solution, and max was then determined.

Standard curve of flubiprofen: The flubiprofen is dissolved in ethanol and then prepared the 5 dilutions 10 µg/ml, upto 50 µg/ml) and calculate the absorbance with the help of UV.

Formulation table

Formulation table of sustained release tablet of flubiprofen represents in table 1.

Table 1. Formulation table of sustained release tablet of flubiprofen

Sr. No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Flubiprofen	200	200	200	200	200	200	200	200
2	HPMC K100M	10	15	15	10	15	10	10	15
3	Carbopol	15	20	15	20	15	20	15	20
4	HPMC K4M	20	20	20	25	25	20	25	25
5	Avicel	15	15	15	15	15	15	15	15
6	Magnesium Stearate	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
7	Talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
8	Lactose	QS	QS	QS	QS	QS	QS	QS	QS

Sr. No: Serial Number, QS: Quantity sufficient

Total weight of each tablet =320 mg

Method of preparation

The Various batch formulations of tablets (F1-F8) were made using the direct compression technique. Flubiprofen, a pure medication, and the polymers, HPMC K4M and K100M Carbapol, were each passed through #40 sieves separately before being thoroughly combined in a mortar and pestle for ten minutes. After going through #40 sieves, lactose and Avicel were added to this mixture and vigorously mixed for five minutes. After going through #60 sieves, there was adequate talc and magnesium stearate to lubricate this powder blend. Next, using 8 mm circular punches to hardness 4-5 kg/cm^3, the necessary amount of powder was weighed and manually fed into the single punch rotary machine to manufacture tablets weighing 320 mg[16,17].

Experimental design

The experimental design was used to optimize the processing parameters. Developing and improving medication delivery systems is frequently accomplished through the application of response surface methodology (RSM). Using a range of experimental designs, polynomial equations are generated, and the response is mapped throughout the experimental domain to determine the optimal formulation or formulations, all in accordance with the design of experiments (DOE) principle. The procedure is substantially more cost-effective and efficient than the conventional methods of producing dose types since it requires the least amount of effort and experimentation. The current study has chosen to maximize yield percentage and flow property while lowering moisture content as its objective function. The formulation parameters were statistically optimized using the factorial design, which also allowed for the evaluation of the primary, interaction, and quadratic impacts of the spray dryer's process parameters on the co-excipient's moisture content, yield percentage, and compressibility index. Using Design Expert, the quadratic and linear response surfaces were investigated using a 3-factor, 3-level design. Based on the Design Expert software's analysis of variance (ANOVA) feature, the polynomials' statistical validity was determined. A significant threshold of p & it; 0.05 was used. Formulation and Development of Flubiprofen Sustained Release Tablet: The mathematical model that fitted the data the best was chosen through comparison of various statistical parameters, such as the predicted residual sum of squares (PRESS), the multiple correlation coefficient (R^2), the adjusted multiple correlation coefficient (adjusted R^2), and the coefficient of variation (CV)[18-20].

When comparing the selected model to the other models being considered, PRESS—a measure of how well the model matches the data—should be small. The 2-D contour plots and 3-D response surface graphs were also generated by the Design Expert® application. To illustrate how the elements, interact to affect answers, these graphs are helpful. The experimental design was employed to maximize the processing parameters[21].

Levels selection of parameters of flubiprofen sustained released tablet:

The trial batch served as the foundation for choosing the level of independent elements. Table 2 shows the translation of the coded level in actual units. Table 3 shows Factorial design was used in the experimental design to optimise the processing parameters of the flubiprofen sustained-release tablet[22].

Dependent factors (response)

- Friability
- Dissolution

Table 2. Translation of the coded level in actual units

Sr. No.	Coded Level	Independent Factor		
		HPMC K4M (X1)	HPMC K100M (X2)	Carbopol (X3)
1	Lower Level (-1)	10	15	20
2	Higher Level (+1)	15	20	25

Table 3. Factorial design was used in the experimental design to optimise the processing parameters of the flubiprofen sustained-release tablet.

