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FORMULATION AND EVALUATION OF NAPROXEN ORAL DISINTEGRAING TABLETS

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ABSTRACT

The aim of the present research was to develop and evaluate taste masked orodispersible tablets (ODT) of naproxen. Over the past three decades, orally disintegrating tablets have gained considerable attention as a preferred alternative to conventional tablets due to better patient compliance. The most preferable route of drug administration (e.g. oral) is limited to drug candidate that show poor permeability across the gastric mucosa and those, which are sparingly soluble. A large majority of the new chemical entities and many new existing drug molecules are poorly soluble, thereby limiting their potential uses and increasing the difficulty of formulating bioavailable drug products. Formulations were prepared using different superdisintegrants such as crosscaramellose sodium, sodium starch glycolate, crosspovidone by direct compression method. The properties of the formulations such as porosity, hardness, friability, wetting time, water absorption ratio and disintegration time were investigated. All the formulations showed good flow properties, low weight variation with rapid disintegration time and in-vitro dissolution. The drug content of all the formulations was within the acceptable limits. The wetting time for F6 & F9 formulations was below one minute. Formulation F9 which contains 6% of crosspovidone showed least in- vitro disintegration time i.e., below 30 seconds and more than 90% drug release within 8 minutes.

The in-vitro drug release of Naproxen ODT were best explained by higuchi's equation as the plots showed the highest linearity follwed by first order and zero order, the korsmeyer-peppas release exponent "n" indicated that all formulations showed a mechanism of both diffusion and erosion mechanism so called anomalous(non- fickian) diffusion. The optimized formulation showed good in-vivo disintegration time and palatable taste. The excipients used in this study did not alter physicochemical properties of the drug, as tested by the Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimeter (DSC).

KEYWORDS

Orodispersable tablets, Naproxen, Wetting time, Disintegration time.

INTRODUCTION

In recent decades, a variety of pharmaceutical research has been conducted to develop novel dosage forms. Considering quality of life, most of the effort has been focused on ease of medication. Among the dosage forms developed to facilitate ease of medication, the orally disintegrating tablet (ODT) is one of them. Oral disintegrating tablets are also called as orodispersible tablets, mouth-dissolving tablet (MDT), quick-dissolve, fast-melt, and rapid disintegrating tablets and freeze-dried wafers, porous tablets and rapimelts[1]. The conventional dosage forms, which include tablets and capsules, are widely used. But, unlike the conventional dosage forms, the mouth dissolving tablets has some unique features like: Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action[2]. Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs. Bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus is increased[3,4&5]. Pre-gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability [6].

Naproxen is a member of propionic acid derivative related to the arylacetic acid group of non-steroidal anti-inflammatory drugs (NSAID), cyclo-

oxygenase inhibitor, used to treat the inflammation and pain of arthritis. Naproxen is rapidly absorbed from the GI tract following oral administration. The mean oral bioavailability of Naproxen from tablets is 95% relative to oral solution and half life of about 12 hrs.

The purpose of the present study was to formulate and evaluate mouth dissolving tablets to avert the problem of swallowing and to provide rapid onset of action.

EXPERIMENTAL

Materials

Naproxen was obtained as gift sample from Dr Reddy's laboratories. Sodium starch glycollate from S.D. Fine Chem. Ltd., Mumbai. Croscarmellose sodium from Signet Corporation, Mumbai. Crospovidone was obtained as gift sample from Aurobindo pharma, Hyderabad, microcrystalline cellulose pH-102, mannitol, aspartame, aerosil, magnesium stearate were obtained from SD Fine chemicals. All other ingredients used were of analytical grade.

METHODS

Characterization of Disintegrate Powder:

Angle of Repose

The angle of repose[7] was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of a funnel was adjusted in such a way that its tip just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder heap was measured and angle of repose was calculated using following equation:

$$\tan(\theta) = h/r$$

Where h and r indicate the height and radius of the powder heap.

Density

The loose bulk density (LBD)[8] and tapped bulk density (TBD) of disintegrant were determined. Disintegrant (2g) was poured into calibrated measuring cylinder (10 ml) then noted initial volume. Then the cylinder was allowed to fall under its own weight onto the hard surface from the height of 2.5 cm at 2 seconds intervals. The tapping was the continued no further change in volume was noted. LBD and TBD were calculated using following equation,

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility:

The compressibility index (Carr's Index)[8] was determined by using following equation,

Carr's Index (%) = [(TBD- LBD) × 100] / TBD

Preparation of tablets

Taste masking of the Naproxen tablets was done by using sweeteners. Orodispersible tablets of naproxen were prepared by direct compression. All the ingredients (except granular directly compressible excipients) were passed through # 120-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 300mg using 9mm flat punches on sixteen station rotary tablet compression machine (Cadmach), as shown in **Table 1**.

