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Design, Fabrication and Optimization of Fast Dissolving Solid Oral Formulations of Nabumetone using Solvent Free Technology by 3^2 Factorial Design

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Bhoyar Pravin Khushalrao*, Rajendra Singh Bapna, Revathi A. Gupta and Karunakar Shulka

Department of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore - 452010 (M.P.)

***Corresponding author**

Email: pravinbhoyar007@rediffmail.com

Keywords:

Nabumetone, Solid oral tablet, Kyron t 314, Musa paradisiaca L, FTIR, XRD, DSC, 3^2 Factorial Design.

Abstract

The objective of the present study was to formulate and evaluate fast dissolving solid oral formulations of Nabumetone using solvent free technology. Nabumetone, Nonsteroidal anti-inflammatory drug, with t1/2 approx. 19 hrs and absolute oral bioavailability about 80-85%, indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. In present study, solvent free technique is used in order to improve the dissolution and oral bioavailability of the model drug with poor solubility and high permeability. Solid oral formulations (F1 – F9) were prepared by direct compression technique using solvent free technology with Kyron t 314 and Musa paradisiaca L as a super disintegrants in different ratios and analyse the usefulness of DOE in the development and optimization of a tablet of a model drug employing 3^2 full factorial statistical design. The drug-polymer compatibility study was carried out to determine the interactions, if any between the drug and the polymers used in the study. The FTIR, XRD and DSC study revealed that, polymers and excipients used were compatible with drug. The prepared tablets were subjected to various evaluation such as hardness (2.80–3.30 kg/cm^2), friability (0.34–0.70%), disintegration time (26–38 s), drug content (95.00–99.05%), water absorption ratio (44–56%), wetting time (44–70 s) and in-vitro drug release shown in 5 min (96.40–99.80%). Optimized batch(F5) when subjected to stability at 40± 2^{0}C temperature with relative humidity 75±5% for six months, showed no degradation and change in tablet and showed rapid dissolution and effective in achieving patient compliance.

1. Introduction

The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self administration ,compact in nature, easy to manufacture and it can be deliver in accurate dose. One important drawback of solid dosage forms is the difficulty in swallowing (Dysphagia) or chewing in some patients particularly pediatric and geriatric patients. The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance[1]. Difficulties in swallowing of tablet and capsule are also occur when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection2. Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention[2].

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as “a solid

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dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue."

Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet. Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water. Most fast dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients[3,4]. It has been concluded that faster the dissolution, faster the absorption (only the unionized form of drug) and onset of action. Some drugs are absorbed from the oral cavity, pharynx and esophagus as the saliva passes down into the stomach. Thus the bioavailability of drug is significantly more than those observed from conventional tablets dosage form[5]. The time for disintegration of fast disintegrating tablets is generally considered to be less than one minute[6-9].

The fast dissolving solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of risk of choking.[10-11] In recent years, a variety of improved methods for delivering drugs have been developed with the aim of improving bioavailability, convenience and patient compliance. Some tablets are designed to dissolve in saliva within a few seconds, and so called true fast-dissolving tablets. Fast dissolving technology offers following advantages[11-16].

- Improved compliance/added convenience
- No water needed
- No chewing needed
- Better taste
- Improved stability
- Suitable for controlled as well as fast release actives
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.

The objective of the present study was to formulate and evaluate fast dissolving solid oral formulations of Nabumetone using solvent free technology. Nabumetone, anti-inflammatory drug, with t1/2 approx. 19 hrs and absolute oral bioavailability about 80-85%, indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. In present study, solvent free technique is used in order to improve the dissolution and oral bioavailability of the model drug with poor solubility and high permeability.

2. Materials and Methods

Materials:

Nabumetone was procured as a gift sample from **Watson Pharma,** Pvt. Ltd., Hyderabad; Kyron t314 (PolacrilinPotassium) was purchased from Aura Pharmaceuticals Pvt. Ltd., Mumbai; Musa paradisiaca L, purchased from Standard commercial supplies; Pearlitol SD200 purchased from Roquette India Private Limited, Mumbai. All chemicals used were of analytical reagent grade and double distilled water was used throughout the experiments.