Sr. No.	Run	Friability (Factor 1)	Dissolution (Factor 2)
1	1	0.518	74.42
2	2	0.515	99.25
3	3	0.520	99.11
4	4	0.520	92.18
5	5	0.518	97.02
6	6	0.512	82.31
7	7	0.520	92.08
8	8	0.526	79.58

Evaluation Parameters of Flubiprofen Tablet

Pre-formulation evaluation methods[23-26]

Determine the bulk density

Flubiprofen granules' bulk density was calculated by measuring the volume of the packing after a weighed quantity of granules was added.

Formula-

$$Bulk\ density = \frac{Weight\ of\ the\ powder}{Volume\ of\ the\ packing}$$

Tapped density

The tapping method was used to determine the tapped density. Once the beginning volume was noted, a predefined quantity of granules was placed within a measuring cylinder. Next, tapping the cylinder was done until the granules' volume stopped changing. The final volume of the tapped packing was then recorded.

Formula -

$$\boldsymbol{Tapped\ density = \frac{weight\ of\ the\ powder}{volume\ of\ the\ tapped\ package}}$$

Carr's index

The compressibility index of the granules was calculated using Carr's index. The proportion Carr's index can be computed using the process below.

Formula -

$$Carr's\ index\ (\%) = \frac{TD - BD}{TD} \times 100$$

Haunser's ratio

The Hausner ratio is the ratio of the bulk density to the tapped density. The granule flow is judged as unsatisfactory if the Hausner ratio is greater than 1.25, while flow properties are regarded as excellent if it is less than 1.25.

Formula-

$$Haunsers\ ratio = \frac{Tapped\ density}{bulk\ density}$$

Angle of repose

The angle of repose is calculated as the arctangent of the ratio between the height (h) and radius (r) of a conical powder pile. It can be achieved within the space between the horizontal plane and the surface of the powder heap that is not supported by anything. The fixed funnel is positioned with its tip set at a vertical distance h above the graph paper, which is laid out on an even and level surface. The powder is progressively added to the funnel until the conical heap's peak is just barely touching the funnel's tip.

Formula -

$$Angle\ of\ repose = tan - 1\frac{h}{r}$$

Where,

r = Radius of the base of the pile

h = Height of the pile

θ= The angle of repose

Post-compression evaluation methods[27-30]

Hardness

The strength of the pill is indicated by its hardness. By calculating the force required to break the tablet, you may test it. The force is measured in kg. Calculate the hardness of 5 tablets from the formulation.

Percent friability

Tablet strength is gauged by friability. In this test, many tablets are dropped to a distance of 6 inches during each rotation of a plastic chamber rotating at a speed of 25 rpm, subjecting the tablets to the combined effects of shock and abrasion. In Roche friability, a sample of pre-weighed tablets was put, and the device was then turned on and off 100 times. The tablets were afterward cleaned and reweighed. Generally speaking, a weight decreases of less than 1 % is acceptable. The formula used to compute percent friability (% F),

Formula -

$$Percent\ friability = \frac{Initial\ Weight - Final\ weight}{Initial\ weight} \times 100$$

Dimension (thickness and diameter)

The thickness and diameter of the tablets determined the uniformity of tablet size. The diameter and thickness of the tablets were measured with a Vernier caliper. For each type of formulation, five tablets were used to calculate the average values.

Disintegration

To find each formulation's disintegration time, we used six Tablets. The pH 6.8 phosphate buffer solution, which served as the disintegration medium, was carefully kept at 37±0.5°C. Using a media capacity of 900 ml, the average disintegration time of six tablets was determined.

In-vitro dissolution studies

The dissolve experiments for the flubiprofen SR tablets were carried out using the USP dissolving testing apparatus II, namely the paddle type. For the first two hours of the in-vitro dissolving experiment, an acidic solution (0.1 N HCl) was used. After that, the mixture was spun at 50 revolutions per minute and 37°C while the 6.8-pH phosphate buffer in 900 mg was utilised as the dissolving medium. Every six hours, 5 mg of the material were taken out of the dissolving apparatus. An equivalent volume of medium was utilised in place of the samples. The absorbance of these solutions was measured with a UV spectrophotometer, and the result was 215 nm. The drug concentration released at various time intervals was calculated using the traditional graph. To analyze the drug release pattern, plotting the cumulative proportion of medication release against time was done. The rates of drug release were established[31,32].

