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Formulation and Evaluation of Sustained Release Matrix Tablet of Ibuprofen by Using Pomegranate Peel and Acacia as Natural Polymers

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ABSTRACT

The main objective of the study is the formulation and evaluation of sustained release matrix tablet of ibuprofen by using pomegranate peel and acacia as natural polymer. The preformulation study of ibuprofen was conducted and λmax was found at 263 nm. The sustained release matrix tablet was prepared using Pomegranate peel as Release rate retardant, Acacia as polymer, Poly vinyl pyrrolidone K30 as Binder, Isopropyl alcohol as Granulation solution, Micro Crystalline Cellulose as Diluent, Magnesium stearate as Lubricant and Talc as Glidant. Several formulations were prepared by taking different drug concentration in Pomegranate peel (Release rate retardant) with varying ratio of binder to lubricants. Various formulations of sustained release matrix tablet of ibuprofen F1, F2, F3, F4, F5, F6 was prepared. The prepared granules were evaluated for different parameters like Bulk density, Tapped density, Angle of repose, Carr's index, Hausner's ratio which shows the excellent flow properties of formulation. The physical characteristic of Ibuprofen sustained release matrix tablets (F1 to F6) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F6) found to be within the limits specified in official books. The drug content of all the formulation were found to be in the range of 90 to 96 % w/w. The drug released from formulation F1 to F3 was found to be 93.7, 92.9 and 93.9 % for Ibuprofen respectively. The drug released from formulation F4 to F6 was found to be 90.8, 93.9 and 95.8% for Ibuprofen respectively. These results are indicating that has higher drug retarding ability for long duration. All the formulations were analyzed for stability testing. All the formulations from F1 to F6 were found to be stable.

Keywords: Sustained release matrix tablet, Ibuprofen, Pomegranate peel, Acacia, drug content, drug released.

1. INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory, analgesic and antipyretic agent. It is a prodrug of Diclofenac, in the inflammatory cells it gets converted into diclofenac and 4-hydroxy diclofenac. Ibuprofen has the more COX-2 specificity than diclofenac, as it is active only in inflammatory cells it has less GI stress than diclofenac. It has short biological half-life (4 hours), and the usual oral dosage regimen is 100 mg taken 2 times aday.
The basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. Sustained release drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases.

Non–Steroidal Anti-Inflammatory Drugs (NSAIDs) are considered to be the first line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Ibuprofen is one of the emerging NSAIDs molecules for arthritis treatment
Among the many techniques used for modulating the drug release profile, the most commonly used method is embedment of the drug into a polymer matrix.
The matrix may be formed by either dissolving or dispersing the drug uniformly in the polymer mass.
Hence, in the present work, an attempt is made to develop sustained-release matrix tablets of Ibuprofen, with the use of Pomegranate peel and Acacia as natural polymers for their sustaining effect. Wet granulation technique is used for tablet formulation along with the addition of suitable additives by using of hydrophilic polymers of HPMC K15M, Carboxy methyl cellulose and Xanthan gum.

MATERIALS AND METHOD

1. MATERIALS

Ibuprofen was received as a gift sample from Gift sample from Cypco Company ,Rau, Indore (M.P). Punica Granatum was purchased from local market. Microcrystalline cellulose(MCC), Magnesium stearate and talc from SD- Fine Chemicals. Polyvinylpyrrolidone K30, Isopropyl alcohol from HiMedia Laboratories. All other solvent and reagent are used was of analytical grade.

2. EXPERIEMENTALS

2.1 Identification of Drug

2.1.1 By UV Spectroscopy

Identification of the drug, Ibuprofen was done by UV Spectrophotometric method using Shimadzu Spectrophotometer UV-1800 (Shimadzu Corp. Japan). 50 mg of Ibuprofen was accurately weighed and transferred to a 50 ml volumetric flask. It was dissolved in sufficient amount of Methanol and volume was made upto 50 ml with Methanol. Exactly 10ml of the stock solution was pipetted out and was diluted to 100 ml with Methanol (10 µg/ml). The spectrum was recorded in the range of 220-370 nm. The λ max of Ibuprofen was obtained at 263nm. The UV spectrum of Ibuprofen drug is shown in the fig. 1.

