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Formulation and Evaluation of Sustained Release Matrix Tablet of Nimesulide Using Pomegranate Peel and Acacia

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ABSTRACT: The main objective of the study is the formulation and evaluation of sustained release matrix tablet of Nimesulide using pomegranate peel and acacia as natural polymer. The preformulation study of Nimesulide was conducted and λmax was found at 300 nm. The sustained release matrix tablet was prepared using Pomegranate peel as Release rate retardant, Acacia as polymer, Polyvinylpyrrolidone 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 Nimesulide 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 Nimesulide 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 99.59 to 99.83 % w/w, which is within the specified limit as per Indian Pharmacopoeia 1996 (i.e. 90-110% w/w). The drug released from formulation F1 to F3 was found to be 93.7, 92.9 and 92.2 % for Nimesulide respectively. The drug released from formulation F4 to F6 was found to be 94.1, 93.9 and 92.8% for Nimesulide respectively. The release rate of F1 and F4 was found to be higher when compared to other formulations this is due to increase in the concentration of polymer.

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, Nimesulide, Pomegranate peel, Acacia, drug content, drug released.

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1. INTRODUCTION

Nimesulide is a relatively COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Its approved indications are the treatment of acute pain, the symptomatic treatment of osteoarthritis and primary dysmenorrhea in adolescents and adults above 12 years old.

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. Nimesulide is one of the emerging NSAIDs molecules for arthritis treatment. To minimize the frequent dosing. To prolong the pharmacological effect and to improve patient compliance, a sustained release formulation of nimesulide is very much desirable. 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. Such polymer matrices can give

- Desirable release profiles
- Cost effective manufacturing method.
- Broad regulatory acceptance.

Hence, in the present work, an attempt is made to develop sustained-release matrix tablets of nimesulide, with the use of Pomegranate peel as natural polymers for their sustaining effect. Wet granulation technique will be used for tablet formulation along with the addition of suitable additives by using of hydrophilic polymers.

2. MATERIALS AND METHOD

2.1. MATERIALS

Nimesulide was received as a gift sample from Gift sample from Ajanta Pharmaceuticals, Pithampur, 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.

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2.2. EXPERIMENTALS

Identification of Drug

a. By UV Spectroscopy

Identification of the drug, nimesulide was done by UV Spectrophotometric method using Shimadzu Spectrophotometer UV-1800 (Shimadzu Corp. Japan). 50 mg of nimesulide 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 1 ml of the stock solution was pipetted out and was diluted to 10 ml with Methanol (10µg/ml). The spectrum was recorded in the range of 200-400 nm. Spectrum was recorded. The λ max of Nimesulide was obtained at 300 nm. The UV spectrum of Nimesulide drug is shown in the fig. 1.

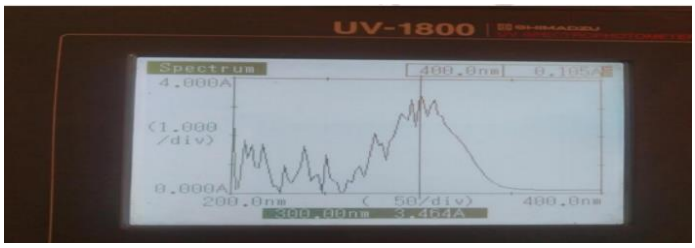

Figure 1: Spectrum of Nimesulide by UV Spectroscopy

b. 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 142-145 °C, which is found to be similar as given in the reference[61]. The melting point of nimesulide is shown in the table: 2.

Table 2: Melting Point of nimesulide

Drug	Observed	Reference
Nimesulide	142-145 °C	143-144.5 °C

2.3 Preparation of standard Calibration curve of nimesulide in methanol (λmax 300nm)

Calibration curve of nimesulide was prepared in methanol at 300nm. The absorbance values (mean of three determinations) with their standard deviation at different concentration in the range of 5-25 µg/ml for methanol are tabulated. The drug obeys Beer's Lambert law in the concentration range. Linear regression analysis for all calibration curves of nimesulide 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 nimesulide is shown in fig. 4.