Table 1 : Composition of Naproxen ODT Formulations

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Naproxen	100	100	100	100	100	100	100	100	100
Sodium starch glycolate	6	12	18	-	-	-	-	-	-
Cross carmellose sodium	-	-	-	6	12	18	-	-	-
Cross povidone	-	-	-	-	-	-	6	12	18
Microcrystalline cellulose 102	134	128	122	134	128	122	134	128	122
Mannitol	50	50	50	50	50	50	50	50	50
Aspartame	4	4	4	4	4	4	4	4	4
Aerosil	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight (mg)	300	300	300	300	300	300	300	300	300

Evaluation of tablet characteristics

Weight Variation [9]

Twenty tablets were selected randomly from each formulation and weighed individually using a Shimadzu digital balance (BL-220H). The individual weights were compared with the average weight for the weight variation.

Thickness variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge.

Hardness and Friability

Hardness of the tablets was measured using the Monsanto Hardness Tester (Pharmalab, Ahmedabad, India). The friability of a sample of twenty tablets was measured using a USP type Roche friabilator (Pharmalab, Ahmedabad, India). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated.

Drug Content Uniformity

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 100 mg of naproxen was mixed with 100ml of methanol and allowed to stand for 30min with intermittent shaking and the total solution was filtered. The naproxen content was determined by measuring the absorbance at 302 nm (using UV-vis spectrophotometer, Eloco) after appropriate dilution with distilled water.

The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

Wetting Time and Water Absorption Ratio (R) [10]

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation:

$$R=100 \times (w_a-w_b)/w_b$$

Where wb and wa were tablet weights before and after water absorption, respectively.

***In-vitro* disintegration time study**

In-vitro disintegration time for ODTs was determined using USP disintegration apparatus with pH 7.4 buffer as the disintegration medium.

In-vitro drug release studies

Dissolution test of Ketorolac Tromethamine tablets was performed using 7.4 pH phosphate buffer with USP dissolution apparatus II at 50 rpm and 37 ± 1°C temperature. Test sample (5 ml) was withdrawn at particular time intervals and replaced with fresh dissolution medium maintained at 37 ± 1°C. The samples then filtered (membrane filter, 0.45µm) and analyzed using a UV spectrophotometer at λmax 332 nm. This test was performed on 3 tablets and mean ± SD calculated.

Kinetic Analysis of Dissolution Data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate **Eq. (1)** describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the system where release rate is concentration dependent. Higuchi (1963) describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion **Eq. (3)**.

$$C = K_0 t \quad (1)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log } C = \text{Log } C_0 - K_1 t / 2.303 \quad (2)$$

where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \quad (3)$$

where, K_H is the constant reflecting the design variables of the system.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model);

Log cumulative of % drug remaining vs. time (First order kinetic model);

Cumulative % drug release vs. square root of time (Higuchi model);

Mechanism of drug release

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (4). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \quad (4)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table 2, for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

Table 2: Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

***In-vivo* disintegration time & Palatability (mouth feel) studies.**

Six healthy male human volunteers in the age group of 18-30 years and 55-70Kg body weight were selected for the study. The Orally Disintegrating tablets of Naproxen were placed on the tongue, the time taken for complete disintegration of the tablet when placed on tongue & palatability (mouth feel) were recorded.

Fourier transform infrared spectroscopy (FTIR)

FTIR studies were performed on drug, excipients and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). About 2-3 mg of samples were mixed with the dried IR grade potassium bromide powder and analyzed between wave numbers 4000 and 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC studies were performed for drug and the optimized formulations. Indium/Zinc standards were used to calibrate the temperature and enthalpy scale. Accurately weighed 5-6 mg samples were hermetically sealed in aluminum pans and heated at constant rate of 10^0C/min over a temperature range of 40^0C to 300^0C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

RESULTS AND DISCUSSION

The present study was carried out to prepare Naproxen oral disintegrating tablets by direct compression method. Preliminary trials were carried out to optimize the taste. Taste masking was done by using sweeteners. To develop the optimized formula, different super disintegrants like Sodium Starch Glycolate, Crospovidone, and Croscarmellose sodium were used at different concentrations

Evaluation of Blend

Physical properties such as bulk density, tapped density, percent compressibility index, hausner ratio, angle of repose were determined (**Table 3**) for the prepared tablet blend. The tablet blend batches in which microcrystalline cellulose was used as diluent, the angle of repose is between 30° to 35°, this indicated the passable flow ability. This property may be attributed due to the presence of microcrystalline cellulose having filamentous particles as diluent. The percent compressibility index and hausner ratio were within the limits.

Table 3: Tablet blend evaluation tests for ODT formulations.