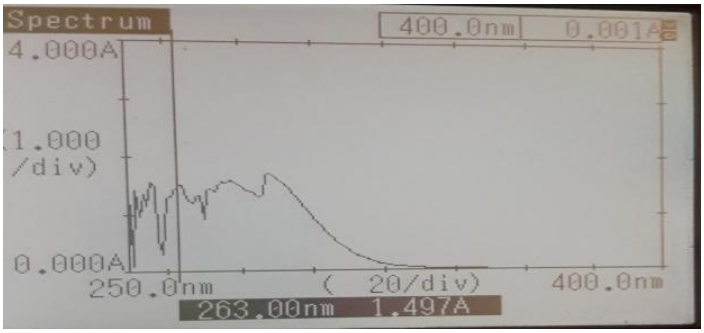

Figure 1: Spectrum of Ibuprofen by UV Spectroscopy

2.1.2 By melting point determination

The melting point of drug sample was determined by using melting point apparatus. The melting point was found to be in the range of 76-77^{0}C. The melting point of Ibuprofen is shown in the table: 2.

Table 2: Melting Point of Ibuprofen

Drug	Observed	Reference
Ibprofen	76-77^{0}C	75^0-78^{0}C

2.3 Preparation of standard Calibration curve of Ibuprofen in Phosphate buffer pH 7.4 (λmax 263 nm)

Calibration curve of Ibuprofen was prepared in phosphate buffer pH7.4 at 263 nm. The absorbance values (mean of three determinations) with their standard deviation at different concentration in the range of 5-30 µg/ml for phosphate buffer pH7.4 are tabulated. The drug obeys Beer'sLambert law in the concentration range. Linear regression analysis for all calibration curves of Ibuprofen is given in Table. So, this equation was used for the calculation of the solubility of the drug in different solvent, drug content and drug release. The calibration curve of Ibuprofen is shown in fig.4.

Table 3: Data of standard calibration curve of Ibuprofen in phosphate buffer 7.4

S.No.	Concentration (µg/ml)	Absorbance (nm)
1.	0	0
2.	5	0.125
3.	10	0.22
4.	15	0.317
5.	20	0.419
6.	25	0.533
7.	30	0.635

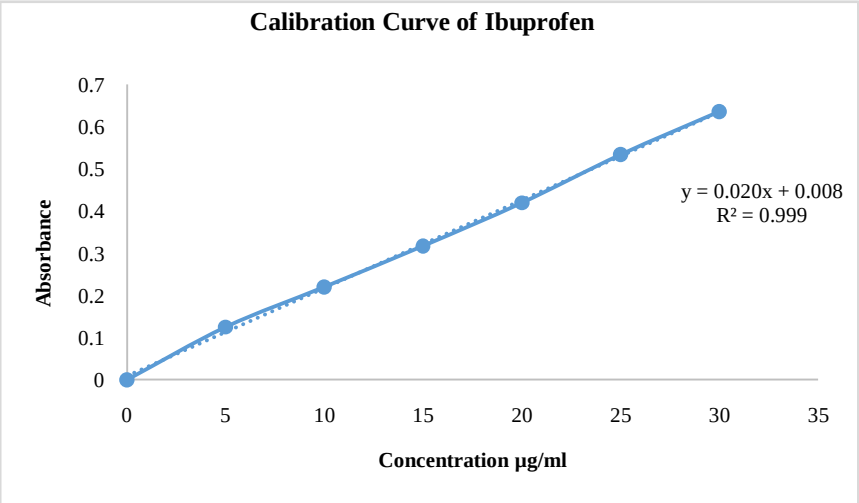

Figure 4: Calibration curve of ibuprofen in Phosphate buffer 7.4.

2.4 Solubility studies of drug

Quantitative solubility analysis of Ibuprofen was determined in different solvents. The Ibuprofen drug was found to be more soluble in ethanol, phosphate buffer and IPA.This shows that drug is soluble only in organic solvents, which shows the lipophilic nature of the drug. The results are found to be similar as given in the reference[64].The results are disclosed in table 5.

Table 5 : Quantitative solubility analysis:

S.no	Solvents	Solubility mg/ml
1.	Water	0.020
2.	Ethanol	0.130
3.	Phosphate buffer 7.4	0.120
4.	Hcl	0.109
5.	IPA	0.150
6.	Chloroform	0.098

2.5 FTIR spectroscopy:

The IR Spectra of sample of Ibuprofen is shown in the fig. 6, 7 and 8. The characteristic peak attribute to various functional groups present in the molecule of drug was assigned to establish the identity of drug sample of ibuprofen. The IR spectrum of drug sample is shown in the fig. 6, 7 and 8.

