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FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLET OF NAPROXEN SODIUM

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ABSTRACT

Naproxen sodium is an analgesic NSAID (non steroidal anti inflammatory drug) used for the treatment of pain, inflammation, fever and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, juvenile arthritis, gout, migraine and dysmenorrhea. However, the gastric discomfort caused by drug results in poor patient compliance associated with its conventional dosage forms. Hence the present investigation was undertaken with a view to develop orodispersible tablet of naproxen sodium, which offers quick onset of action of drug and minimizes the problem of gastric discomfort associated with it. Thus improves patient compliance, generates rapid response, enhances bio-availability and also reduces the dose of drug. In this study, orodispersible tablets were prepared by direct compression method using three different superdisintegrants e.g. sodium starch glycolate, croscarmellose sodium and crospovidone in three different concentrations e.g. 3%, 5% and 7% along with other excipients. The tablets were evaluated and the results compared for all three superdisintegrants revealed crosspovidone to be the most efficacious superdisintegrant to formulate orodispersible tablet of naproxen sodium as suggested by the dispersion time, disintegration time and drug dissolution profiles.

INTRODUCTION: Oral drug delivery is the most widely accepted route of administration. But conventional oral dosage forms like tablet and capsule bear certain drawbacks such as difficulty in swallowing to pediatric and geriatric patients, need of water for ingestion, adverse interaction of drug with GIT (like gastric degradation, first pass hepatic metabolism of drug), slower onset of action of drug and inconvenience to patients suffering from nausea and vomiting. So as to overwhelm these loopholes of conventional oral dosage forms there is a need of an alternative delivery system that can be an orodispersible tablet (ODT). An ODT is a solid unit pharmaceutical dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. It dissolves rapidly in mouth to provide quick onset of action of drug and overcomes the problems of swallowing. There is no risk of obstruction of this dosage form, which is beneficial to travelling patients who do not have access to water. Pregastric absorption of drugs through ODT avoids first pass hepatic metabolism and gastric degradation, which reduces the dose and increase the bioavailability. Thus, ODT enhances safety and efficacy of drug molecule by being a convenient and more patient compliant dosage form [1, 2, 3].

Naproxen sodium [(+)-(*S*)-2-(6-methoxynaphthalen-2-yl) sodium propanoate] is a NSAID used for the treatment of pain, inflammation, fever and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, juvenile arthritis, gout, migraine and menstrual cramps. As it is an analgesic drug its rapidity of action is a desired feature. Gastric discomfort is one of the major side effects associated with the drug, which can be minimized by formulating its ODT.

The drug having half life of 12-24 h is well absorbed after oral administration achieving peak plasma concentration (C_{max}) within 1 to 2 h after dosing [4]. It has good solubility in water and saliva and inherent ability to permeate through oral mucosal tissue. The drug moiety is a weakly acidic drug, so remains in partially non ionized form at oral cavity's pH, which favors its pregastric absorption. So, all the mentioned traits make the drug ideal candidate for ODT with regards to patient compliance by minimizing its side effects and rapidifying the action.

MATERIALS AND METHODS: Naproxen sodium was obtained as a gift sample from Shreya Life Sciences Pvt. Ltd., Ankleshwar, India. Sodium starch glycolate, Croscarmellose sodium and Crospovidone were the generous gifts from Wockhardt Research Centre, Aurangabad, India. All other chemicals used were of Analytical Reagent grade.

Preformulation study: Micromeritic properties, (like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose) solubility, (in various solvents like water, phosphate buffer pH 6.8, ethanol, methanol and acetone) partition coefficient, LOD, % purity and melting point of drug were determined. Standardization of the drug was carried out using phosphate buffer pH 6.8 by UV spectrophotometer (SHIMADZU 1700, Japan). Identification and authentication of drug by IR, UV and DSC analysis and determination of drug excipient compatibility by IR and DSC studies was done.

Preparation of ODTs by Direct Compression Method: Selection of excipients and optimization of their concentration: ODTs of naproxen sodium were prepared using three different concentrations of three different superdisintegrants and then evaluated for various parameters like hardness, friability, weight variation, drug content uniformity, wetting time, dispersion time, disintegration time and dissolution profile to select the best combination for development of optimized formulation of naproxen sodium ODT. The combination with lowest disintegration time and most rapid and highest percentage cumulative drug release was chosen as the optimized formulation, which was further used for stability study. Table1 shows the composition of different trials, which were undertaken for formulating ODTs.

TABLE 1: FORMULATION OF ODTs

Ingredients	**Quantity (mg)**								
Formulae→	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Naproxen Sodium	120	120	120	120	120	120	120	120	120
SSG	10.8 [3%]	18 [5%]	25.2 [7%]						
CCS				10.8 [3%]	18 [5%]	25.2 [7%]			
CP							10.8 [3%]	18 [5%]	25.2 [7%]
MCC	50	50	50	50	50	50	50	50	50
Mannitol	175.2	168	161	175	168	161	175	168	161
Talc	1	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Silicon dioxide	1	1	1	1	1	1	1	1	1
Flavor	1	1	1	1	1	1	1	1	1
Total	**360**	**360**	**360**	**360**	**360**	**360**	**360**	**360**	**360**

In this method, drug was mixed with suitable portion of superdisintegrant properly. Then, microcrystalline cellulose (MCC) was added and mixed thoroughly. This was followed by addition of diluent. Then, the whole mixture was passed through sieve no. 44. Magnesium stearate, talc, colloidal silicon dioxide and flavoring

agent were then blended with the sieved mixture. Finally the mixture was subjected to compression using single punch tablet compression machine [5].

