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Formulation and Evaluation of Hydrogel Based Drug Delivery System of BCS Class Ⅱ Drug

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ABSTRACT: The goal of this study was to develop Ibuprofen hydrogel tablets using the physical crosslinking method and to assess the relationship and influence of freeze/thaw cycles, as well as varied degrees of HPMC and β-Cyclodextrin content, on Ibuprofen sustained release. Direct compression was used to create the tablets. Fitting the in-vitro drug release data to the Korsmeyer equation revealed that diffusion could be the drug release mechanism. Finally, the results indicate that the drug release kinetics from these formulations best related to Higuchi (matrix) kinetics.

KEYWORDS: Hydrogel, Freeze/Thaw, Tablets, Ibuprofen, β Cyclodextrin, Poly vinyl alcohol.

I. INTRODUCTION

The creation of sustained release techniques of drug delivery offers the advantages of minimizing fluctuations in plasma drug concentration, slowing input rates, and allowing for continuous drug administration. To achieve prolonged drug release, the design and development of hydrogel-based drug delivery systems can be done utilizing a green and cost-effective method known as the freeze/thaw method (1).

Hydrogels are made up of hydrophilic polymers that have been covalently cross-linked to resist dissolution. The level of cross-linking, the degree of hydration of the gel, the kind of permeates, and the device design all have an impact on a hydrogel's permeability. (2)

Hydrogels can also be made without water and then equilibrated with water or a concentrated solution of the active component. By freezing and thawing a polymer solution without adding any electrolytes or organic crosslinking agents, hydrogels can be created. (3)

Polymer freezing and thawing is a polymer solidification process that results in an ultrapure three-dimensional network linked together by crystallites that act as physical crosslinks. The freeze-thaw method of hydrogel synthesis includes repeatedly freezing and thawing an aqueous solution of polymers. A freeze/thaw cycle is formed by a freezing phase followed by a thawing phase. This work focuses on pharmaceuticals and polymers. (5, 6, 7)

Ibuprofen is a BCS class II medication with a molecular weight of 206 and a half-life of 1.2-2 hours, making it an excellent candidate for the development of an oral sustained release hydrogel drug delivery system. In addition, no Ibuprofen hydrogel pills have previously been documented in the literature.

Polyvinyl alcohol is the most commonly utilized polymer in the Freeze/Thaw method of preparing hydrogels. In this investigation, PVA with a molecular weight of 1,25000Da was utilized at a concentration of 5% W/W to crosslink all polymers. The concentration is chosen so that the frozen/thawed polymer combination can be simply air dried at the end, minimizing the stages in preparation and making this a cost-effective procedure.

HPMC is widely used to make sustained and controlled-release dosage forms as it is a hydrophilic polymer and controls the release of drugs at a wide range. (8)

β Cyclodextrin is used so that it may act as a carrier in drugs and other polymers. This research also investigates the effect of β-Cyclodextrin presence and absence. (9)

In the current research topic, hydrogel tablets are prepared by direct compression of cross-linked drug-polymer powders.

II. MATERIALS AND METHODS

2.1 Materials

Ibuprofen was procured from Carechem Pvt. Ltd., Mumbai. Polyvinyl alcohol and β-Cyclodextrin were procured from Vishal Chem. Mumbai. Hydroxypropyl Methylcellulose E15 LV

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(premium) and lactose were procured from Loba Chemie Pvt. Ltd., Mumbai. Microcrystalline cellulose was procured from Research Lab Fine-Chem Industries.

III. EXPERIMENTAL

3.1 Identification of Drug and Polymer [11, 12, 13]

FTIR and DSC analysis of pure drugs and polymers is done for identification purposes.
Further, the physical mixtures and hydrogels were also analysed to determine the effect of polymer concentration, the effect of freeze-thaw cycles, and drug-polymer interactions.

3.1.1 Infra- Red Absorption Spectroscopy

Fourier Transform Infrared Spectroscopy of drug and polymers was recorded on a Shimadzu Fourier transform infrared spectrophotometer using diamond ATR. The instrument was operated under dry air purge;the number of scans was 35 with a resolution of 4 cm^{-1} over the region 4000-400 cm^{-1}. The identified peaks were compared with the principal peaks of the reported infra-red spectrum, and the sample was authenticated.

3.1.2 Differential Scanning Calorimetry

Differential Scanning Calorimetry was performing of drug and polymers such as Polyvinyl Alcohol, Hydroxypropyl methylcellulose E15 LV, β-Cyclodextrin, lactose and microcrystalline cellulose using Setline Thermographs were obtained by heating 1-5 mg sample in crimped aluminium pans at heating rate 10^0C/min, from 30^0C to 300^0C, in a nitrogen atmosphere (flow rate 40 Ml / min).