Results

Preformulation study

Organoleptic properties of flubiprofen: The sample of flubiprofen was studied for organoleptic such as color is White, odour is slight and appearance is crystalline power.

Melting point determination result: Flubiprofen melting point was measured by using the capillary technique. According to IP, the melting point of flubiprofen was found to be between 74 °C to 76 °C.

Solubility determination: The solubility of flubiprofen was checked in different solvents and it is soluble in ethanol and is insoluble or partially soluble in Water.

UV spectrum (λ max):

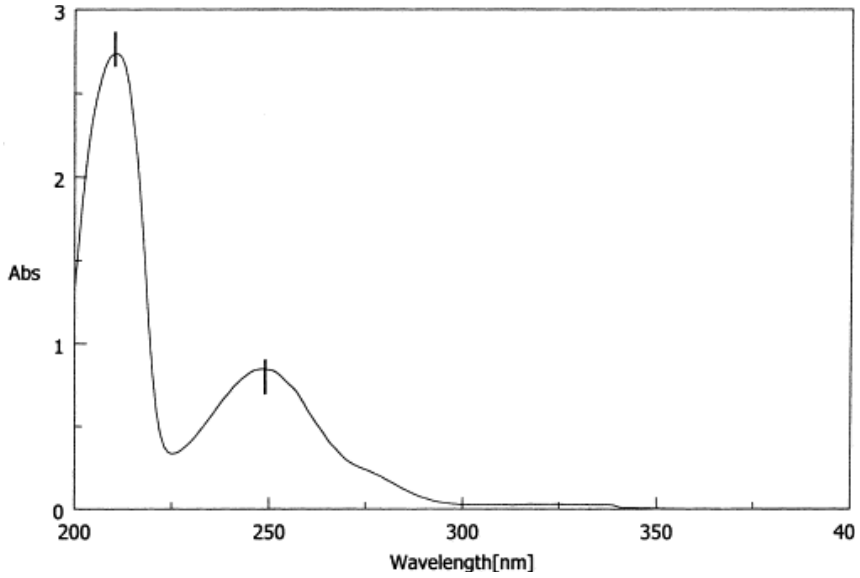

Figure 1. UV visible Spectrum of flubiprofen in ethanol

Standard curve of Flubiprofen

Table 4. Concentration and absorbance of flubiprofen drug

Sr. No.	Concentration (ppm)	Absorbance
1	10	0.177
2	20	0.261
3	30	0.295
4	40	0.393
5	50	0.505

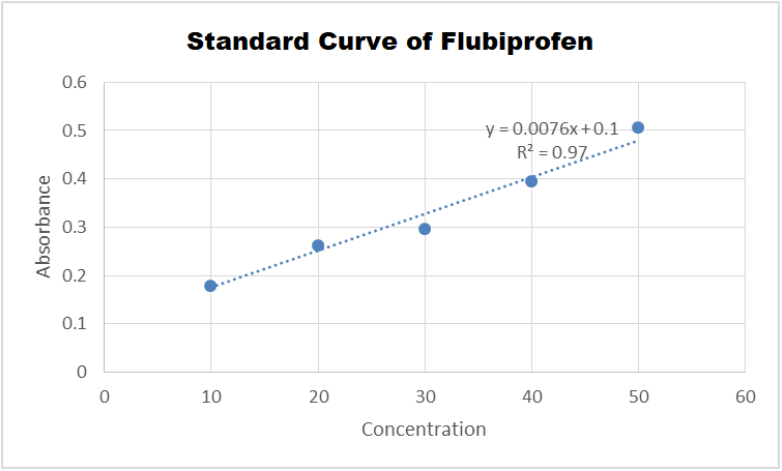

Figure 2. Calibration curve of flubiprofen

The flubiprofen was scanned and the wavelength (max) was found to be 215 nm in ethanol using a UV spectrophotometer. It was found that flubiprofen shows absorbance in the UV range of 200 to 350 nm. The equation of the regression line was obtained Y= 0.0079x + 0.0898 and the regression value R^2= 0.97. Figure 1 shows UV visible spectrum of flubiprofen in etanol and figure 2 shows calibration curve of flubiprofen.