Identification test for Nabumetone[18].

Identification of Nabumetone was performed by various parameters like colour, odour, solubility, Melting point range and FT Infraredspectrophotometer etc. In Ultra-violet Spectrum, electronic excitation occurs in the range from 200-800 nm and involves the promotion of electron to the higher energy molecular orbital.

Drug Excipient Compatibility Study using Fourier Transform Infrared Spectroscopy[19,20].

The samples were crushed with KBr to make pellets under hydraulic pressure of 10 tons, and then the FTIR spectra were recorded between 400 and 4000 cm^{-1}. It was used to study the interactions between the drug and polymer. IR spectral analysis of pure Nabumetone (physical mixture of Nabumetone with gelatin, glycine, Kyron t 314 and Musa paradisiaca L, optimized lyophilized Nabumetone tablet were carried out.

Preparation of fast dissolving oral solid tablets of Nabumetone by lyophilization method[21,22].

Fast dissolving oral solid tablets of

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Nabumetone were prepared by lyophilization method using Kyron t 314 and Musa paradisiaca L as superdisintegrants in different concentration, gelatin in certain concentration as a matrix former, a sugar alcohol (Pearlitol SD200) and a collapse protectant (glycine) as shown in Table1.

Table 1. Formulation of Nabumetone fast dissolving oral solidtablets

Sr. No.	Batch	NAB (mg)	Kyront 314 (mg)	Musa paradisiaca L. (mg)	Gelatin (mg)	Glycine (mg)	Pearlitol SD200 (mg)	Aspartame (mg)	Avicel pH 102 (mg)
1	F1	400	30	70	7	6	30	5	102
2	F2	400	30	30	14	6	30	5	135
3	F3	400	30	50	7	6	30	5	122
4	F4	400	50	30	7	6	30	5	122
5	F5	400	50	50	14	6	30	5	95
6	F6	400	70	30	14	6	30	5	95
7	F7	400	70	70	14	6	30	5	55
8	F8	400	70	50	7	6	30	5	82
9	F9	400	70	50	21	6	30	5	68

Total weight of Tablet = 650 mg

Optimization of formulation for Nabumetone fast dissolving oral solid tablets by Taguchi design[23]

In this study, an experimental design matrix was formed with 2 factors,3 level, and 9 runs to optimized the influence of variable by using Minitab Statistical Software Ink. In this matrix design independent variable such as (A) Concentration of Kyron t 314 and (B) Concentration of Musa paradisiaca L. were selected and their impact on formulation was predicted. All these dependent variables are summarized in Table 2. On the behalf of this design set goals, nine Fast dissolving tablet formulation were prepared and characterized for in-vitro drug release (R1), disintegration time (R2), water absorption ratio (R3), and wetting time (R4) which were taken as a dependent variable (response parameters).

Table 2. Variables and constraints in the experimental design

Variables	Constraints	
	Lower limit	Upper limit
	NAB	NAB
Independent variables		
A. Concentration of Kyron t 314	30	70
B. Concentration of Musa		70

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paradisiaca L.	30	
Dependent variables	**Goals**	
R1. = In-vitro drug release	Maximize	
R2. = Disintegration time	Minimize	
R3. = Water absorption ratio	Optimize	
R4. = Wetting Time	Minimize	

ETO = Nabumetone

Evaluation of Nabumetone fast dissolving oral solid tablets[24]

Prepared fast dissolving oral solid Nabumetone tablet batches (F1 - F9) were evaluated for thickness, shape, hardness, friability, weight variation, wetting time, water absorption ratio, In- vitro disintegration study, drug content and in vitro drug release study were carried out. Shape and thickness was measured using sliding Caliper scale. hardness was measured using Monsanto hardness tester . Tablets were tested for friability using Roche Friabilator.