Formulations	Angle of Repose ± S.D.	Bulk Density ± S.D.	Tapped Density ± S.D.	Percent Compressibility Index ± S.D.	Hausner Ratio ± S.D.
F_1	31.8 ± 0.08	0.30 ± 0.08	0.36 ± 0.15	16.6 ± 0.69	1.20 ± 0.22
F_2	30.1 ± 0.12	0.25 ± 0.05	0.31 ± 0.09	19.3 ± 0.78	1.24 ± 0.57
F_3	30.2 ± 0.08	0.21 ± 0.46	0.25 ± 0.2	16.0 ± 0.01	1.19 ± 0.63
F_4	31.6±0.09	0.25 ± 0.18	0.30 ± 0.44	16.6 ± 0.71	1.20 ± 0.26
F_5	32.5±0.04	0.33 ± 0.12	0.37 ± 0.11	10.8 ± 0.9	1.12 ± 0.81
F_6	30.9±0.08	0.25 ± 0.75	0.30 ± 0.34	16.6 ± 0.51	1.21 ± 0.19
F_7	31.2±0.04	0.37 ± 0.18	0.45 ± 0.3	17.7 ± 0.74	1.21 ± 0.64
F_8	31.3±0.04	0.21 ± 0.66	0.25 ± 0.51	16.0 ± 0.18	1.19 ± 0.45
F_9	32.6±0.02	0.20 ± 0.57	0.25 ± 0.31	20.0 ± 0.12	1.25 ± 0.58

Evaluation tests for Naproxen ODT's.

The Naproxen orally disintegrating tablets were evaluated for hardness, friability, thickness, weight variation and content uniformity for all the batches and the results (**Table 4**) were found to be within the acceptable limits.

The *in-vitro* disintegration time, wetting time & water absorption ratio were determined for all the prepared formulations (Table 5). The wetting time for the optimized formulations was below one minute, which indicated quicker disintegration of the tablet. In the water absorption ratio test, F9 has loosened the shape because it absorbed large amount of water, when compared with other batches of formulations.

The *in-vitro* disintegration test was carried out for all the prepared formulations. Tablet disintegration was affected by the wicking and swelling nature of the disintegrants[11]. From the results the formulations in which crospovidone was present showed less disintegration time when compared with other super disintegrants because it has excellent wicking nature, crospovidone has a finer particle size distribution which improves mixing and minimizes changes in swelling properties on the tablet surface resulting from atmospheric humidity, so it swells only to a very less extent.

The mechanism involved in cross carmellose sodium and sodium starch glycolate is when it comes in contact with water it swells to a large extent to disintegrate the tablet. Also it has fibrous nature that allows intra-particulate as well as extra-particulate wicking of water at low concentration levels [12]. The probable reason for delayed disintegration time of cross carmellose sodium and sodium starch glycolate might be due to their tendency to gel more than Crospovidone.

Table 4: Evaluation tests for Naproxen oral disintegrating tablets .

Formulations	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Content uniformity (%)
F_1	300.15 ±1.83	3.5 ±0.02	0.52±0.04	3.88 ± 0.02	96 ± 0.08
F_2	300.13±1.99	3.5±0.10	0.65±0.01	3.84±0.03	97±0.03
F_3	300.3±1.13	3.2±0.02	0.54±0.01	3.81±0.02	95±0.68
F_4	301.8±1.16	3.5±0.01	0.52±0.03	3.89±0.03	97±0.75
F_5	298.8± 0.74	3.5±0.04	0.51±0.01	3.85±0.09	99±0.05
F_6	299.3±0.33	3.4±0.00	0.51±0.02	3.88±0.06	98±0.88
F_7	300.3±0.14	3.5±0.10	0.56±0.05	3.89±0.03	103±0.94
F_8	300.7±0.28	3.5±0.06	0.62±0.03	3.83±0.03	98±0.03
F_9	300.5±0.23	3.5±0.09	0.66±0.07	3.86±0.08	103±0.13

Table 5: Evaluation tests for Naproxen oral disintegrating tablets.

Formulations	*In-vitro* disintegration time (sec)	Wetting time(Sec)	Water absorption ratio
F_1	113 ± 1.34	122 ± 1.21	55.7 ± 0.56
F_2	90 ± 1.24	98 ± 1.21	63.9 ± 0.45
F_3	55 ±1.32	68 ± 1.24	75.6 ± 0.64
F_4	52 ± 1.26	63 ± 0.95	78.9 ± 0.24
F_5	37 ± 1.26	48 ± 1.24	84.7 ± 0.88
F_6	28 ± 1.34	40 ± 0.92	90.6 ± 0.78
F_7	42 ± 1.45	51 ± 0.95	76.9 ± 0.24
F_8	31 ±1.24	38 ± 1.13	90.8 ± 0.45
F_9	22 ± 0.98	29 ± 1.24	94.8 ± 0.65

***In-vitro* drug release studies**

The maximum drug release time for the formulations F1, F2 & F3 in which sodium starch glycolate was used were, at 45 min (90.2 ± 0.69), 45 min (92.8 ± 0.72) and 15 min (91.6 ± 0.10) respectively (Figure 1).