3.2 Development of Spectroscopic Method [14, 15]

3.2.1 UV-Spectrum of Ibuprofen

UV-spectra of pure Ibuprofen were obtained using a UV spectrophotometer (Model UV 1700, Shimadzu). The drug (100 mg) was dissolved in a 100-ml phosphate buffer having a pH of 7.4 to obtain the stock solution of concentration 1000 µg/ml. From this stock solution, 1 ml was withdrawn and diluted up to 100 ml, and the resultant solution was scanned between 200 and 400 nm to determine the absorption maxima (λ max).

3.2.2 Preparation of standard Calibration Curve for Ibuprofen in Phosphate Buffer pH7.4

An accurate quantity of 100 mg Ibuprofen was weighed and transferred to a 100 ml volumetric flask. The drug was dissolved in a 100 mL 7.4-pH phosphate buffer with shaking. The volume was made up to the mark with the same solvent to obtain standard stock solution A of known concentration (1000 µg/ml). 1 ml of solution was withdrawn from stock solution A and diluted it with 100 ml of 7.4pH phosphate buffer solution to obtain standard solution B of known concentration (10µg/ml). Appropriate dilution of the standard stock solution was done; working, standard solutions of a suitable concentration of drug were prepared by diluting 1 to 10 mL to get a working standard solution of 1-10µg/ml. The UV absorbance of these solutions was measured by a UV-visible spectrophotometer at 221.5 nm. The values of absorbance vs. concentration of drug were plotted on a standard curve. Its slope and regression coefficient were calculated from the graph.

3.2.3 Preparation of standard Calibration Curve for Ibuprofen in Methanol.

An accurate quantity of 100 mg Ibuprofen was weighed and transferred to a 100 ml volumetric flask. The drug dispersed in 100 ml of methanol with shaking. The volume was made up to the mark with the same solvent to obtain standard stock solution A of known concentration (1000 µg/ml).1 ml of solution was withdrawn from stock solution A and diluted it with 100 ml of methanol to obtain standard solution B of known concentration (10µg/ml). Appropriate dilution of the standard stock solution was done; working standard solutions of a suitable concentration of drug were prepared by diluting 1 to 5 ml to get working standard solutions of 1-5µg/ml. The UV absorbance of these solutions was measured by a UV-visible spectrophotometer at 221 nm. The values of absorbance vs. concentration of drug were plotted on a standard curve. Its slope and regression coefficient were calculated from the graph.

3.3. Solubility Study [16, 17]

Solubility Study in 7.4 pH phosphate buffer

Solubility studies of Ibuprofen were performed when an excess amount of solid Ibuprofen (100 mg) was added to 10 ml 7.4 pH phosphate buffers. β-Cyclodextrin was added to these solutions at varying concentrations. One sample was prepared without adding β-Cyclodextrin to the drug and 7.4 pH phosphate buffers. These solutions are filled with a 10 ml vial shake using a rotator shaker with a rotation speed of 50 RPM for 72 hrs. The contents of each vial were collected with a 1 ml syringe to get clear solutions and the 1 ml solutions were diluted up to 10 ml with the respective solvent. The

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absorbance of solutions was measured using a UV-spectrophotometer at 221.5 nm.

3.4. Preparation of Physical Mixture without Freeze/Thaw Method and Hydrogel with Freeze/Thaw Method [18, 19]

Formulations were prepared by 2(2*2) factorial designs. A total of eight formulations were prepared. From these 8 formulations, 4 samples were subjected to 3 consecutive freeze/thaw cycles, and 4 were prepared without freeze/thaw cycles. Formulations (powders) prepared with the Freeze/Thaw Method are called hydrogels, and powders prepared without the Freeze/Thaw Method are called physical mixture powders.

Factor	Lower Level (-1) Concentration in mg	Higher Level (+1) Concentration in mg
HPMC	12.5	25
β-CD	0	20

Table 1. Study design for preparation of powders with freeze/thaw and without freeze/thaw method.

3.4.1 Preparation of PVA solutions:

PVA solutions (5% w/v) were prepared by adding 5g of PVA powder to 100 ml of distilled water. The mixture was stirred using a magnetic stirrer along with heating up to 80°c for 1-2h until it was clear solutions.

3.4.2 Preparation of Physical Mixture:

A total number of four formulations (F10, F20, F30, and F40) were prepared by direct mixing. Ibuprofen mixtures were created using HPMC E15LV (polymer), PVA (polymer), and β -Cyclodextrin. The above mixtures were analysed by FTIR spectroscopy and Differential Scanning Calorimetry before adding diluent and lubricant. Other excipients like microcrystalline cellulose (as a lubricant, 25 mg in each tablet) and lactose (as a diluent to make a 265 mg tablet) were added to the above mixtures. All ingredients used were passed through a BSS 22 sieve, weighed and blended, and evaluated for their pre-compression properties.