Evaluation parameters

Pre-compression parameters

Table 5. Pre-compression Evaluation parameters results

Sr. No	Batch	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Haunser s Ratio	CI (%)
1	F1	0.40	0.48	32.61	1.20	16.66
2	F2	0.40	0.47	32.61	1.17	14.89
3	F3	0.39	0.49	32.52	1.25	20.40
4	F4	0.38	0.52	33.06	1.36	26.92
5	F5	0.40	0.50	31.59	1.25	20.00
6	F6	0.41	0.52	33.22	1.26	21.15
7	F7	0.43	0.47	33.42	1.09	8.51
8	F8	0.41	0.52	32.29	1.21	21.15

CI: Compressibility Index

A number of characteristics, including as tapped density, bulk density, Haunser's ratio, Carr's compressibility index, and angle of repose, were evaluated for formulating flubiprofen and other excipients. flubiprofen and the other excipients were also subjected to measurements and analyses of these parameters. The bulk density ranged from 0.38 to 0.43 g/cm^3, and the tapped density ranged from 0.47 to 0.52 g/cm^3. It was found that both values fell within the required range. These two density measurements were used to calculate Carr's compressibility index. Hausner's ratio and the compressibility index were used to find that all powder mixes had flow characteristics that ranged from good to acceptable.

The compressibility index ranged from 8.57 % to 26.92 %, and the Hausner's ratio varied from 1.09 to 1.36. The angle of repose provided the best explanation for the flow characteristic of all powder combinations. It was found that the angle of repose ranged from 32.29° to 33.42°. All powder blends exhibited well to acceptable flow characteristics, according to the angle of repose test (Table 5).

Post-compression evaluation parameters result

Table 6. Evaluation parameters result of post compression

Sr. No	Formulation n number	Hardness (kg/cm^2)	Thickness (mm)	Diameter	Friability (%)	Weight Variation
1	F1	4.00	5.776	8.00	0.518	315
2	F2	4.00	5.846	8.00	0.515	320
3	F3	5.00	5.798	8.00	0.520	317
4	F4	4.00	5.822	8.00	0.520	319
5	F5	5.00	5.832	8.00	0.518	320
6	F6	4.00	5.832	8.00	0.512	322
7	F7	5.00	5.776	8.00	0.520	321
8	F8	4.00	5.940	8.00	0.526	320

The table displays the post-compression parameters for all formulas. The thickness ranged from 5.766 mm to 5.846 mm, suggesting a consistent thickness across all samples. All formulations had a diameter of 8mm and there was no statistically significant difference seen. The hardness of all formulations falls within the range of 4.00 to 5.00 kg/cm^2. The friability, which measures the tendency of the tablet to crumble or break, was found to be less than 1%, showing that the tablets have good integrity (Table 6).

In-vitro dissolution studies result

Table 7. In vitro dissolution studies of different batches.

Sr. No	Buffer Medium (pH)	Time	F1	F2	F3	F4	F5	F6	F7	F8
1	0.1 N HCl	00	00	00	00	00	00	00	00	00
2		1	10.22	4.01	3.08	5.06	3.87	3.47	9.432	14.86
3		2	20.84	20.17	27.57	31.95	15.27	9.45	16.23	33.47
4	Phosphate buffer 6.8 pH	3	28.32	52.29	38.70	55.00	18.51	18.34	38.14	53.96
5		4	35.05	66.49	49.48	65.58	33.52	18.92	52.52	58.04
6		5	46.40	81.79	65.95	75.84	62.13	31.50	67.00	59.78
7		6	56.78	86.38	88.41	84.75	79.4	50.37	81.80	63.76
8		7	63.46	87.46	94.09	90.46	90.42	63.83	90.89	71.73
9		8	74.42	99.25	99.11	92.78	97.02	82.31	92.08	79.58