The maximum drug release time for the formulations F4, F5 & F6 in which crosscarmellose sodium was used were at 15 min (89.86 ± 1.26), 10 min (90.68 ± 0.46) and 8 min (91.34 ± 0.53) respectively (Figure 2). The maximum drug release time for the formulations F7, F8 & F9 in which crospovidone was used were at 8 min (91.09 ± 0.29), 8 min (93.46 ± 0.33) and 8 min (96.56± 0.74) respectively. From the above observations, all concentrations of crospovidone gave better release in very less time (8 min) and at higher concentration gave maximum drug release (**Figure 3**).

The maximum drug release was shown by formulation F9 containing crospovidone 6% (96.56% drug release in 8 min) when compared to other super disintegrants because it is a synthetic insoluble, swellable, cross-linked polymer with rapid wicking effect which rapidly wicks solvents into the particle to speedup swelling and enhance disintegration and dissolution of tablets. . The order followed is crosspovidone > croscaramellose > sodium starch glycolate .

Figure 1: Plot of *in-vitro* drug release studies of Naproxen oral disintegrating tablets containing different concentrations of sodium starch glycolate.

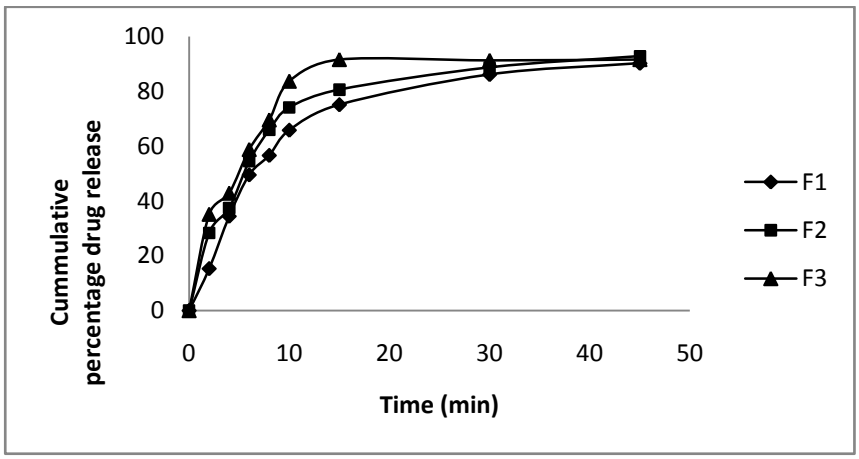


Figure 2: Plot of *in-vitro* drug release studies of Naproxen oral disintegrating tablets containing different concentrations of cross carmellose sodium.

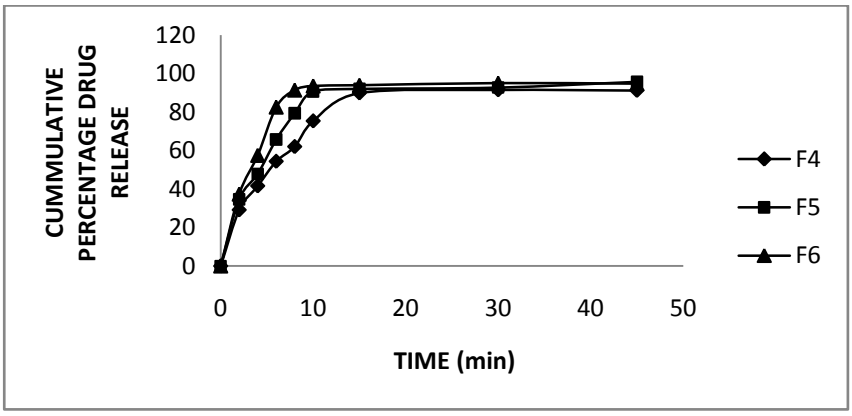
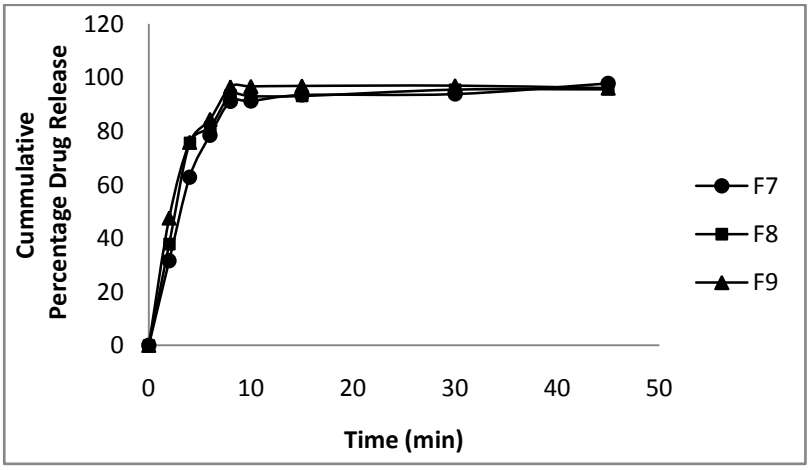


Figure 3: Plot of *in-vitro* drug release studies of Naproxen oral disintegrating tablets containing different concentrations of Crospovidone.



