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FORMULATION AND EVALUATION OF IMMEDIATE-RELEASE TABLETS OF NAPROXEN

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ABSTARCT
Tablets prepared by wet granulation method were found to be good without any chipping, capping and sticking. The hardness of the prepared tablets was found to be in the range of 4 to 5kg/ cm2. The friability values were found to be in the range of 0.50 to 0.72%. Disintegration time was found to be in the range of 1-3min. Formulation F6 showed good results than rest of the formulations in pre and post compression studies. The average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared. Formulation F6 (98.5%) displayed maximum drug release which shows similar drug release as that of F7, F8, but F7 and F8 were failed in mechanical properties like hardness and friability.IR-spectroscopic studies indicated that there is no drug–excipients interactions. The optimized formulation follows first order kinetics.

KEYWORDS: Naproxen, Wet granulation, Immediate release, kinetics.

INTRODUCTION

Immediate release tablets are invented to disintegrate and release their dosage form with no special rate controlling features, such as special coatings and other techniques. Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments.[1] The oral bioavailability of drug dependent on disintegration, dissolution and various physiological factors.[2] An immediate release dosage form helps a manufacture to diversify market and simultaneously offering patients a convenient dosage form or dosage regimen.[3]

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and or absorption. This term excludes formulations which are adapted to provide for modified, controlled, sustained, prolonged, extended or delayed release of drug. Release term includes the provisions of drug from the formulation to the gastrointestinal tract, to body tissues and or into systemic circulation. For gastrointestinal tract release, the release is under pH conditions such as pH=1 to 3, especially at, or about, pH=1. In one of the invention a formulation as described herein with a compound of formula, or an acid addition salt thereof, in crystalline form release drug under a range of PH conditions. Thus, formulations of the invention may release at least 70 % of active ingredients within 3-4 hours and more preferably 2hours [such as within 30 minutes], of administration, whether this be oral or parenteral.

MERITS

- Improved stability, and bioavailability.
- Decreased disintegration and dissolution times for immediate release oral dosage forms.
- Suitable for controlled, sustained release actives.
- High drug loading is possible.
- Ability to provide advantages of liquid medication in the form of solid preparations.
- Cost-effective.
- Improved compliance added convenience.[4,5]
- Ease of swallowing is possible.[6]
- Bilayers tablet is possible for sequential release of two drugs in combination and separate two incompatible substances.[7]

The immediate release tablets of naproxen were prepared by using wet granulation process. The wet granulation procedure facilitates the efficient production of tiny

particles for medication manufacture. Typically, the quick release formulation is granulated by adding a binding polymer to an aqueous solution, resulting in the formation of fine particles. A controlled release formulation was produced by including a binder polymer solution.[8]

As with other non-selective NSAIDs, naproxen exerts its clinical effects by blocking COX-1 and COX-2 enzymes leading to decreased prostaglandin synthesis. Although both enzymes contribute to prostaglandin production, they have unique functional differences. The COX-1 enzymes are constitutively active and can be found in normal tissues such as the stomach lining, while the COX-2 enzyme is inducible and produces prostaglandins that mediate pain, fever and inflammation. The COX-2 enzyme mediates the desired antipyretic, analgesic and anti-inflammatory properties offered by Naproxen, while undesired adverse effects such as gastrointestinal upset and renal toxicities are linked to the COX-1 enzyme.

MATERIALS AND METHODS

Table 1: List of materials used.

S. No.	Name of the ingredients	Category
1	Naproxen	Drug
2	Magnesium stearate	Lubricant
3	Water	Solvent
4	Starch	Binder
5	Micro crystalline cellulose	Diluent
7	Crospovidone	Super Disintegrant
8	CCS	Super Disintegrant
9	Aerosil	Glidant
10	0.1N HCL	Dissolution medium

Table 2: List of Equipment's used.