3.4.3 Preparation of Hydrogel:

A total of four formulations (F11, F21, F31, and F41) were prepared by the freeze/thaw method. Aqueous solution of polyvinyl alcohol (5% w/v) (polymer) was added, along with other polymers such as Hydroxypropyl Methylcellulose E15 LV (polymer) and β-Cyclodextrin. Ibuprofen (150 mg) was then added and mixed continuously. The mixture was transferred to containers. Each mixture is subjected to freezing at -18°C for 20 hours. For the first cycle, samples were withdrawn from the deep freezer and thawed for 4 hours at room temperature. After withdrawing samples from the first cycle, other samples were subjected again to the same conditions in the deep freezer for the second and third cycles.

Following the completion of all cycles, the obtained samples were air dried at room temperature to remove any remaining water. All dried products were collected carefully and stored in an airtight container pending further formulation and evaluation studies. The above mixtures were analysed by FTIR spectroscopy and Differential Scanning Calorimetry before adding diluent and lubricant.

Other excipients like microcrystalline cellulose (as lubricant, 25 mg in each tablet) and lactose (as diluent to make a 265 mg tablet) were added to the above mixtures. All ingredients used were passed through BSS 22 sieve, weighed and blended, and evaluated for their pre-compression properties.

Sr. No.	Formulation Code	Polymers			Drug (mg)
		PVA (mg)	HPMC E15 LV (mg)	β-CD (mg)	
1	F10	25	12.5	0	150
2	F20	25	25	0	150
3	F30	25	12.5	20	150
4	F40	25	25	20	150
5	F11	25	12.5	0	150
6	F21	25	25	0	150

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7	F31	25	12.5	20	150
8	F41	25	25	20	150

Table No. 2 Composition of Drug and Polymers for 1 Tablet by three Freeze/Thaw Cycles

3.5 Pre-compression Properties [20]

3.5.1. Angle of Repose:

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which is kept 2cm above graph paper that is placed on a flat horizontal surface. Where, r being the radius of the base of the conical pile, the angle of repose can be determined by using the following formula.

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

Where, Θ is the angle of repose, h is height of pile; r is radius of base of the pile.

3.5.2. Bulk Density:

A quantity of hydrogel powders of each formulation was introduced into a 10 ml measuring cylinder. The powder was carefully levelled without compacting it and the apparent volume was measured (V0). The bulk density was obtained by dividing the mass of a powder by the bulk volume in cm3. It was calculated by using the equation given below.

Bulk density = weight of powder in grams / bulk volume of the powder in cm^3.

3.5.3. Tapped Density:

The pre - weighed samples were placed in a cylinder; its initial volume was recorded (bulk volume) and subjected to tapings for 100 times, then the final volume (tapped volume) was noted.

Tapped density = weight of powder/tapped volume of packing.

3.5.4. Carr's Index:

The Carr's index is determined from the tapped density and bulk density using following formula

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

3.5.5. Hausner's Ratio:

The Hausner's ratio is determined from the ratio of tapped density to bulk density as by the formula given below.

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

3.6 Preparation of Tablet

3.6.1 Preparation of Physical Mixture Tablets

All Tablets were prepared by using a direct compression method.

3.6.2 Preparation of Hydrogel Tablet

All Tablets were prepared by direct compression method.

3.7. Evaluation of Post- Compression Properties[22]

The prepared Tablets were evaluated for Post- Compression PropertieslikeWeight Variation, Hardness, Friability, Swelling Index and In-Vitro Drug Release.

3.7.1 Weight Variation

The weight variation test was conducted using 20 tablets, which were randomly selected and individually weighed using an analytical balance. The average weight of twenty tablets was calculated, and we compared the individual tablet weights to the average.

3.7.2 Hardness

The resistance of the tablet during shipping or breakage under conditions of storage, transportation, and handling before use depends on its hardness. The hardness of each tablet of each formulation was measured by a hardness tester. Hardness was measured in terms of $kg/cm^{2.}$ For eachbatch, three tablets were tested, and the average hardness and standard deviation are reported.

3.7.3 Friability

Friability used to measure the Tablet strength. The Friability Tester was used for testing the friability using the following procedure.

Procedure: 20 Tablets were weighed accurately and placed in the apparatus at 25 rpm dropping the Tablets through a distance of six inches with each revolution. After 100 revolutions, Tablets were weighed and the Precent Friability was calculated.

3.7.4 Drug Content Uniformity

Drug content uniformity performed to ensure the proper mixing of Tablet constituents. It provides information about the amount of the drug present in single formulation.

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Tablets of each formulation batch were weighed and powdered and powder equivalent to one Tablet of Ibuprofen was transferred into 100 ml volumetric flask and volume was made up with methanol. 1 ml of the solution was diluted to 100 ml with methanol. The solution was filtered through whatman filter paper No.45 and absorbance of the solution was observed at 221.5 nm.