Drug Content

Nabumetone Tablets were selected randomly, and the average weight was calculated. Tablets were crushed in a mortar and accurately weighed the amount of tablet powder was taken from the crushed blend. Then the samples were transferred to 100 ml volumetric flask and diluted with phosphate buffer pH 6.8. The contents were shaken periodically and kept for 2 h for solvation of drug completely. The mixture was filtered in Whatmann filter paper and absorbance was measured at 270 nm for Nabumetone using phosphate buffer pH 6.8.

In-Vitro Dissolution Study (In vitro drug release study)[25]

Dissolution was carried out using USP apparatus II taking 900 ml of Phosphate buffer pH 6.8. The rotational speed of the paddle was set at 50 rpm. One ml of aliquots was withdrawn at predetermined time interval several minutes and was being replaced by same volume of fresh medium. The sample were analyzed for drug content using double beam UV spectrophotometer at 270 nm for Nabumetone against blank using Phosphate buffer pH 6.8. The dissolution was carried out in triplicate for each formulated batch. The cumulative % drug release was calculated using the equation generated from the standard calibration curve. Cumulative % drug release Vs time graph was plotted.

X-Ray Diffraction (X-RD)[26]

For the structural, crystal and physical state characterization of Nabumetone, X-Ray diffraction studies were performed for pure drugs, Physical mixture of drug with excipients, and optimized lyophilized tablets. The study was carried out using X-ray powder diffraction system, Model No. XPERT-PRO Diffractometer System. By using copper target, a voltage of 45 Kv and a current of 40 mA. The scanning was done over 2θ range of 5º to 100º.

Differential Scanning Calorimeter (DSC)[27]

For the structural, crystal and physical state characterization of Nabumetone, DSC studies were performed for pure drugs, and optimized lyophilized tablets. The DSC study was carried out using Model No. METTLER DSC 30S. By using crucible Al 40µL, at of 10^0C/min heating rate, under nitrogen environment. The temperature range used was 25^0C – 300^0C.

Scanning Electron Microscopy (SEM)[28]

Optimized lyophilized Nabumetone tablet were coated with platinum and visualized under Analytical Scanning Electron

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Microscope (SEM), using Model No. JSM-6380A. The SEM Photomicrographs showing surface morphology.

Stability Studies[29, 30]

The optimized lyophilized Nabumetone tablet batches were selected and wrapped in aluminum foil of thickness 0.04 mm and stored at stored at 40±2^{0}C temperature with relative humidity of 75±5%. The sampling was done after every two months for total 6 months and evaluation was done for appearance, thickness, hardness, friability, drug content and cumulative % drug release.

3. Result and Discussion

Nabumetone (NSAIDs) fast dissolving solid oral formulations (tablet) has been made in order to improve bioavailability and patient compliance. Organoleptic property such as colour, taste, odour and melting point of procured ENabumetone sample was complies as per IP.

Solubility study of Nabumetone in different solvents like water, pH 6.8 Phosphate buffer and ethanol was carried out and found to be 0.450 mg/ml, 22.35 mg/ml, 21.50 mg/ml for Nabumetone as shown in Table 3.

Table 3. Solubility study of Nabumetone in differentsolvents

Sr. No	Solvents	Solubilit (mg/ml)
1.	Water	0.450
2.	pH 6.8 PhosphateBuffer	22.35
3.	Ethanol	21.50

Retention of basic characteristics peaks in FTIR of physical mixture of Nabumetone with excipients at 1620 cm^{-1}, 2900 cm^{-1}, 2860 cm^{-1}, 1650 cm^{-1}, 1725 cm^{-1} for C=C stretch, C-H stretch, Ether O-CH3 and C=O Stretch respectively suggesting no incompatibility between dug and polymersas shown in figure 1.