S. No.	Equipment	Manufacturer	Model no
1	Electronic Balance	CAL-ON	AUX220
2	Sieves	Scientific Engineering corporation Ltd.	ASL00
3	Tap density Tester	Electro lab	ETD-020
5	Laboratory Stirrer	Remi	RQT-124A
6	Tray dryer	Retsch	TG-200
7	pH Meter	Thermo	Orion 2 Star
8	Dissolution test apparatus	Electro lab USP XXII	TDT-08L
9	Stability chambers	Thermo labs	Standard
10	Disintegration Tester	Tanco labs	T3
11	Hardness tester	Tanco labs	T3
12	Friabilator	Tanco	41F
13	16 Station Compression machine	Cadmach	CLD3-16
14	Digital Vernier	Electro lab	PP-50V
16	IR moisture balance	Sartorious	SARTORIUS

PREFORMULATION STUDIES

Pre-formulation testing was an investigation of the physical and chemical properties of a drug substance alone and when combined with excipients.

Organoleptic Evaluation: These are preliminary characteristics of any substance which is useful in identification of specific materials. Test for Color, odor, taste, and appearance, and solubility analysis and melting point tests were conducted further.

Bulk density: Bulk density was determined by pouring gently 20 gm of sample (Naproxen) through a glass funnel into a 50 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as

Bulk density *= weight of sample in gram /volume occupied by the sample.*

Tapped density: An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume is noted, and the sample is then tapped (500, 750, or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%. Volume was noted and taped density is calculated using the following formula.

Tapped density *= Wt. of sample in gm / Tapped volume.*

Compressibility Index and Hausner ratio

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and

popular methods of predicting powder flow characteristics. Both the Compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

Relation of flow property with HR & CI

C.I=tapped-untapped*100/tapped.

Table 3: Compressibility Index and Hausner's ratio.

Compressibility Index (%)	Flow Character	Hauser's Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids.

Tan = h/r

θ = Tan–1 h/r.

Where: θ = angle of repose, h = height, r = radius.

Table 4: Flow Properties and Corresponding Angles of Repose.

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair - aid not needed	36–40
Passable - may hang up	41–45
Poor - must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

DRUG EXCIPIENT COMPATIBILITY STUDIES

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

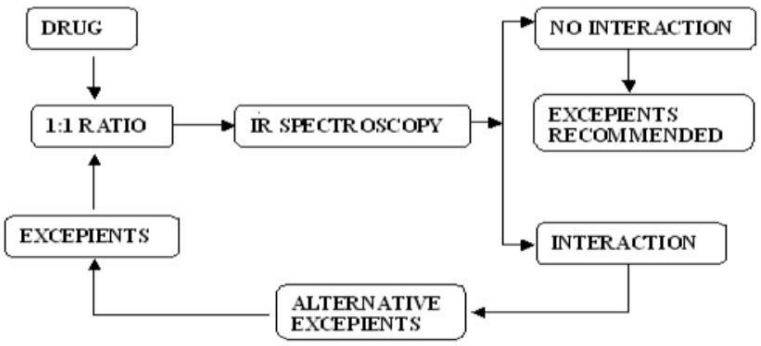

Figure 1: Drug-Excipient Compatibility Studies by FTIR.

In the present study, the potassium bromide disc (pellet) method was employed. Fourier-transform infrared (FTIR) spectra of the Drug and polymer were obtained on Alpha Brooker FTIR (Tokyo, Japan). The spectra were scanned over the wave number range of 4000 to 400 cm–1.

Preparation of Calibration Curve of Naproxen in 0.1N HCl

Preparation of Dissolution Media (0.1N HCL): Pipette out 8.5ml of concentrated HCL into 1000ml volumetric flask and make up with water to 1000ml.