3.7.5 Swelling Study of Tablet

Swelling characteristics of Tablet were expressed in terms of water uptake study. Tablets from each batch were selected randomly and weighed. These tablets were then placed in a petri dish and the phosphate buffer pH 7.4 was added until the upper surface of the tablet got covered with the solution. Swollen tablets were removed and weighed at specific time intervals. Weights for maximum swollen tablets were taken. Swelling index of the tablets was calculated by the equation given below:

$$\text{Swelling index (\%)} = \frac{\text{Weight of tablet at time t} - \text{initial weight of tablet}}{\text{Initial weight}} \times 100$$

3.7.6 In Vitro Dissolution Study

In vitro dissolution study was performed using USP Dissolution Testing Apparatus II (DRS-8 Campbell Electronics).The dissolution test was performed using 900 mL of Phosphate Buffer 7.4, at 37 ± 0.5^0C and paddle speed was at 50 rpm. Sample (5 ml) of the solution was withdrawn at a predetermined time interval and replaced with the same fresh dissolution media. The samples collected were diluted taking dilution factor as 10 i.e. 1 ml sample from 5 ml diluted up to 10 ml. Samples were then analysed at 221.5 nm using UV spectrophotometer. Dissolution tests were performed in triplicates.

3.7.7 Study of Release mechanism by curve fitting analysis [23, 24, 25]

Release data (up to 60% of drug release) were fitted to various mathematical models for describing the release mechanism from Tablet. The cumulative amount of ibuprofen release from formulation was fitted to Zero-order, First-order, Higuchi's (matrix) model, Korsmeyer-Peppas model.

3.7.8 Statistical Analysis

Results of In-Vitro Drug Release profiles were analysed with Student t- test (unpaired) and One Way ANOVA to study the significant difference in the formulation due to change in polymeric composition, Addition of β-Cyclodextrin or change in cycles of freeze thaw method. P value of less than 0.05 was considered as evidence of a significant difference.

3.7.9 Mathematical Modelling

Polynomial equations were obtained for 2*2 factorial design for both formulations prepared without Freeze/Thaw method and prepared with Freeze/Thaw method.

IV. RESULT AND DISCUSSION

4.1 Identification of Drug and Polymer [26, 27]

4.1.1 Infra- Red Absorption Spectrum of Drug

The observed IR peaks of Ibuprofen matched with the reported peaks,

The I.R. spectra of physical mixture of ibuprofen with physical mixture and hydrogel powder showed peaks at same regions according to their functional groups, as compared with pure drug thereby proving the absence of incompatibility between the drug and the polymer.

The presence of peaks at 2953.02 cm-1, 1710.86 cm-1, 1064.71cm-1 and 933.55 cm-1 confirmed the CH_3 Stretching C=O stretch, =C-H stretch , and CH_3 rocking for the drug Ibuprofen. The mixture of Ibuprofen prepared with Freeze/Thaw method and Without Freeze/Thaw method confirmed that there was no chemical interaction between the drug and the mucilage powder by exhibiting peaks at same or slightly shifted wave number.

4.1.2 Differential scanning Calorimetry

The DSC curve of ibuprofen has shown a sharp endothermic peak(T_{Peak} = 88.75°C; T_{Onset} = 77.24°C; Intensity = -71.07)corresponding to the melting point, followed by otherendothermic peak due to decomposition (T_{Peak} = 324.272°C; T_{Onset} = 294.66°C; Intensity = -136.104).

4.2 Development of Spectroscopic Method

4.2.1 UV-spectrum of Ibuprofen

The ultraviolet spectrum of Ibuprofen in 7.4 pH phosphate buffer was measured between 200-400 nm and showed absorbance maxima at wavelength at 221.5 nm.

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4.2.2 Preparation of Standard Calibration Curve for Ibuprofen in 7.4 Phosphate Buffer

Following is the data for Calibration Curve ofIbuprofen in 7.4 pH phosphate buffer. The maximum absorbance was found to be at 221.5 nm.