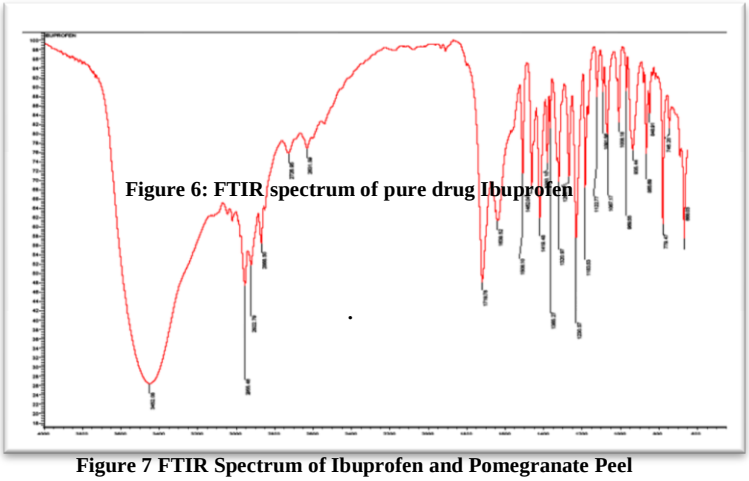

Figure 6: FTIR spectrum of pure drug Ibuprofen

Figure 7 FTIR Spectrum of Ibuprofen and Pomegranate Peel

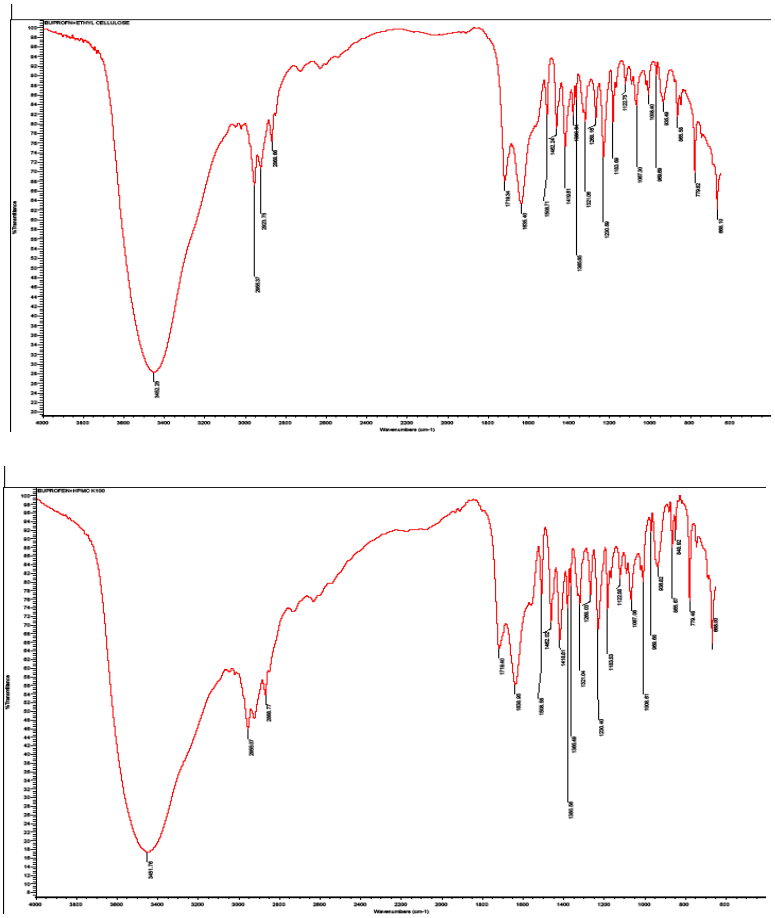

Figure 8 FTIR Spectrum of Ibuprofen and Acacia

Table no. 9 IR peaks of functional groups (cm^{-1})

Sr. No	Name of the ingredient	-C = O	-COOH	-NH	-OH
1.	Ibuprofen	3452.08	2955.4	1183.53	668.03
2.	Ibuprofen and Pomegranate peel	3461.76	1230.5	779.48	668.60
3.	Ibuprofen andAcacia	3452.25	2956.37	1230.50	663.10