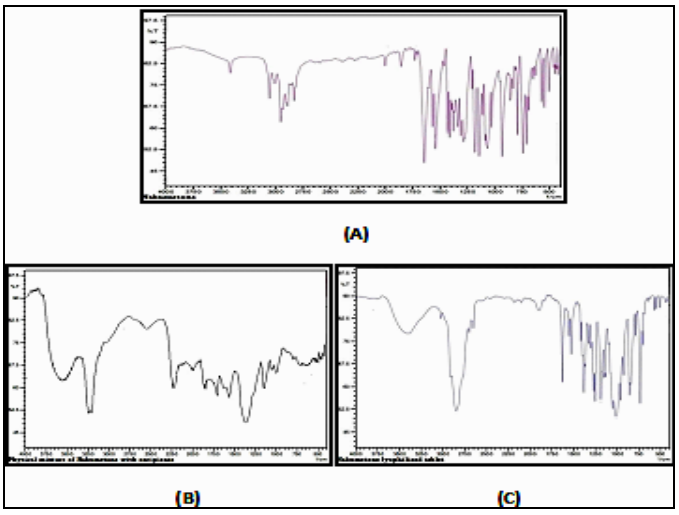

Figure 1: FTIR Spectra of (A) Nabumetone (B) Physical mixture of Nabumetone withexcipients (C) optimized lyophilized Nabumetone tablet

Fast dissolving oral solid tablets of Nabumetone were prepared by

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lyophilization method using Kyron t 314 and Musa paradisiaca L as superdisintegrants in different concentration, gelatin in certain concentration as a matrix former, a sugar alcohol (Pearlitol SD200) and a collapse protectant (glycine), an experimental design matrix was formed with 2 factors, 3 level, and 9 runs to optimized the influence of variable with Taguchi design by using Minitab Statistical Software Ink and characterized for in-vitro drug release (R1), disintegration time (R2), water absorption ratio (R3), and wetting time (R4) which were taken as a dependent variable (response parameters).

Prepared fast dissolving oral solid Nabumetone tablet batches (F1 - F9) were evaluated for thickness, shape, hardness, friability, weight variation, wetting time, water absorption ratio, In- vitro disintegration study, drug content and in vitro drug release study and found to be complies as per specification given in I.P.

Nabumetone lyophilized tablet with thickness was in the range of 8.60±0.10 to 9.65±0.16 mm, hardness was in the range of 2.30±0.08 to 3.30±0.12 kg/cm^2, friability was in the range of 0.34±0.10 to 0.70±0.09 %, weight variation ranges from 644±1.20to 650±0.02 mg, wetting time ranges from 44 to 70 seconds, waterabsorption ratio ranges from 30.36±0.14 to 46.10±0.16 % whereas in-vitro disintegration was in the range of 26 to 38 seconds and drug content was in the range of 93.70±0.18 % to 99.05±0.24 %, was maximum in F5 batch and results were summarized in Table 4.

Table 4. Post-compression Evaluation of Nabumetone tablets (Mean±SD)

Batches / **Parameters**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Thickness (mm)±SD	9.34± 0.08	8.60± 0.10	8.85± 0.22	8.75± 0.14	9.65± 0.16	9.45± 0.18	9.20± 0.24	9.50± 0.26	8.80± 0.16
Hardness (kg/cm^2)±SD	3.10± 0.12	2.80± 0.26	3.15± 0.14	2.60± 0.22	2.90± 0.28	3.30± 0.12	2.90± 0.22	2.30± 0.08	3.10± 0.16
Friability (%) ±SD	0.70± 0.09	0.68± 0.11	0.52± 0.16	0.64± 0.11	0.66± 0.08	0.62± 0.14	0.64± 0.18	0.34± 0.10	0.40± 0.12
Weight Variation (mg) ±SD	648± 0.22	650± 0.02	646± 1.28	647± 0.12	645± 0.06	648± 0.80	649± 1.10	646± 1.04	644± 1.20
Wetting time (Sec)	45	50	48	46	56	52	55	44	70
Water absorption ratio %	42.22 ±0.12	34.28 ±0.32	46.10 ±0.16	34.50 ±0.08	32.34 ±0.04	30.36 ±0.14	34.00 ±0.22	38.40 ±0.26	30.38 ±0.20
In-vitro disintegration (Sec)	34	26	38	36	25	24	23	33	30
Drug Content (%) ±SD	95.00 ±0.12	96.60 ±0.06	96.55 ±0.20	93.70 ±0.18	99.05 ±0.24	96.98 ±0.16	95.90 ±0.10	96.30 ±0.12	95.15 ±0.06