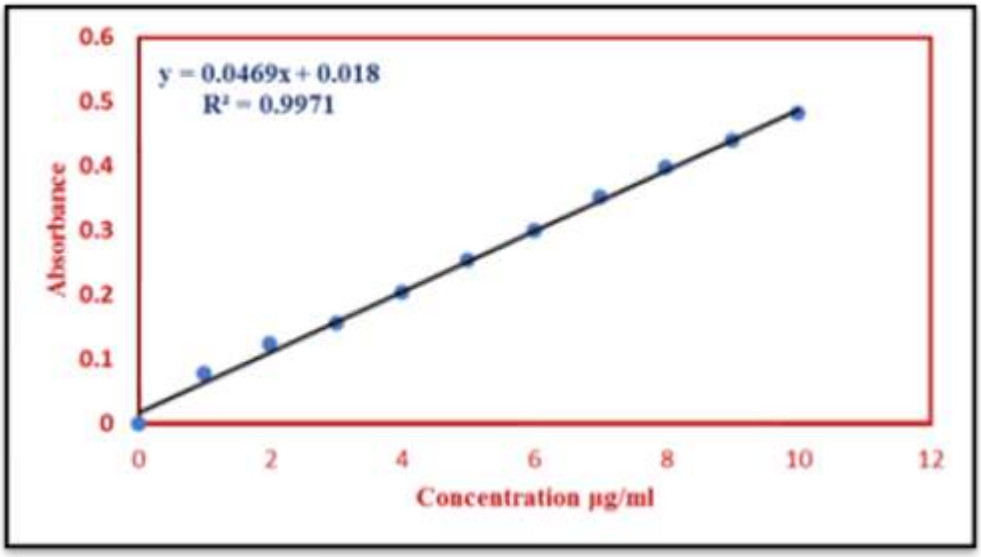

Figure No. 1. Calibration Curve of Ibuprofen in a 7.4 pH Phosphate Buffer.

Calibration Curve ofIbuprofen in 7.4 phosphate buffer. The maximum absorbance was found to be at 221.5 nm. The y = 0.0469 x+0.018 and R^2 = 0.9971.

The ultraviolet spectrum of Ibuprofen in 7.4 pH phosphate buffer was measured between 200-400 nm and showed absorbance maxima at wavelength at 221.5 nm.

4.2.3 Preparation of Standard Calibration Curve for Ibuprofen in methanol

Following is the data for Calibration Curve ofIbuprofen in Methanol. The maximum absorbance was found to be at 221 nm.

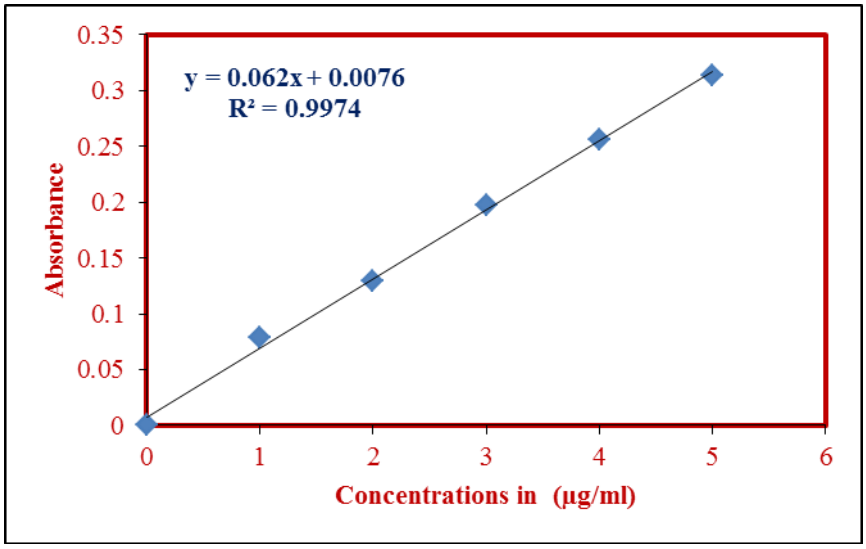

Figure No. 2.Calibration Curve of Ibuprofen in Methanol

Calibration Curve ofIbuprofen in Methanol was performed. Maximum absorbance was found to be at 224 nm. The y = 0.062x + 0.0076 and R^2 = 0.9974.

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The ultraviolet spectrum of Ibuprofen in methanol was measured between 200-400 nm and showed absorbance maxima at wavelength at 221 nm.

4.3 Solubility study:

Solubility Study in 7.4 pH phosphate buffer and β-Cyclodextrin

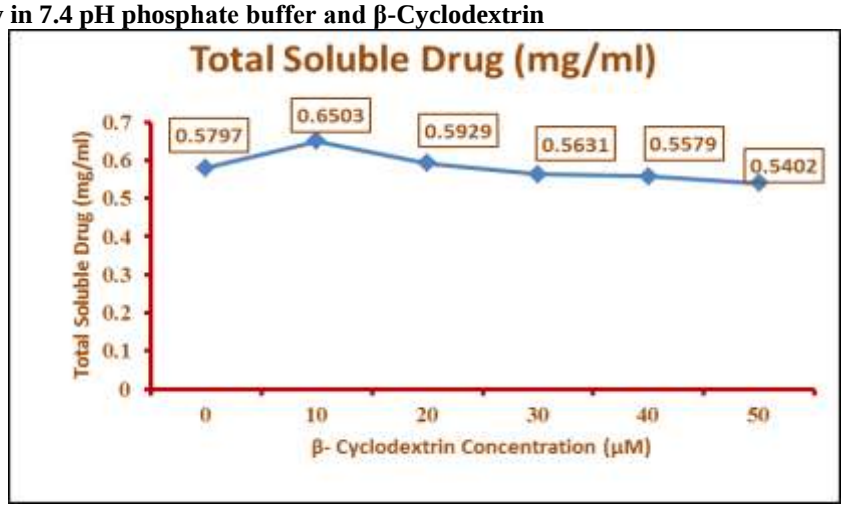

Figure No.3.Solubility Study in 7.4 pH phosphate buffer and β- Cyclodextrin.