Kinetic Analysis of Dissolution Data

The release rate kinetic data for all equations were calculated and the regression coefficients were determined (**Table 6**). From the regression coefficients the *in-vitro* drug release of Naproxen ODT were best explained by higuchi's equation which showed the highest linearity followed by first order and zero order.The corresponding korsmeyer-peppas release exponent values indicated a coupling of diffusion and erosion mechanism so called anomalous (non- fickian) diffusion.

Table 6. Regression coefficient values for Naproxen oral disintegrating tablets containing different disintegrants.

Formulations	Zero	First	Higuchi	Peppas	Peppas(n)
F3	0.9493	0.9633	0.9835	0.9583	0.543
F6	0.9095	0.9815	0.9833	0.9692	0.606
F9	0.8331	0.9635	0.9773	0.9445	0.458

***In-vivo* disintegration time**

The *in-vivo* disintegration time and taste evaluation (palatability) studies were performed on human volunteers for formulations containing croscaramellose and crospovidone (F6 & F9). The *in-vivo* disintegration time for all the above mentioned formulations was below 1min and were having acceptable taste (**Table 7 & 8**).

Table 7: *In-vivo* disintegration time evaluation test for Naproxen oral disintegrating tablets on human volunteers.

Formulations	*In-vivo* disintegration time(seconds)
F 6	46
F 9	36

Table 8: Evaluation of taste of Naproxen ODT on human volunteers.

Formulations	H1	H2	H3	H4	H5	H6
F6	+	++	++	+	+	+
F9	+	+	++	++	+	+

0 = Sweet, + = Acceptable, ++ = Less bitter taste, +++ = High bitter taste

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the drug, excipients and the optimized formulation were recorded in range of 4000-400 cm^{-1}. Naproxen exhibits sharp bands at 1227cm^{-1} due to C-O stretching(ether), 1264cm^{-1} due to C-O stretching(acid), 1394cm^{-1} to 1363cm^{-1} due to CH_3 bending, 3420cm^{-1} due to aromatic stretching, 2963cm^{-1} and 2938cm^{-1} due to aliphatic stretching and 3002cm^{-1} and 2838cm^{-1} due to C-H aliphatic stretch.

In the optimized formulations, the presence of all the characteristic peaks of the Naproxen indicates lack of any strong interaction between the drug and the excipients which are indicated in figure 8, 9 & 10 for formulations F3, F6 & F9 respectively.

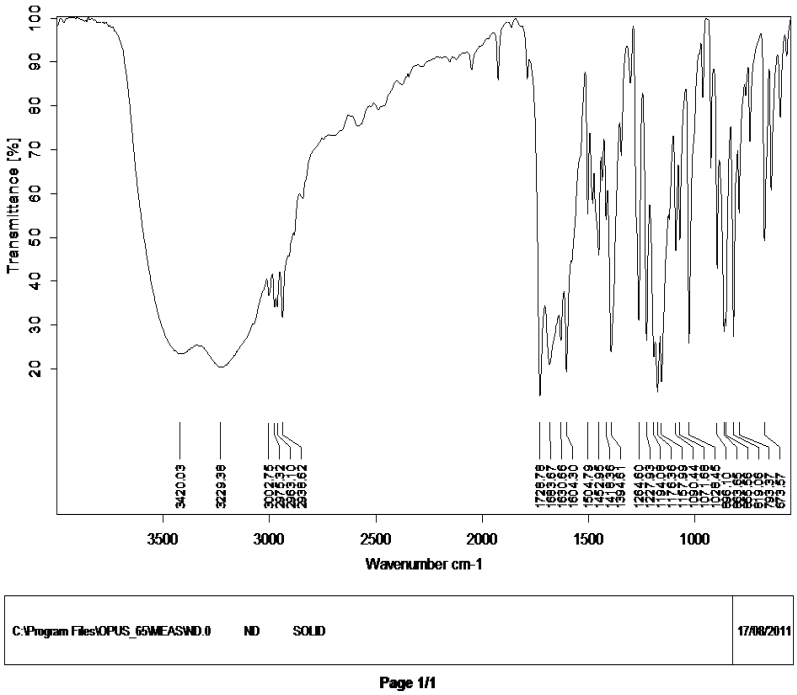


Figure 4: FTIR graph of pure drug (Naproxen)