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Table 3: Data of standard calibration curve of Nimesulide in Methanol

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

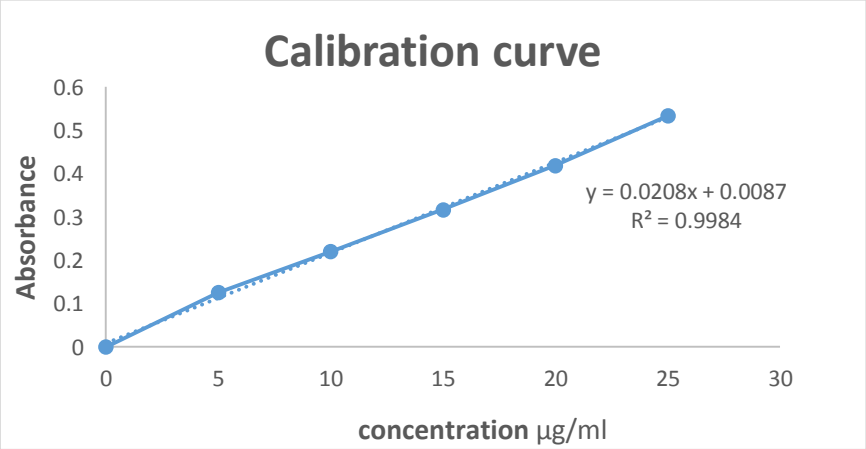

Fig 4: Calibration curve of nimesulide in methanol.

2.4 Solubility studies of drug

Quantitative solubility analysis of nimesulide was determined in different solvents. The nimesulide drug was found to be more soluble in ethanol, methanol 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.

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Table 5: Quantitative solubility analysis:

S.no	Solvents	Solubility mg/ml
1.	Water	0.01
2.	Ethanol	0.030
3.	Methanol	0.020
4.	Hcl	0.09
5.	IPA	0.150
6.	Chloroform	0.048

3. FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF NIMESULIDE:

3.1. Formulation of sustained release matrix tablet of nimesulide by wet granulation method

Formulation of sustained release matrix tablet of nimesulide includes the selection of release rate retardant, polymer, and binder, granulation solution, diluent, lubricant and glidant. The sustained release matrix tablet was prepared using Pomegranate peel as Release rate retardant, Acacia as polymer, Polyvinylpyrrolidone K30as Binder, Isopropyl alcohol as Granulation solution, Micro Crystalline Cellulose as Diluent, Magnesium stearate as Lubricant and Talcas Glidant**.** Several formulations were prepared by taking different drug concentration in Pomegranate peel (Release rate retardant) with varying ratio of binder to lubricants[65]. The formula is shown in the table 6.1.2.
The formulation of sustained release matrix tablet includes as follow:

Preparation of sustained release matrix tablet

Six different formulations of Nimesulide matrix tablets with natural polymers pomegranate peel and acacia powders according to table (6.1.1) were prepared by wet granulation methods. Nimesulide, natural polymers, diluents, binders, lubricant and glidants were weighed and passed through sieve no.30-mesh.Then nimesulide, 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.

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Table 6: composition of Nimesulide matrix tablets

Ingredients (Mg)	F1	F2	F3	F4	F5	F6
Nimesulide	100	100	100	100	100	100
Pomegranate Peel	70	60	50	-	-	-
Acacia	-	-	-	70	60	50
Microcrystalline cellulose	15	25	35	15	25	35
Polyvinyl pyrolidine K30	10	10	10	10	10	10
Isopropyl alcohol	4ml	4ml	4ml	4ml	4ml	4ml
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5	0.5	0.5
Total	200	200	200	200	200	200

3.2 Evaluation of of sustained release matrix tablet of nimesulide:

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 show 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 7.1.1.

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Table 7: Determination of flow properties of granules:

F. code	Angle of repose (^{0})*	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

*All the values are expressed as mean± SD, n=3.

3.2.2 Physico-Chemical Characterization of Nimesulide SR matrix Tablets

Table 8: Physico-Chemical Characterization of Nimesulide SR matrix Tablets

Fomulation 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	198.25±.139	99.61±0.65
F2	4.37±0.06	6.65±0.01	0.503±0.04	197.25±2.39	99.59±1.05
F3	4.40±0.09	6.75±0.03	0.417±0.02	197.65±1.94	98.95±0.87

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F4	4.38±0.07	6.46±0.01	0.568±0.06	195.05±1.75	99.72±0.87
F5	4.54±0.02	6.54±0.03	0.515±0.03	197.05±1.94	99.65±0.66
F6	4.27±0.06	6.74±0.02	0.667±0.03	196.75±2.04	99.83±0.69

3.2.3 Drug Content

The drug content of all the formulation were found to be in the range of 99.59to 99.82 % w/w. Which is within the specified limit as per Indian Pharmacopoeia 1996 (i.e. 90-110% w/w).