Procedure: 100 mg of Naproxen was accurately weighed and dissolved in 20ml of 0.1N HCL into a 100ml volumetric flask and finally the volume was

adjusted to 100ml with 0.1N HCL (1000 µg/ml). The standard solution of Naproxen was subsequently diluted with 0.1N HCL to obtain a series of dilutions containing 2, 4, 6, 8, 10, 12 µg/ml. The absorbance of the above dilutions was measured on a spectrophotometer at 240nm using 0.1N HCl as the blank. The concentration of Naproxen used and the corresponding absorbance is given in table. The absorbance was plotted against concentration.

FORMULATION DEVELOPMENT

Table 5: Formulation table.

INGREDIENTS (mg)	FORMULATION CODE								
INTRAGRANULAR									
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Naproxen	300	300	300	300	300	300	300	300	300
MCC PH 101	111	101	91	111	101	91	111	101	91
Mannitol	20	20	20	20	20	20	20	20	20
CCS	-	-	-	10	15	20	-	-	-
CP	10	15	20	-	-	-	-	-	-
SSG							10	15	20
BINDER SOLUTION									
Pre gelatinized starch	24	24	24	24	24	24	12	19.2	24
Water	Q. s	Q. s	Q. s	Q. s	Q. s	Q. s	Q. s	Q. s	Q. s
EXTRAGRANULAR									
MCC PH 102	20	20	20	20	20	20	20	20	20
CCS	-	-	-	10	15	20	-	-	-
CP	10	15	20	-	-	-	-	-	-
SSG	-	-	-	-	-	-	10	15	20
Mg. stearate	2	2	2	2	2	2	2	2	2
Aerosol	3	3	3	3	3	3	3	3	3
Total weight(mg)	500	500	500	500	500	500	500	500	500

Procedure

Step1: Weigh the all ingredients in required quantity and then, pass through sieve no #40 and bend the mixture (drug, mcc, mannitol) in double cone blender for 15min.

Step2: Preparation of binder solution: Take the required quantity of PG starch and color in dissolve in purified water.

Step3: Addition of binder solution to the above mixture and the wet mass was sieved through #40 is dried in an oven for 2 hours until the moisture is below 2%.

Step4: Extra granular portion to the above dried granules was done by passing through #40 and the mixture was blended for 15min in double cone blender.

Step 5: Perform the flow properties of the granules.

Step 6: Tablets were compressed in round punches 9mm diameter. (Compression machine: cadmach 16station rotatory compression machine).

Evaluation Of Tablets

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made. The important parameters in the evaluation of tablets can be divided into physical and chemical parameters. Parameters like Physical appearance, Hardness test, Tablet size and Thickness, Friability, Weight variation, Disintegration test, Dissolution test.

Kinetic Data Analysis: The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero, first-order, diffusion and exponential equations. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics.

Stability Studies: Compatibility study was performed by preparing compatibility blends at different ratios of different excipients with the drug, based on tentative average weight. These blends were stored at accelerated condition of 400C/75% RH. Control samples were stored at 400C. The ratio of drug to excipient varies from 1:1to1:10 depending on the purpose of use, and the samples were kept in double lined poly-bags. The samples were evaluated for any change in the physical characteristics with reference to its controlled sample stored at 400C for a period of 15 days.

RESULTS AND DISCUSSION

Calibration curve of Naproxen in 0.1N HCl at λmax240nm.

Table 6: Standard curves of Naproxen 0.1N HCl at λmax 240nm.

Concentration (µg/mL)	Absorbance
0	0
2	0.160
4	0.280
6	0.434
8	0.582
10	0.845
12	0.891