3.FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF IBUPROFEN

3.1 Formulation of sustained release matrix tablet of ibuprofen by wet granulation method:

Formulation of sustained release matrix tablet of ibuprofen includes the selection of release rate retardant, polymer, and binder, granulation solution, diluent, lubricant and glidant. The sustained release matrix tablet was prepared usingPomegranate peel as Release rate retardant, Acacia as polymer, Polyvinylpyrrolidone K30as Binder, Isopropyl alcohol as Granulation solution, Micro Crystalline Cellulose as Diluent, Magnesium stearate as Lubricantand Talcas Glidant**.** Several formulations was prepared by taking different drug concentration inPomegranate peel (Release rate retardant) with varying ratio of binder to lubricants[65]. The formula is shown in the table 10. The formulation of sustained release matrix tablet includes as follow:

Preparation of sustained release matrix tablet

Six different formulations of Ibuprofen matrix tablets with natural polymers pomegranate peel and acacia powders according to table (6.1.1) were prepared by wet granulation methods. Ibuprofen, natural polymers, diluents, binders, lubricant and glidants were weighed and passed through sieve no.30-mesh.Then ibuprofen, polymers, diluents and binders were mixed, then a sufficient volume of granulating agent (isopropyl alcohol) was added slowly to form enough cohesiveness mass in stainless steel container by rotating the wet mass by stainless stile rod. The wet mass formed was sieved through sieve no. 16-messh to obtain wet granules. The formed wet granules were dried at 40c for 30 minutes, There after, the dried granules were passed through sieve no. 16-mesh to resize the granules. Then Talc and magnesium stearate as glidants and lubricant for each formulation were added and mixed thoroughly.

Table 10: composition of Ibuprofen matrix tablets

Ingredients (Mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Ibuprofen	100	100	100	100	100	100
Pomegranate Peel	30	50	70	_	_	_
Acacia	_	_	_	30	50	70
Microcrystalline cellulose	54	34	14	54	34	14
Polyvinyl pyrolidine K30	10	10	10	10	10	10
Isopropyl alcohol	4ml	4ml	4ml	4ml	4ml	4ml
Magnesium stearate	4	4	4	4	4	4
Talc	2	2	2	2	2	2
Total	200	200	200	200	200	200

3.2 Evaluation of of sustained release matrix tablet of ibuprofen:

3.2.1 Bulk Characterization of sustained release granules:

The bulk density of various formulations were found to be between 0.261 to 0.616, tapped density between 0.296 to 0.531, Hausner's ratio between 4.76 to 5.73 , Carr's index between 8.448 to 10.38, which shows the good compressibility index of formulations. The angle of repose was found to be between 28.7 to 37.43, which shows the excellent flow properties of formulation. Results of measurements such as Tapped density, Angle of repose, Carr's index, Hausner's ratio are presented in the table 11.

Table 11: Determination of flow properties of granules:

F. code	Angle of repose (^{o})*	Loose bulk density (g/ml)*	Tapped bulk density (g/ml)*	Carr's index (%)*	Hausner's ratio*
F1	30.16±0.04	0.261±0.19	0.296±0.19	9.717±0.22	5.44 ±0.19
F2	37.43±0.06	0.525±0.528	0.359±0.242	8.448±0.93	4.76 ±1.22
F3	32.2.±1.57	0.504±0.518	0.333±0.226	8.902±1.2	5.01 ±1.21
F4	28.7±0.72	0.568±0.509	0.449±0.305	10.38±0.82	5.73±1.31
F5	30.2±1.76	0.616±0.506	0.531±0.361	10.01±0.64	5.49±0.68
F6	29.3±1.67	0.549±0.538	0.389±0.264	9.455±0.87	5.24±1.34

3.2.2 Physico-Chemical Characterization of Ibuprofen SR matrix Tablets

Table 12 Physico-Chemical Characterization of Ibuprofen SR matrix Tablets

A. Code	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Weight variation (mg)	Drug content (%w/w)**
F1	4.44±0.02	6.32±0.05	0.679±0.01	398.25±.139	99.83±0.69
F2	4.37±0.06	6.65±0.01	0.503±0.04	397.25±2.39	99.59±1.05
F3	4.40±0.09	6.75±0.03	0.417±0.02	397.65±1.94	98.95±0.87
F4	4.38±0.07	6.46±0.01	0.568±0.06	395.05±1.75	99.72±0.87
F5	4.54±0.02	6.54±0.03	0.515±0.03	397.05±1.94	99.65±0.66
F6	4.27±0.06	6.74±0.02	0.667±0.03	396.75±2.04	99.61±0.65

3.2.3 Drug Content:

The drug content of all the formulation were found to be in the range of 90 to 96 % ws/w. Which is within the specified limit as per Indian Pharmacopoeia 1996 (i.e. 90-110% w/w).