Table 9: Drug content of various formulations.

S.NO	Formulation Code	% Drug content
1.	F1	99.62±0.65
2.	F2	99.59±1.05
3.	F3	98.98±0.87
4.	F4	99.74±0.87
5.	F5	99.66±0.66
6.	F6	99.82±0.69

3.2.4 In-vitro dissolution studies:

Nimesulide 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 a Lubricant and talc as glidant.

The drug released from formulation F1 to F3 was found to be 93.7, 92.9 and 92.2% for Nimesulide respectively. The drug released from formulation F4 to F6 was found to be 94.1, 93.9 and 92.8% for Nimesulide respectively.

The release rate of F1 and F4 was found to be higher when compared to other formulations this is due to increase in the concentration of polymer.

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These results are indicating that has higher drug retarding ability for long duration.

Table 10: In- Vitro drug release rate:

S.No	Time (h)	F1	F2	F3	F4	F5	F6
1	1	8.91	8.97	10.22	9.29	9.38	8.99
2	2	15.2	29.2	25	26.6	28.4	29.6
3	3	39.9	36.7	39.6	40.4	40.2	36.8
4	4	57.9	55.2	45.2	49.5	53.2	49.0
5	5	75.5	82.4	69.5	66.9	67.1	59.2
6	6	93	92	25	26.6	74.6	68.6
7	7	93.2	92.3	39.6	40.4	87.3	77.1
8	8	93.4	92.5	45.2	49.5	93	80.9
9	9	93.6	92.8	85.3	82.4	93.5	95
10	10	93.7	92.9	92.2	94.1	93.9	92.8

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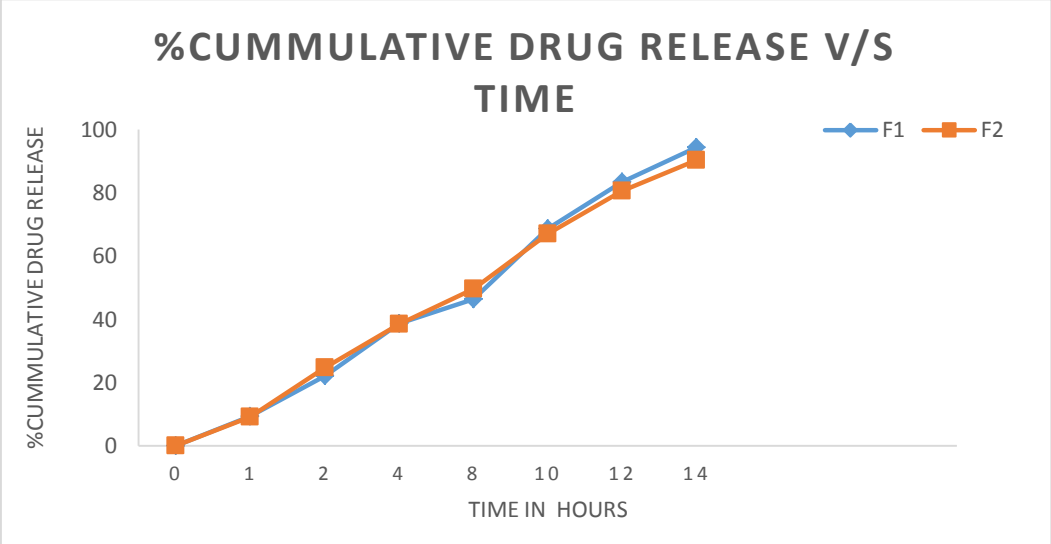