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In vitro dissolution of Nabumetone tablet batches F1 to F9 at different time interval is reported in Figure 2. Formulations F5 showed maximum drug release 97.60±0.28 % with 50 mg Kyron t 314 and Musa paradisiaca L 50 mg as superdisintegrant and concentration of 14 mg matrix former Gelatin as compared to other batches.

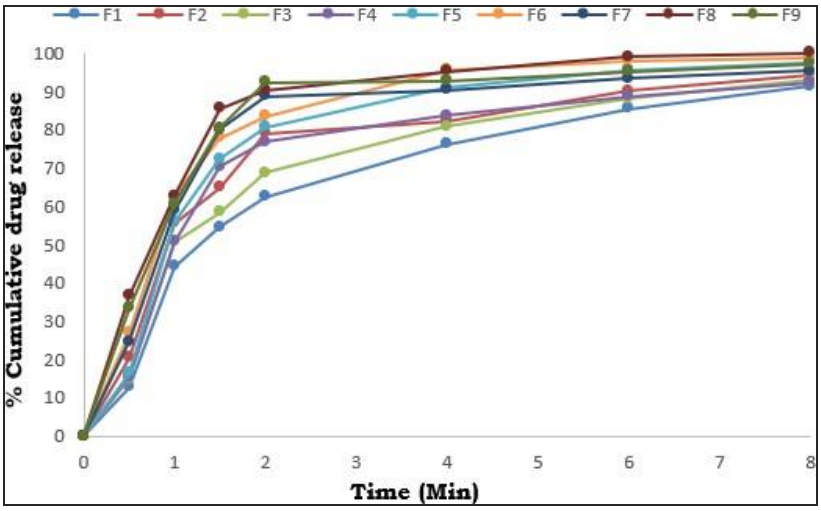

Figure 2. In-Vitro dissolution Profile of Nabumetone F-1 to F-9

The X-Ray diffraction pattern of Nabumetone exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. The X-Ray diffraction pattern of physical mixture of drug with excipients were simply a superimposition of each component with peaks of both drug and excipients.