Table no.13 Drug content of various formulations.

S.NO	Formulation Code	% Drug content
1.	F1	92%
2.	F2	90%
3.	F3	94%
4.	F4	94%
5.	F5	96%
6.	F6	92%

3.2.4 In-vitro dissolution studies:

The in-vitro dissolution studies were performed using USP type I dissolutionapparatus at 50rpm. Dissolution test was carried out for a total period of 8 hours using0.1N HCl (pH 1.2) solution (900 ml) as dissolution medium at 37 ± 0.5° for first 2 h,and pH 7.4 phosphate buffer solution (900 ml) for the rest of the period An aliquot(5ml) was withdrawn at specific time intervals and absorbance was determined by U.V. spectrophotometer at 263 nm.

Ibuprofen is a water insoluble drug; its release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the sustained release layer was a key factor in controlling the drug release. Various sustained release matrix formulations were formulated with pomegranate peel, acacia, and methyl cellulose, polyvinyl pyrrolidone as binder and magnesium stearate as aLubricant and talc as glidant.

The drug released from formulation F1 to F3 was found to be 93.7, 92.9 and 93.9 % for Ibuprofen respectively. The drug released from formulation F4 to F6 was found to be 90.8, 93.9 and 95.8% for Ibuprofen respectively.

Table no. 14 In- Vitro dissolution rate:

S.No	Time (h)	F1	F2	F3	F4	F5	F6
1	1	8.91	8.97	9.23	9.29	9.38	8.99
2	2	15.2	29.2	22.4	29.3	28.4	29.6
3	3	39.9	36.7	38.7	39.4	40.2	36.8
4	4	57.9	55.2	46.4	49.2	53.2	49.0
5	5	75.5	82.4	59.8	69.9	67.1	59.2
6	6	93	92	72.1	81.4	74.6	68.6
7	7	93.2	92.3	93.1	90.1	87.3	77.1
8	8	93.4	92.5	93.4	90.2	93	80.9
9	9	93.6	92.8	93.6	90.5	93.5	95
10	10	93.7	92.9	93.9	90.8	93.9	95.8