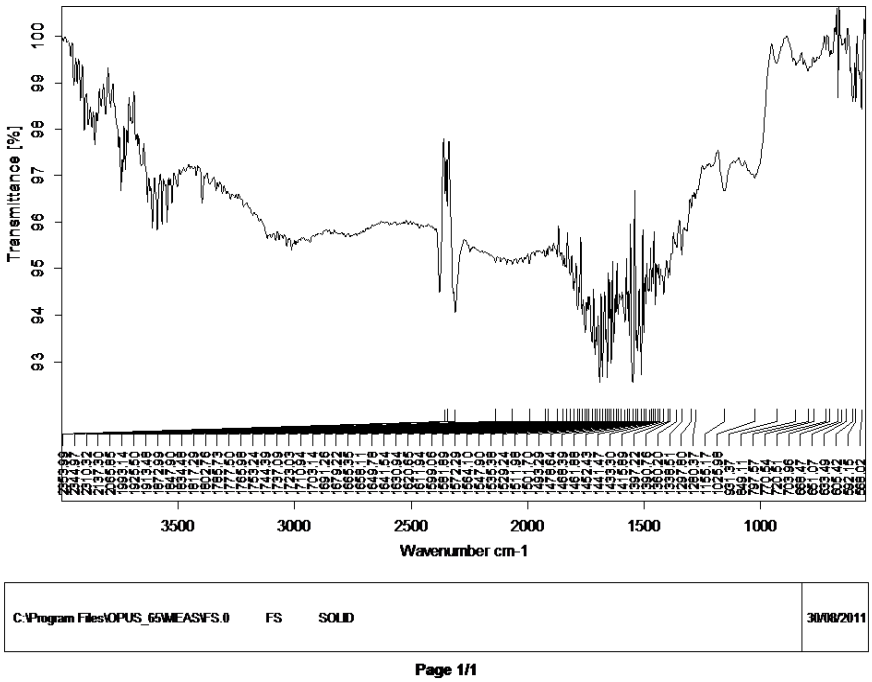


Figure 5: FTIR graph of Sodium Starch Glycolate

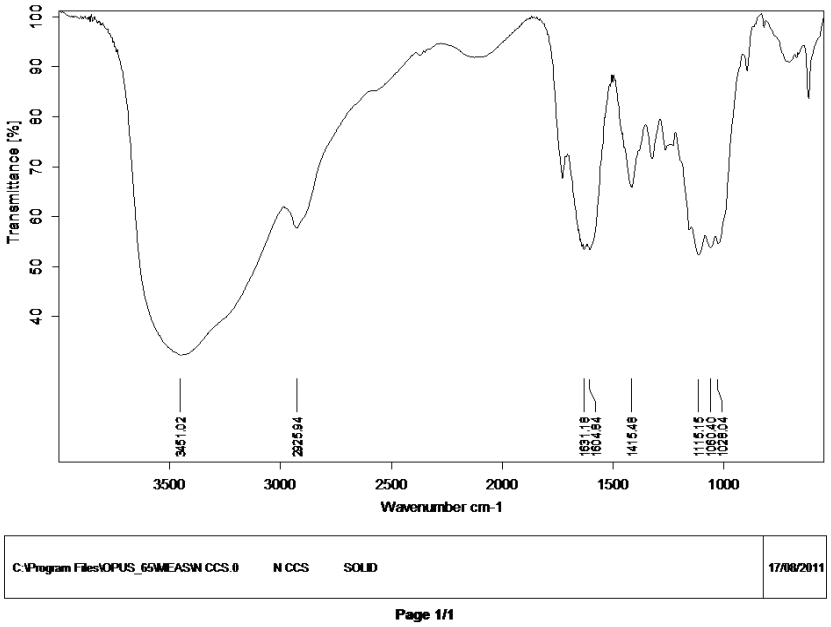


Figure 6: FTIR graph of Croscarmellose sodium

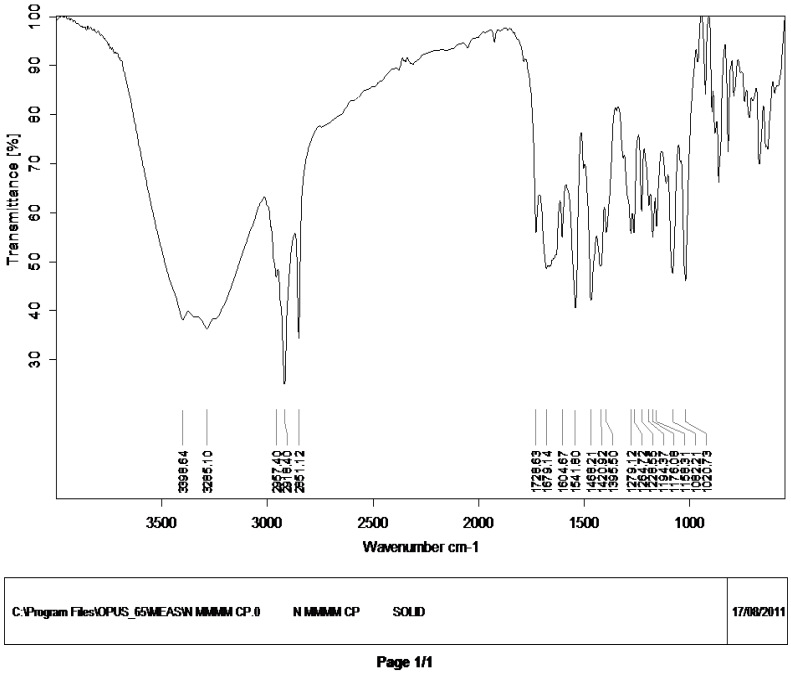


Figure 7: FTIR graph of Crosspovidone.