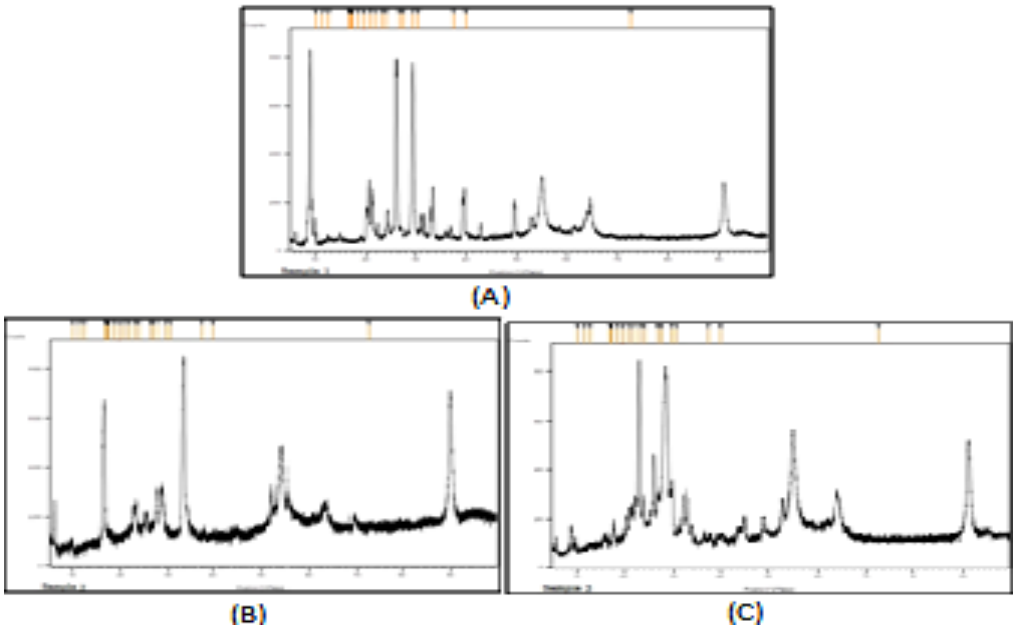

Figure 3: XRD Spectra of (A) Nabumetone (B) Physical mixture of Nabumetone with excipients(C) optimized lyophilized Nabumetone tablet

However with lower intensity whereas optimized lyophilized Nabumetone tablet showed less intense and highly diffused peaks of drug which was very poor in reflections which testified to a reduced ordering of crystal lattice indicating formation of amorphous

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state and molecular dispersion of drug and this amorphous, less crystalline and metastable form as compared to pure drug dissolvesat a faster rate as shown in Figure 3.DSC curve of pure components and of the various drug-polymers binary system are shown in Figure 4.

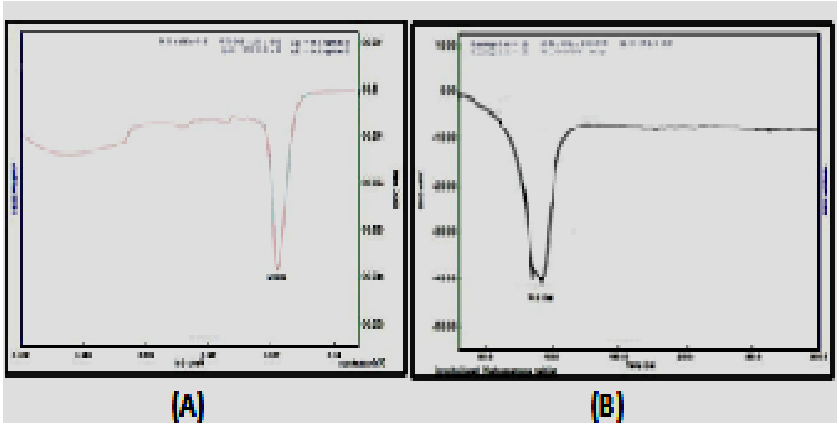

Figure 4: DSC Spectra of (A) Nabumetone (B) optimized lyophilized Nabumetone tablet

The thermal curve of Nabumetone (T_{peak} =80.5^{0}C,) indicated its crystalline anhydrous state. Thermal curves of binary system of optimized lyophilized Nabumetone tablet showed typical drug melting endotherm which progressively reduced its area and shifted to lower temperature (T_{peak} =79^{0}C) as consequence of gradually increasing interaction between components.Surface photomicrographs of optimized lyophilized Nabumetone tablet as shown in Figure 5 indicate that homogenious or heterogeneous conditions during the preparation of tablet.

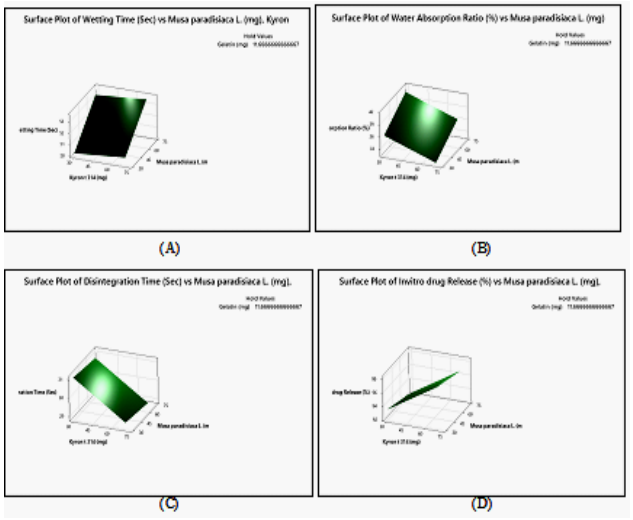

Figure 5. Surface plots for Nabumetone showing effect of concentration of Musa Paradisiaca L. and Kyron t 314 on measured responses (A) Wetting time (sec), (B) Water absorption ratio (%), (C) Disintegration time (sec), (D) In-vitro drug release (%) keeping hold values of gelatin 10 mg.