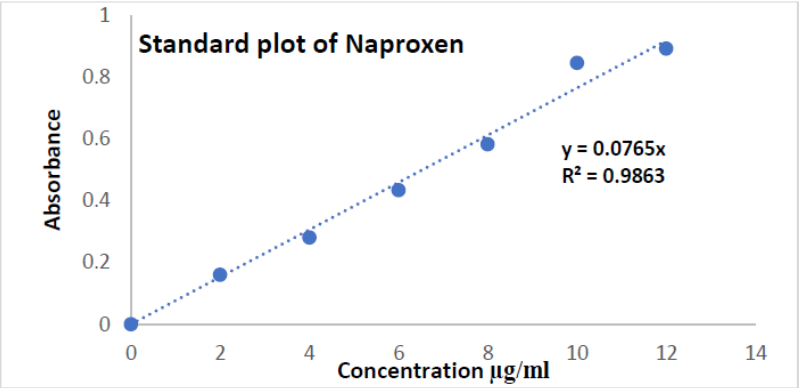

Figure 2: Standard plot of Naproxen in 0.1HCl buffer.

2. Evaluation of Blend: Bulk density, Tapped density, % Compressibility index, Hausner ratio, and Angle of repose.

Table 7: Pre-compression studies data.

Formulation code	Bulk density (gm /ml)	Tapped density (gm/ml)	Hausner ratio	Carr's index (%)	Angle of repose (θ)
F1	0.541	0.691	1.276	16.62	34^0
F2	0.484	0.615	1.27	14.30	33^0
F3	0.710	0.873	1.251	12.714	31^0
F4	0.712	0.870	1.206	15.126	32^0
F5	0.718	0.871	1.223	14.513	30^0
F6	0.410	0.483	1.178	15.113	32^0
F7	0.420	0.462	1.131	15.010	35^0
F8	0.541	0.691	1.276	11.62	34^0
F9	0.450	0.585	1.300	13.07	31^0

Table 8: Post-compression studies data.

Formulation code	Weight variation	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Content uniformity	Disintegration Time (min)
F1	500	4.4	0.72	2.6	99.28	3.1
F2	497	4.3	0.68	2.6	97.16	2.6
F3	498	4.8	0.69	2.7	101.1	2.4
F4	502	3.6	0.66	2.75	97.68	2.7
F5	498	3.7	0.68	2.6	99.41	2.3
F6	499	4.4	0.65	2.62	98.19	1.4
F7	497	4.0	2.3	2.6	102.6	1.0
F8	496	4.5	1.8	2.56	99.5	1.2
F9	499	4.4	0.70	2.59	99.6	1.3

3. *In-vitro* drug release study

Table 9: In -vitro drug release data.

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	36	40	48	39	46	54	55	53	38
10	68	73	76	72	78	86	84	88	50
15	79	81	85	80	87	91	92	90	79
20	85	92	90	89	93	98	97	99	90
30	93	97	96	93	97	98	97	99	98
45	98	97	96	98	97	98	97	99	98
60	98	97	96	98	97	98	97	99	98

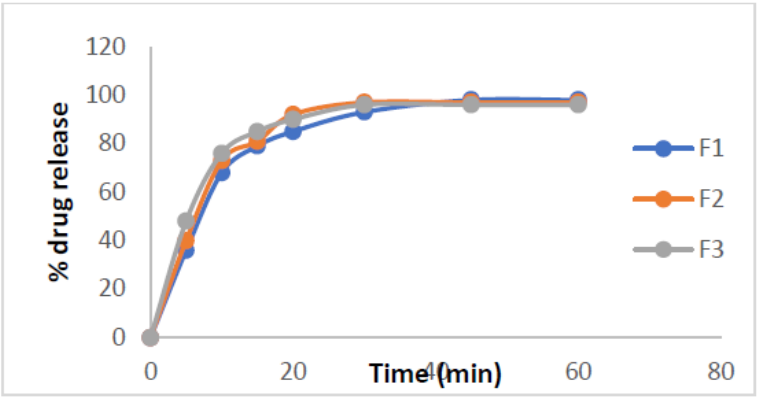

Figure 3: Cumulative % drug release of formulations F1, F2, F3.