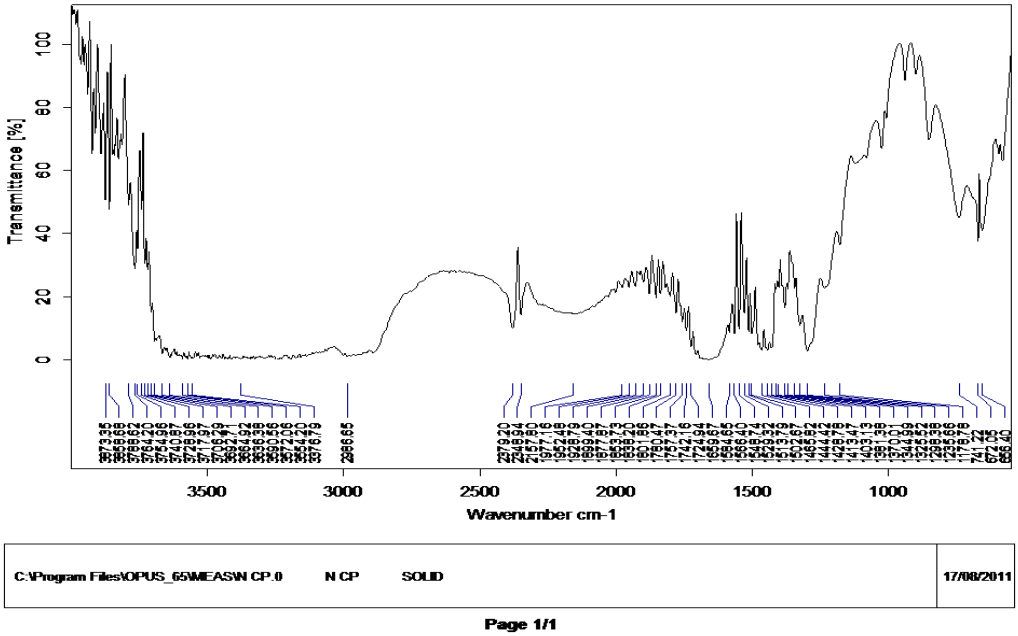


Figure 8: FTIR graph of formulation F3

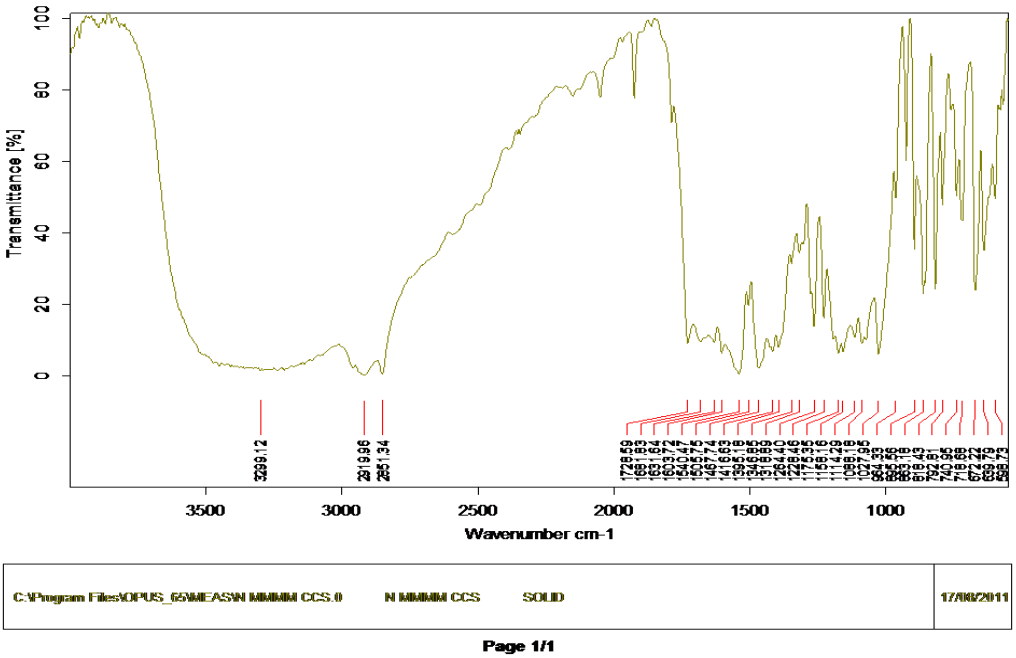


Figure 9: FTIR graph of formulation F6.