The solubilityof Ibuprofen in 0µM, 10µM, 20µM, 30µM, 40µM, 50µM β-Cyclodextrin solution were found to be 0.579mg/ml, 0.650mg/ml, 0.592mg/ml, 0.563mg/ml,0.557mg/ml and 0.540mg/ml respectively.

4.4 Preparation of Physical Mixture without Freeze/Thaw method and Hydrogel by Freeze/Thaw Method.

4.5 Pre-compression Properties

Formulation code	Angle of Repose (0)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Precent Drug Content (mg/ml)
F10	24±0.22	0.26±0.26	0.30±0.19	17.35±0.13	1.2±0.15	6.67±0.13
F20	22.29±0.19	0.24±0.14	0.28±0.15	14±0.11	1.16±0.14	6.65±0.15
F30	20.80±0.18	0.22±0.15	0.28±0.23	21.4±0.125	1.27±0.12	6.22±0.12
F40	20.80±0.14	0.23±0.23	0.27±0.15	14.81±0.26	1.17±0.23	6.23±0.23
F11	25±0.14	0.30±0.12	0.39±0.16	18.91±0.22	1.23±0.24	7.73±0.21
F21	17±0.24	0.32±0.21	0.396±0.18	15.70±0.13	1.18±0.12	7.72±0.18
F31	21.80±0.27	0.24±0.18	0.30±0.15	22±0.23	1.29±0.16	6.66±0.15
F41	20.48±0.17	0.24±0.15	0.30±0.21	22±0.11	1.29±0.21	6.65±0.14

Table No. 3. Pre Compression Properties of Physical Mixture and Hydrogel.

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4.6 Preparation of Tablet

4.6.1 Preparation with physical mixture (formula for one tablet)

Matrix tablets of 265 mg of Ibuprofen were prepared by using HPMC E15 LV, PVA, and β-Cyclodextrin as matrix forming material, microcrystalline cellulose as lubricant (25 mg per tablet) and lactose as diluents.

4.6.2 Preparation of Hydrogel Tablet (formula for one tablet)

Hydrogel powder, HPMC, Microcrystalline cellulose & lactose were mixed and prepared 265mg hydrogel tablets.

4.7 Evaluation of Post- Compression Properties

Formulation code	Weight Variation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Content Uniformity (%)	Mean Swelling (%)
F10	265.66±0.17	3.2±0.11	0.67±0.17	4.46±0.13	99.51±0.14	78.54±0.15
F20	264.33±0.15	3.2±0.13	0.83±0.18	4.76±0.11	98.55±0.12	79.56±0.13
F30	264.33±0.13	2.9±0.11	0.76±0.14	3.83±0.12	100.47±0.11	65.74±0.15
F40	263.00±0.12	3.5±0.12	0.62±0.12	4.30±0.15	98.58±0.17	84.95±0.11
F11	265±0.21	3.5±0.13	0.82±0.11	4.33±0.13	98.10±0.16	70.57±0.13
F21	263±0.23	3.2±0.17	0.52±0.13	3.19±0.11	99.05±0.14	85.56±0.11
F31	266.00±0.17	2.7±0.14	0.65±0.17	4.90±0.12	100.49±0.11	78.12±0.12
F41	265.66±0.16	3.5±0.15	0.66±0.14	4.17±0.11	97.15±0.12	90.56±0.14

Table No.3.Evaluation of Post- Compression Properties of Physical Mixture and Hydrogel Tablet.

4.7.7 In Vitro Dissolution Study:

In vitro dissolution study shows that all tablets completely dissolved in maximum 6 hours except for formulation F41 which release drug up to 8 hours.

Time (h)	% Drug Release							
	Formulation							
	F10	F20	F30	F40	F11	F21	F31	F41
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	2.12±0.15	11.29±0.15	2.63±0.12	1.99±0.15	7.09±0.11	7.73±0.11	4.79±0.12	6.45±0.17
0.5	9.01±0.12	23.59±0.12	7.23±0.16	6.59±0.11	10.44±0.18	16.18±0.11	12.34±0.13	10.31±0.18
1	27.42±0.11	41.44±0.14	20.78±0.11	21.79±0.17	19.80±0.19	38.45±0.18	25.66±0.13	12.79±0.14
2	39.17±0.13	53.27±0.13	28.93±0.14	29.94±0.14	21.57±0.17	39.30±0.14	31.54±0.14	21.14±0.15
3	42.19±0.19	55.98±0.11	41.45±0.12	31.51±0.11	29.72±0.15	47.16±0.16	38.22±0.11	21.90±0.11
4	57.97±0.12	67.12±0.17	79.28±0.15	51.95±0.15	33.07±0.16	52.90±0.14	64.17±0.18	25.20±0.16
5	90.92±0.11	95.28±0.16	89.78±0.17	86.01±0.13	72.12±0.11	94.10±0.15	91.80±0.18	68.93±0.16
6	93.71±0.13	97.71±0.14	91.30±0.11	95.41±0.11	79.28±0.18	95.51±0.11	95.36±0.11	80.27±0.1