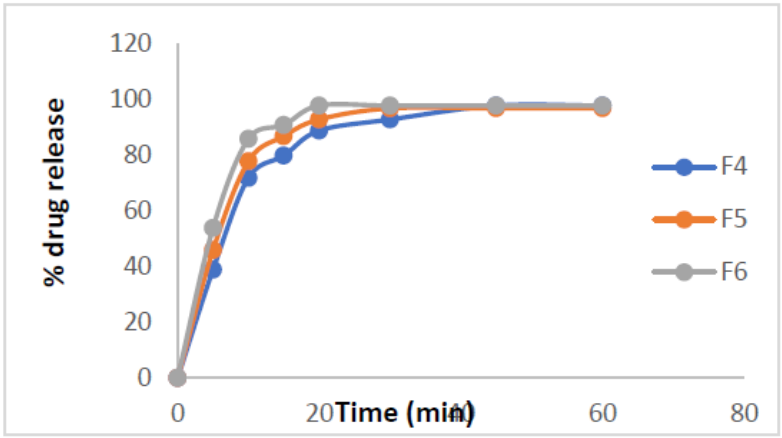

Figure 4: Cumulative % drug release of formulations F4, F5, F6.

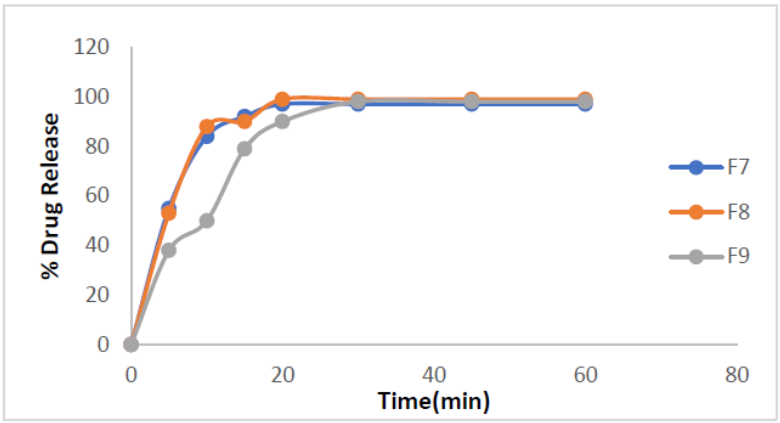

Figure 5: Cumulative % drug release of formulations F7, F8, F9.

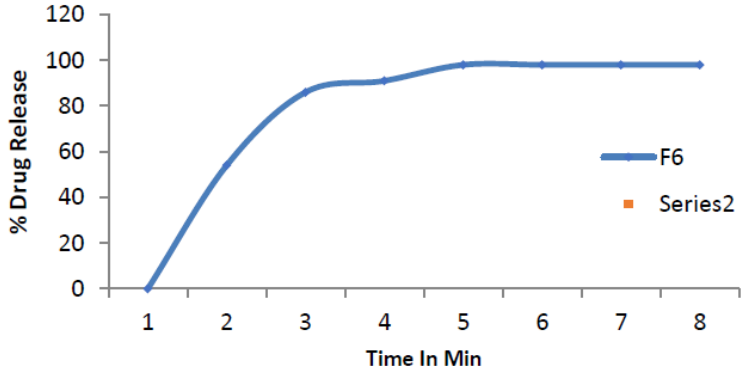

Figure 6: Cumulative % drug release formulation F6.

Model-Dependent Approaches

Discussion

The kinetic investigation of the release profile gave us useful insight into the mechanism of drug release from the tablets. The release did not show any burst effect or lag time, which is indicative of a homogeneous drug distribution in the polymer matrix. The dissolution data was subjected to regression analysis and were fitted to kinetic models, viz., Zero order, and First order. It was found that most of the formulations followed the First order (R2=0.835). It describes the systems where the drug release rate is dependent on its concentration.

TABLE 10: Release kinetics profile.