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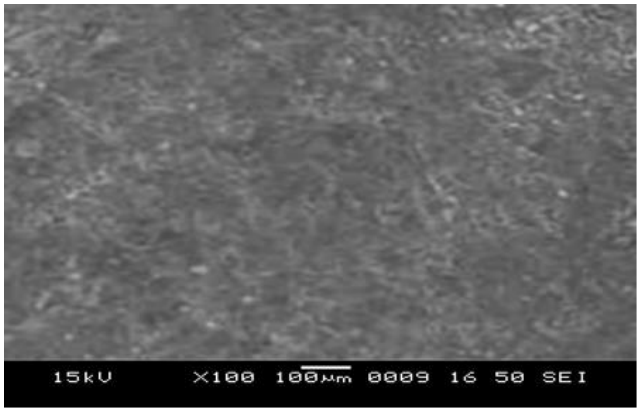

Figure 6: SEM of optimized lyophilized Nabumetone tablet

The optimized formulation F5 batches of Nabumetone were subjected to stability study when stored at 40□2^{0}C temperature with relative humidity of 75□5% for a period of six months. No significant change in physiochemical properties, drug release profile as well as drug content indicating there was no degradation and change in the matrix system and shown in Table 5 and Figure 7 and for lyophilized Etodolac tablet.

Table 5: Evaluation of formulation F5 lyophilized Nabumetone tabletkept for stability at 40^{0}C /75% RH

Parameters	0 Month	2 Months	4 Months	6 Months
Appearance/Colour	Off-white	Off-white	Off-white	Off-white
Thickness (mm)	9.65	9.60	9.50	9.65
Hardness (Kg/cm^2)	2.90	2.90	3.00	2.90
Friability (%)	0.66	0.60	0.65	0.60
Drug content (%)	99.05	99.00	99.40	99.30

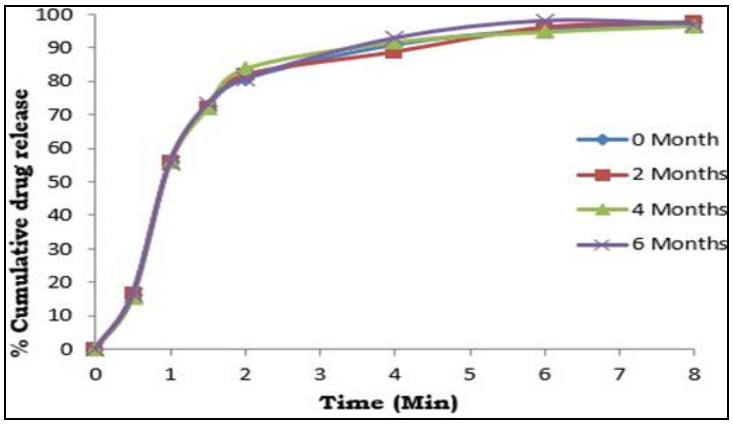

Figure 7: In-vitro release profiles of formulation F5 lyophilized Nabumetone tablet kept for stability at 40^0± 2^{0}C and 75 ± 5% RH for 6 months

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4. Conclusion

In present study, fast dissolving solid oral formulations for NSAIDs (Nabumetone) was prepared using different types and concentrations of superdisintegrant by lyophilization method which was confirmed by various characterization and evaluation studies. Kyron t 314 and Musa paradisiaca L as superdisintegrant with certain concentration of matrix former Gelatine gives better result when design and optimized from surface plots by Taguchi design. Prepared optimized lyophilized tablets of Nabumetone disintegrate within 25 seconds in mouth having better mouth feel.

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