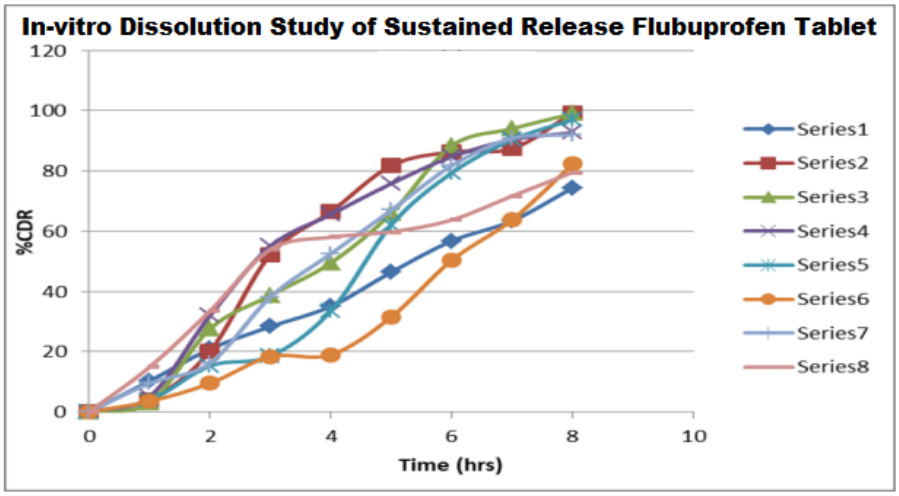

Figure 3. In-vitro dissolution study of flubiprofen sustained release tablets

The USP type II dissolution test apparatus paddle type was used to investigate the dissolution of the manufactured formulation using 900 ml of phosphate buffer solution (PH 6.8). The medication release data expressed as a percentage in a table. The F2 formulation in this formulation research demonstrates 99.25% drug release (Table 7 and Figure 3).

Discussion

We examined the Flubiprofen sample's white color, mild flavor, and crystalline power look. Flubiprofen melts at 74–76°C, according to IP. It dissolves in ethanol, whereas water does not. We used a UV spectrophotometer to scan Flubprofen in ethanol and discovered the maximum wavelength at 215 nm. We found that flubiprofen absorbs 200–350 nm UV light. When synthesizing flubiprofen and other excipients, we considered tap density, bulk density, Haunser's ratio, Carr's compressibility index, and angle of repose. We tested and studied flubiprofen and other excitants. The bulk density was 0.38–0.43 g/cm^3, while the tapped density was 0.47–0.52. Both values met the criteria. Using these two densities, we estimated Carr's compressibility index. According to Hausner's ratio and compressibility index, all powder blends had a good to acceptable flow. The compressibility index was 8.57 %–26.92 %, and Hausner's ratio was 1.09–1.36. Angle of Repose provided the best explanation for the angle of flow in all powder combinations. The reposing angle was 32.29°–33.42°. The angle of repose tests showed that all powder blends had a good flow.

The thickness ranged from 5.766 to 5.846 mm, indicating consistency between samples. All formulations were 8 mm in diameter, and there was no statistical difference. All formulations are 4.00–5.00 kg/cm^2 hard. The tablets' friability was less than 1 %, indicating good integrity. We tested the formulation's solubility with 900 ml of phosphate buffer solution (PH 6.8) and the USP type II paddle-type dissolution test device. A table presents the data on the percentage of drug release. This investigation shows that the F2 formulation releases 99.25 % of the medication.

Conclusion

In this study, the sustained release tablets of flubiprofen were formulated and developed, for the formulation development Quality by design was used. The direct compression methods were used to

formulate sustained-release flubiprofen tablets, the goal of the current work study was established. Controlled release formulations are designed for achieving plasma drug concentrations for a longer duration by controlling the rate, time, and site of the drug release. Utilizing a suitable polymer, such as HPMC K100M, HPMC K4M, and Carbopol, the formulation was prepared. The final product was tested for friability, hardness, diameter, thickness, and in-vitro release after being crushed into tablets. The dissolution experiments were conducted using acidic solutions (0.01 N HCl for the initial two hours, followed by six hours in the pH of the phosphate buffer is 6.8). The study concluded that the investigation of in vitro dissolution was carried out successfully. According to the formulation result, batch F2 exhibited the greatest drug release rate of 99.25 %. Therefore, batch F2 is considered the optimized batch

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