RELEASE KINETICS				
	ZERO	**HIGUCHI**	**PEPPAS**	**FIRST**
	1	2	3	4
	Q Vs T	Q Vs √T	Log C Vs Log T	Log % Remain Vs T
Slope	4.6600	19.0748	0.4282	-0.0260
Intercept	19.2000	16.7116	1.4573	3.1566
Correlation	0.9105	0.9432	0.9560	-0.9811
R 2	0.8290	0.8896	0.9140	0.9626

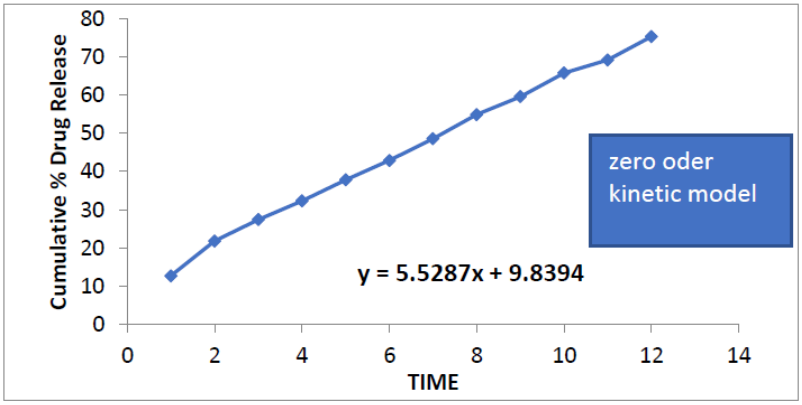

Figure 7: Release kinetics profile indicating Zero order kinetic model.

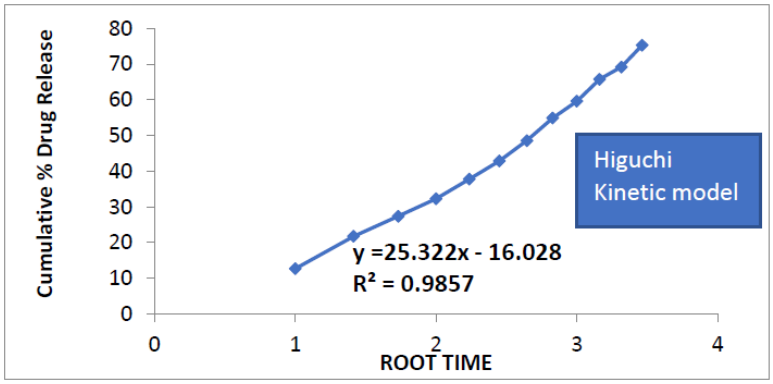

Figure 8: Release kinetics profile indicating Higuchi kinetic model.

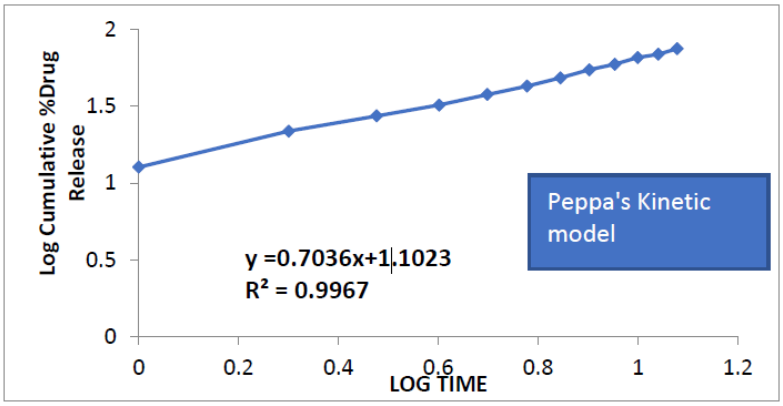

Figure 9: Release kinetics profile indicating Peppas kinetic model.