Table No. 4 In Vitro Drug Release from Physical Mixture Tablet

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4.7.8 Study of Release mechanism by curve fitting analysis [28]

In order to understand the mechanism of drug release from the factorial batches, the in vitro release data was fitted to zero-order models, the Higuchi model, and the Korsmeyer-Peppas release model. The value of the release exponent (n) aids in understanding the mechanism of dosage form release. If the value of n is between 0.5 and 1, it indicates non-Fickian diffusion. If the value of n is 0.5, it indicates Fickian diffusion. If the value of n is 1, it indicates the zero-order release. If the value of n is greater than 1, it indicates Super Case II transport.

The values of n were between 0.5 and 1 for formulation F41, indicating that the drug release was found to be non-Fickian diffusion. Thus, results revealed that the release of Ibuprofen from sustained release tablets was dominated by diffusion. The in vitro release data was analysed using various kinetic models like zero-order, first-order, Higuchi matrix, and Korsmeyer-Peppas in order to find out the mechanism of drug release. These values were compared with each other for the model and drug equation as represented in Table No. 5.

The Korsmeyer-Peppas model fits the data to the following general equation:

$Mt/M = kt^n$

Where Mt/M is the fraction of the drug release at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms and is calculated from the slop of the plot of fraction of drug released versus log of time.

Formulation Code	Zero order		First order		Matrix(Higuchi)		Korsmeyer-Peppas			Hixon-crowell	
	R^2	K_0 (h^{-1})	R^2	K_0 (h^{-1})	R^2	K_0 (h^{-1})	R^2	K_0 (h^{-1})	N	R^2	K_0 (h^{-1})
F10	0.9576	15.4809	0.9787	-0.2138	0.9560	25.9790	0.9547	15.6676	1.1132	0.9741	-0.0636
F20	0.8503	19.7638	0.9423	-0.3014	0.9836	34.4510	0.9667	32.3104	0.6053	0.9175	-0.0865
F30	0.9719	17.3000	0.8993	-0.2924	0.8816	27.7667	0.9858	14.8773	1.1324	0.9290	-0.0801
F40	0.9648	12.7953	0.9669	-0.1671	0.9370	21.2379	0.9644	12.7191	1.0921	0.9684	-0.0507
F11	0.8833	9.6136	0.9218	-0.1137	0.9897	16.6398	0.9838	16.0321	0.5515	0.9101	-0.0358
F21	0.8378	15.8417	0.9015	-0.2151	0.9659	27.6138	0.9482	24.7070	0.6640	0.8824	-0.0645
F31	0.9657	15.4228	0.9561	-0.2205	0.9433	25.6712	0.9742	19.0013	0.8340	0.9642	-0.0647
F41	0.8355	7.5351	0.8723	-0.0854	0.9905	13.1701	0.9897	13.4151	0.4865	0.8608	-0.0273

Table No. 5. Kinetic assessment of drug release from all formulations

In the case of tablets prepared without the freeze/thaw method, F10 follows first-order kinetics. Formulation F20 follows Higuchi-Matrix modelling. Formulation F30 followed the Korsmeyer-Peppas model, indicating the mechanism of drug release to be diffusion-controlled. The formulations in the F40 Hixon-Crowell model were followed. The n values for the formulation F10, F20, F30, and F40 were found to be 1.1132, 0.6053, 1.1324, and 1.0921, respectively. The n value is greater than 0.5 and less than 1; the release can be concluded as an anomalous transport pattern.

The formulation F31 follows Korsmeyer-Peppa's model. Whereas for formulations F11, F21, and F41, the Higuchi-Matrix model was followed, indicating the mechanism of drug release to be diffusion controlled. The Peppas model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved. The n values for the formulations F11, F21, and F31 were found to be 0.5515, 0.6640, and 0.8340, respectively. The n value is greater than 0.5 and less than 1; the release can be concluded as an anomalous transport pattern.

The n value for the formulation F41 was found to be 0.4865. The n value is less than 0.5; the release can be concluded as Fickian diffusion.