Fig. 11 % cumulative drug release of batch F1 & F2

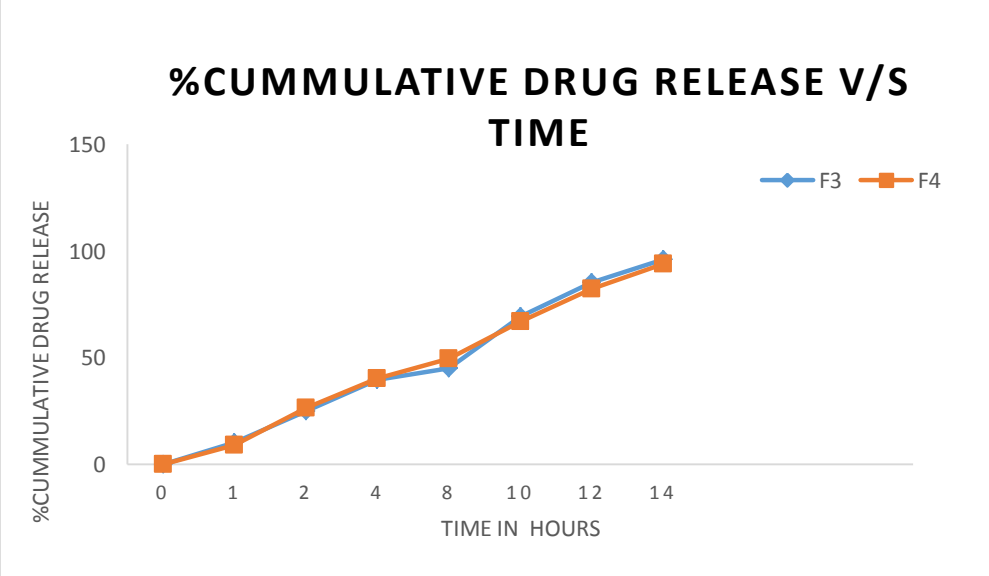

Fig. 12 % cumulative drug release of batch F3& F4

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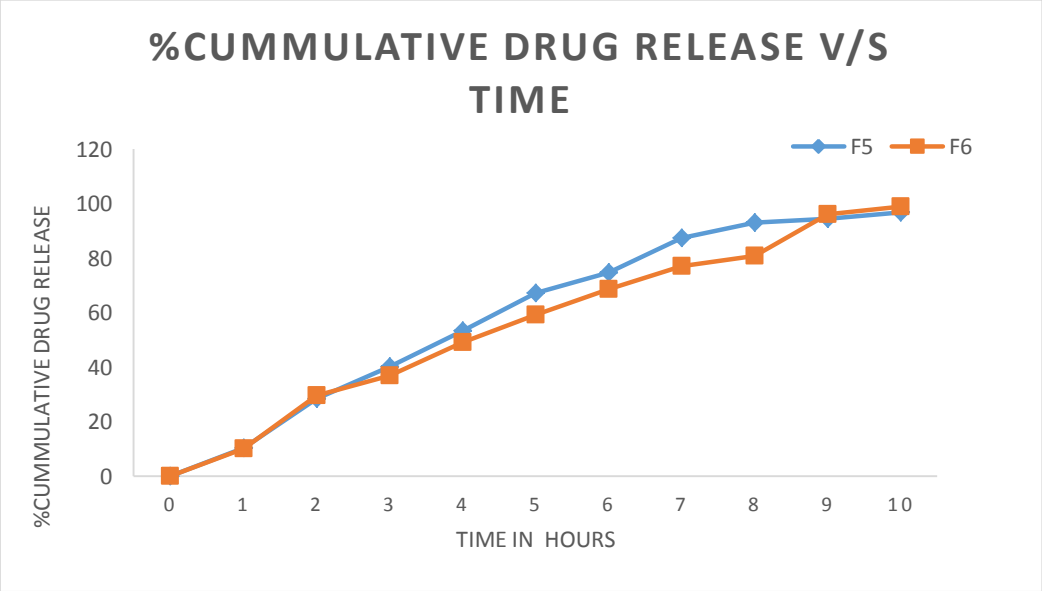

Fig. 13 % cumulative drug release of batch F5& F6

3.2.5 Stability Study:

After storage the formulation was analyzed for various physical parameters, results are showed in Table 7.2.7.

Table 14: 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 to off white	No change	No change	No change

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4. CONCLUSION

Result of the present study demonstrated that natural polymers could be successfully employed for formulating sustained release matrix tablets of Nimesulide. 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 Nimesulide 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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