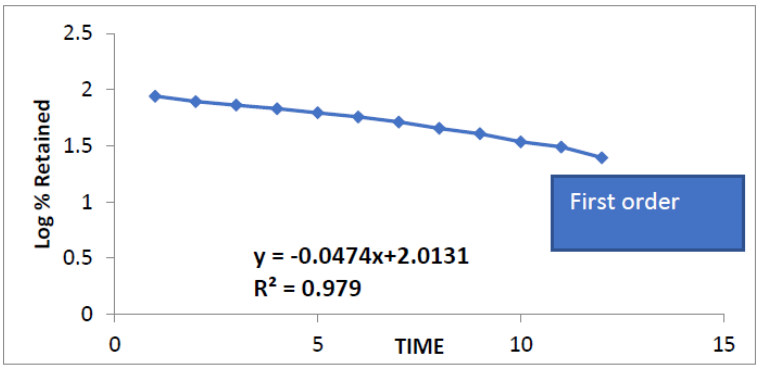

Figure 10: Release kinetics profile indicating First order kinetic model.

FT-IR Studies

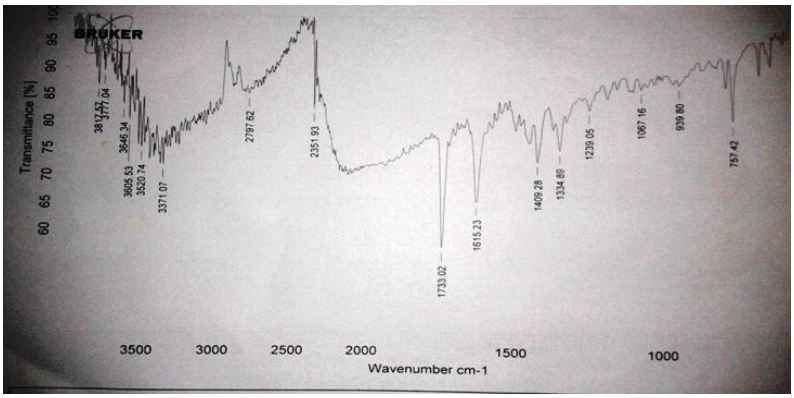

Figure 11: FTIR Spectra for Naproxen Pure drug.

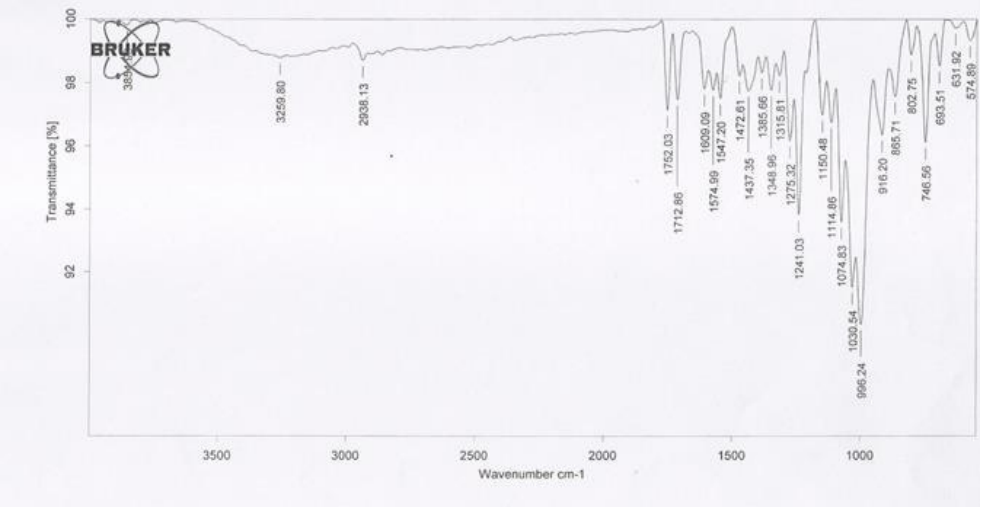

Figure 12: FTIR Spectra for Naproxen drug with excipients.