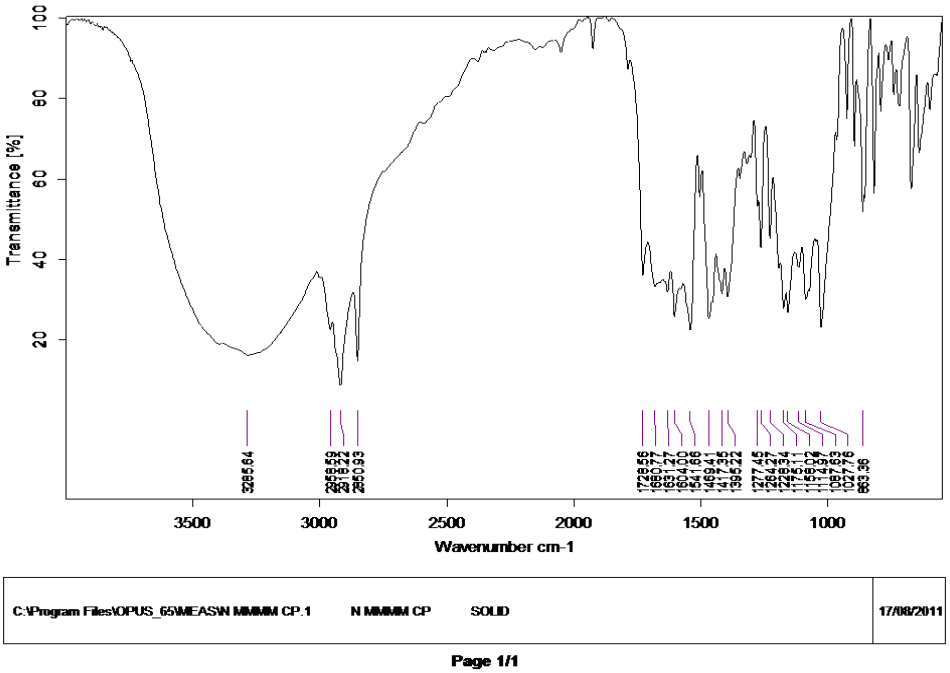


Figure 10: FTIR graph of Formulation F9.

DSC Studies

DSC was performed to characterize thermal changes in the melting behavior of Naproxen with other excipients present in different formulations. Figures 23 and 24 depict thermograms of heat flow versus temperature for Naproxen and F9 formulations in the temperature ranging from 40 to 300^{0}C. The prominent and sharp endothermic peak at 255.6^{0}C (ΔH is -19.6J/g) in the thermogram of pure Naproxen represents its melting point. In all the DSC spectrums the characteristic drug melting point peak was observed. The endothermic

peak corresponding to Naproxen in the thermograms of pure drug, F9 and F15 formulations were found at 255.6^{0}C, 258.2^{0}C and 257.3^{0}C respectively. The minor peak variation in the endothermic peaks of Naproxen formulations might be due to the differences in the moisture contents of the samples as reported by Biliaderis [12]. The results of the DSC studies indicated that Naproxen was compatible with the excipients used in the study.

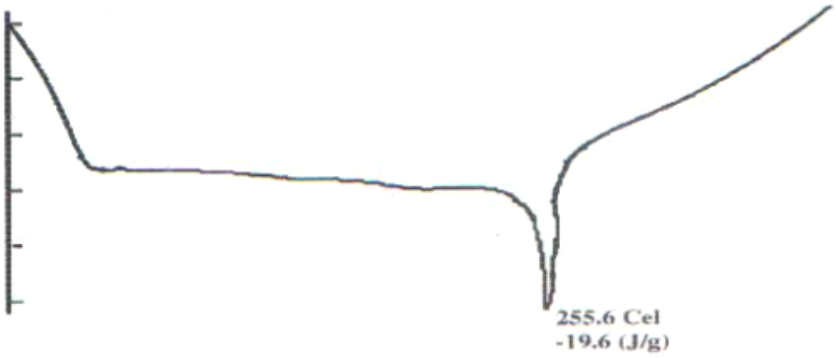


Figure 12: DSC of formulation F9.

Figure 12: DSC of formulation F9.

CONCLUSION

Oral disintegrating tablets of Naproxen were developed by using different disintegrants to avert the problem of swallowing and to provide rapid onset of action, which improves patient compliance and quality of life. The results of this study concluded that superdisintegrants addition technique was an interesting way of formulating oral disintegrating tablets using direct compression technique which is easy, inexpensive and does not require special production equipment.

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