4.7.9 Statistical Analysis

Statistical analysis was performed by using a one-way ANOVA and a student t-test. One way ANOVA for both groups i.e. formulations prepared without Freeze/Thaw method and formulations

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prepared with Freeze/Thaw method was applied to check effect of polymer concentration. P-values for one-way ANOVA were (without freeze/thaw = 0.8756 and with freeze/thaw = 0.6596) higher than 0.05, which means there is no significant difference between the means. Further, to check the effect of freeze/thaw and the concentration of individual polymers on the release kinetics, a student's t-test was applied to the data. By comparing the p-values in groups F10 VS F20 (0.4301) and F30 VS F40 (0.2666) having constant β-Cyclodextrin concentration within groups but increasing in second group (F30 VS F40) with respect to first group (F10 VS F20). The p-value decreases as the concentration of beta-Cyclodextrin is increased. By comparing the p-values in groups F11 VS F21 (0.102) and F31 VS F41 (0.102) having constant β-Cyclodextrin concentration within groups but increasing in second group (F31 VS F41) with respect to first group (F11 VS F21). The p- value is unchanged for change in concentration of β-Cyclodextrin. By comparing the p-values in groups F10 VS F30 (0.1886) and F20 VS F40 (0.3197), HPMC concentration is constant within groups and increasing in the second group (F20 VS F40) with respect to the first group (F10 VS F30). The p-value increases as the concentration of HPMC is increased. By comparing the p-values in groups F11 vs. F31 (0.172) and F21 vs. F41 (0.175), HPMC concentration is constant within groups but increasing in the second group (F21 vs. F41) with respect to the first group (F11 vs. F31). The p-value is changed slightly for the change in concentration of HPMC.

4.7.10 Mathematical Modelling

Polynomial equations were constructed and the effect of factors on drug release kinetics was accessed as follows:

For formulations without freeze/thaw (physical mixture tablets):

$Y = \beta0 + \beta1\ X1 + \beta2\ X2 + \beta12X12$

$Y= 93.44 + 1.91\ X1 - 3.05\ X2 + 2.12\ X1X2$

For Formulations with Freeze/Thaw (Hydrogel tablets):

$Y = \beta0 + \beta1\ X1 + \beta2\ X2 + \beta12X12$

$Y= 83.24 – 4.2675\ X1 + 5.4575\ X2 + 5.445\ X1X2$

Maximum drug release was obtained for formulations prepared without the freeze/thaw method (physical mixture tablets), followed by formulations prepared with the freeze/thaw method (hydrogel). Higher levels of HPMC E15 LV exerted prominent effect on drug release kinetics in case of formulations prepared without Freeze/Thaw Method while, β Cyclodextrin failed to contribute in drug release kinetics in case of formulations prepared without Freeze/Thaw method. Also, Combination of β Cyclodextrin and HPMC did not contribute in improvement of release kinetics in case of formulations without Freeze/Thaw method.

Higher levels of β Cyclodextrin exerted prominent effect; while, HPMC failed to contribute at higher levels on drug release kinetics in case of formulations prepared with Freeze/Thaw method. Combination of HPMC and β Cyclodextrin showed prominent effect in improvement of drug release kinetics in case of formulations prepared with Freeze/Thaw method. The magnitude of coefficients showing a combined effect is higher in formulations with the freeze/thaw method. Thus, the effectiveness of the freeze/thaw method with the stated polymer combinations can be proved.

CONCLUSION

From the present study, the following conclusions can be drawn.

The study's goal was to develop and test hydrogel-based drug delivery systems containing Ibuprofen in various polymer concentrations. Preformulation studies like the melting point and solubility of the pure drug Ibuprofen and all polymers complied with the official IP standard, indicating the purity of the drug and polymer samples. All analytical parameters such as solubility and calibration curve were found to be significant and within acceptable limits. The results of Differential Scanning Calorimetry (DSC) and Fourier Transmission Infrared Spectroscopy confirm that both drugs and excipients are compatible with each other and are devoid of interactions. Formulations showed significant and acceptable limits for various evaluation parameters, i.e., weight variation, hardness, friability, thickness, and content uniformity that complied with official IP standards. In-vitro drug release was performed in 7.4 phosphate buffer as a dilution medium, and the result revealed that drug release was followed in a sustained manner for 8 hours in formulation F41 Prepared with the freeze/thaw method The overall curve fitting into various mathematical models was found to be average. The developed F41 hydrogel tablets followed the Higuchi-Matrix model, indicating that the mechanism of drug release was diffusion-controlled. Based on the "n" value obtained in the Peppas-Korsmeyer equation, it can be concluded that formulation F41 obeys Fick's law, but other formulations exhibit anomalous release behaviour. Thus, because formulation F41 exhibits

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sustained release behaviour for up to 8 hours and a fickian diffusion mechanism for drug release, it is concluded that the formulation is the best of all. In this research work, the drug-polymer ratio was optimized for hydrogel and physical mixture tablets. This drug and polymer combination was not reported earlier. Also, the effectiveness of the freeze/thaw method with the stated polymer combinations is proven.

Thus, based on the above discussion, the effectiveness of the freeze/thaw method can be proved.

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