B) Optimized formula

Stability Studies

There was no significant change in the physical and chemical properties of the tablets of formulation F-1 after 3 Months. Parameters quantified at various time intervals were shown.

Table 11: Results of stability studies of optimized formulation F-1.

S.NO	Parameters	Initial	1 month	2nd month	3rd month	Limits as per specification
1	40^0C/75% RH % Release	98	98.52	97.79	96.56	Not less than 85 %
2	40^0C/75% RH Assay Value	98	97.96	96.22	96.00	Not less than 90 % Not more than 110 %

DISCUSSION

In the present study, an attempt has been to formulate and evaluate IR tablets of Naproxen by wet granulation (aqueous granulation) technique, employing Cellulose (MCC 101, 102) and mannitol were taken along with pharmaceutically acceptable easily available inert excipients and eleven formulations were prepared. The formulation was subjected to both pre and post-formulation studies.

The procured drug sample of Naproxen was tested for its identification through organoleptic properties, melting point, UV spectra, and FTIR spectrum. The drug sample showed similar results as reported in the literature. The solubility of a drug is an important factor affecting its release from the drug delivery system.

UV Spectroscopic Analytical Method

The standard curve of Naproxen in 0.1 N HCl as shown in Table 13 & Fig 12 Wavelength of maximum absorption was found to be 240 nm. The Drug Naproxen Obeyed Beer's-Lambert law in the concentration range of 0-12 µg/ml.

Pre-compression studies: The granules prepared by wet granulation method were evaluated for various flow properties. The granules of all batches showed good flow properties evident from the results shown in table-14. The angle of repose values was ranged from 30-34 the results were found to be below 35; hence they have good flow ability. The Carr's index value ranged from 11 to 16 and Hausner's ratio value ranged from 1.1 to 1.3 hence they have good flow and free flow ability.

Physical characterization of IR Tablets of Naproxen: Tablet thickness, hardness, weight variation, friability, and drug content of formulated. Tablets of batches from F1 to F9 are presented in Table 8.

Uniformity of weight: All the prepared tablets of Naproxen were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ±7.5%.

Hardness and friability: The hardness of the tablet formulations was found to be in the range of 3 to 5 kg/cm2. The friability values were found to be in the range of 0.50 to 0.72 %.

Exceptionally F7 and F8 formulations failed in their friability. And hardness is also out of range compared to the other formulations, which was mentioned above.

Uniformity of drug content: The low values of standard deviation indicate uniform drug content within the tablets. The percent drug content of all the tablets was

found to be in the range of 97.06 to 101.1 percent (which was within the acceptable limits of ±5%.).

In vitro dissolution study: In vitro dissolution studies were performed in 0.1N HCl on the above promising formulation, namely, formulation 6.

In the dissolution studies, the maximum drug release was found to be with formulation F6 of maximum drug release (98%) within 20 minutes.

Release kinetics: The release kinetics follow the first order and Higuchi model of kinetics with an R2 of 0.9626, and 0.8896 respectively.

Stability Studies: There was no significant change in physical and chemical properties of the tablets of formulation F6 after 3 Months, parameters like % drug release and assay values at various conditions (at 400C/ 75% RH) as per ICH guidelines quantified at various time intervals.

CONCLUSION

In the present work, we conclude that Tablets prepared by wet granulation method were found to be good without any chipping, capping and sticking.

- The hardness of the prepared tablets was found to be in the range of 4 to 5kg/ cm2.
- The friability values were found to be in the range of 0.50 to 0.72%.
- Disintegration time was found to be in the range of 1-3min.
- Formulation F6 showed good results than rest of the formulations in pre and post compression studies.
- The average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.
- Formulation F6 (98.5%) displayed maximum drug release which shows similar drug release as that of F7, F8, but F7 and F8 were failed in mechanical properties like hardness and friability.
- IR-spectroscopic studies indicated that there is no drug–excipients interactions.
- The optimized formulation follows first order kinetics.

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