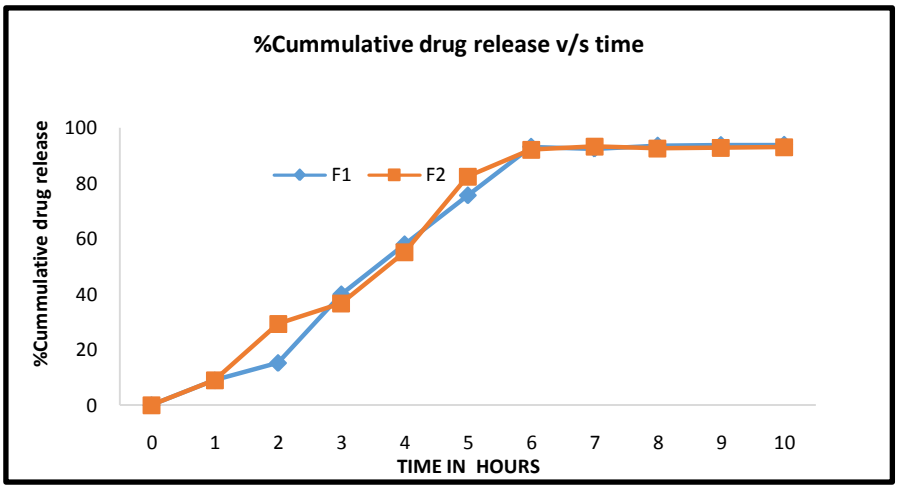

Fig. 15 % cumulative drug release of batch F1 & F2

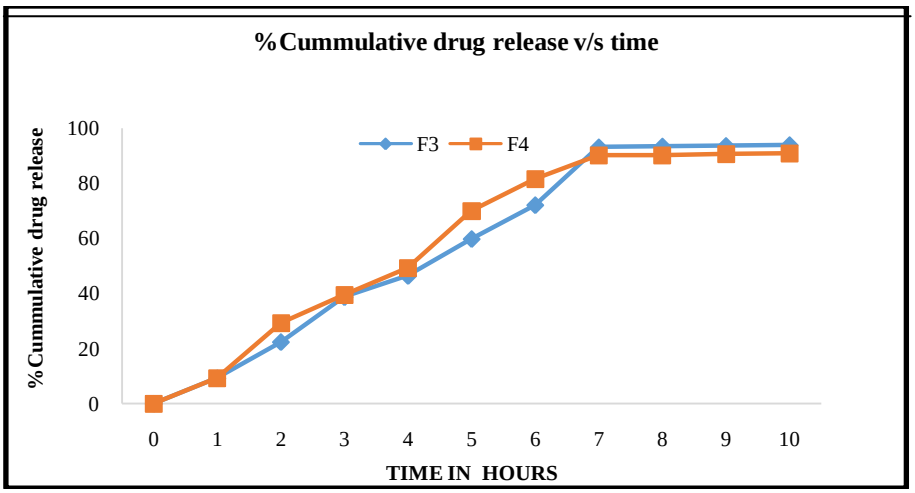

Fig. 16 % cumulative drug release of batch F3 & F4

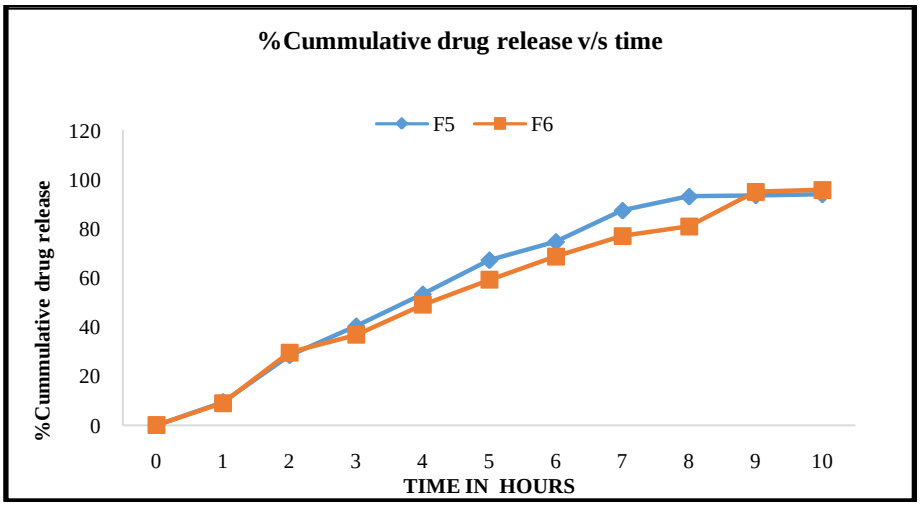

Fig. 17 % cumulative drug release of batch F5 & F6

A) **Stability Study:**

After storage the formulation was analyzed for various physical parameters, results are showed in Table 18.

Table 18: Stability study of best formulation F6

Characteristic	Initial	1st Month	2nd Moth	3rd Month
Hardness (kg/cm^2)*	6.85±0.03	6.82±0.26	6.80±0.28	6.77±0.29
Drug content (%)*	99.9±0.63	99.5±0.79	99.04±0.63	98.9±0.58
In vitro drug release at 10th hour*	96.2±0.65	95.9±0.56	95.8±0.59	95.2±0.57
Appearance	White	No change	No change	No change

3.CONCLUSION

Result of the present study demonstrated that natural polymers could be successfully employed for formulating sustained release matrix tablets of Ibuprofen. The investigated sustained release matrix tablet was capable of maintaining constant plasma concentration upto 10 hours. This can be expected to reduce the frequency of administration and decrease the dose dependent side effects. The efficacy and safety of Ibuprofen tablet dosage form are expected to offer optimum therapeutic efficacy and improved patient compliance.

In the present study the effect of types and concentration of polymer were studied on In-Vitro drug release. It shows that increase in concentration of polymer results in the sustained drug release for 10 hours. The study has revealed that by increasing concentration of polymer, release rate of drug was retarded and results confirmed that the release rate from hydrophilic matrix tablets depends on type and concentration of polymer.

In present studies, matrix formulation containing pomegranate peel and acacia is probably showing release up to 95.8 % within 10 hrs.

According to stability study, it was found that there was no significant change in hardness, drug content and dissolution rate of formulation F6 was 96% and 95.8 % within 10 hrs.

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