Evaluation of ODTs:

Hardness: Hardness is the force required to break a tablet in a diametric compression test. It was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Friability: Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed sample of ten tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not loose more than 1% of their weight. The friability (F) is calculated by the following formula-

$$F = \frac{Wt_{initial} - Wt_{final}}{Wt_{initial}} \times 100$$

Weight Variation Test: Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average.

Disintegration Time: The time required for disintegration of six ODTs, placed in each tube of basket rack assembly of disintegration test apparatus running at a speed of 28-32 cpm, was measured using distill water maintained at 37 ± 2 ^{0}C. [6].

Dispersion Time: An ODT was added to 10 ml of PBS (pH=6.8; simulated saliva fluid) at 37 ± 0.5 ^{0}C. Time required for complete dispersion of a tablet was measured.

Wetting Time: Five circular tissue papers of 10 cm diameter were placed in a small Petridish (ID = 10 cm) containing 10 ml of PBS (pH = 6.8). A tablet was put on the surface of the paper and the time required for buffer to reach upper surface of the tablet was noted as the wetting time [1].

Drug content uniformity: Five tablets were powdered and the blend equivalent to 120 mg of drug was weighed and dissolved in suitable quantity of PBS (pH= 6.8). The solution was then filtered and diluted suitably. The drug content was then analyzed spectrophotometrically at 272 nm [7]

***In-vitro* dissolution Study:** Dissolution study of samples was performed using USP type II apparatus in phosphate buffer pH = 6.8 (simulated salivary fluid). The temperature was maintained at 37±0.5°C and the rotation speed was 50 rpm. The samples were withdrawn at uniform time intervals of 2 minutes and analyzed spectrophotometrically at 272 nm. [3].

Stability Study: Stability study of optimized formulation was carried out to determine the effect of formulation additives on stability of drug and also to determine physical stability of formulation under specified storage conditions. Stability study was conducted by storing ODTs at temperature 40 ^{0}C ± 2 ^{0}C/75% ± 5% relative humidity for three months. The dissolution, drug content and disintegration behaviors of ODTs were tested after each month. Tablet from each batch was individually weighed and wrapped in an aluminium foil and packed in black bottle and kept at above specified conditions in a heating humidity chamber for three months. After each month, tablet sample was analyzed for drug content, dissolution and disintegration time [8].

RESULT AND DISCUSSION: The results of preformulation study indicated that the drug was of acceptable standards with 99.12% purity. Micromeritic properties like bulk density and tapped density of drug were found to be 470.588 mg/ml. and 615.384 mg/ml respectively. Angle of repose of drug was found to be 33.424^o; Carr's index and Hausner's ratio were found to be 23.529 % and 1.3076 respectively. All the three values indicate passable flow property of drug sample. Solubility analysis of drug was performed in solvents like distill water, phosphate buffer (pH=6.8), methanol, ethanol and acetone. The drug was found to be soluble in all the solvents except acetone, with highest solubility in distill water. This shows hydrophilic nature of drug. Partition coefficient of drug was determined

by using octanol: water system. It was found to be 0.174, indicating that the drug has been partitioned more in aqueous phase. Thus drug was found to be hydrophilic in nature. LOD of drug was found to be 0.80 %, which exists within acceptable limit that is loss should not be more than 1% of its weight [10]. Standardization of the drug was carried out using phosphate buffer pH 6.8 by UV spectrophotometer (SHIMADZU 1700, Japan).

U.V. spectrum of drug sample in methanol (scanned in range of 200-400nm) showed absorption maxima at 272 nm, which was found to comply with the prescribed value of absorption maxima for naproxen sodium [10]. Thus, drug sample was indicated to be authentic and devoid of impurities by U.V. analysis (**fig. 1**).

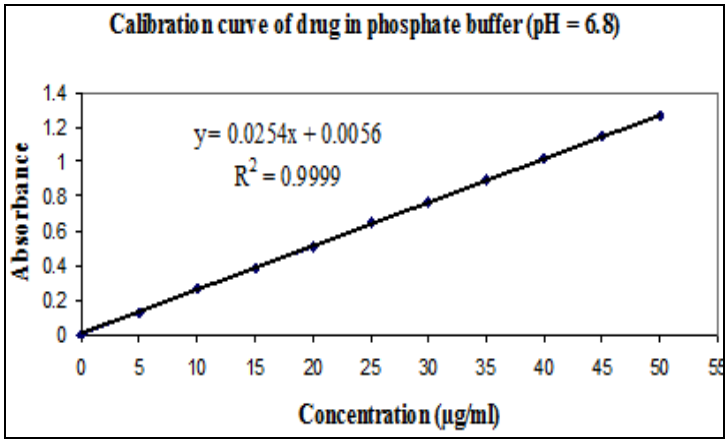

FIG. 1: CALIBRATION CURVE OF DRUG IN PHOSPHATE BUFFER (pH = 6.8).

IR identification analysis of drug sample was done. The sample drug IR spectrum bands (**Fig. 2**) matched with that reported for pure naproxen sodium.

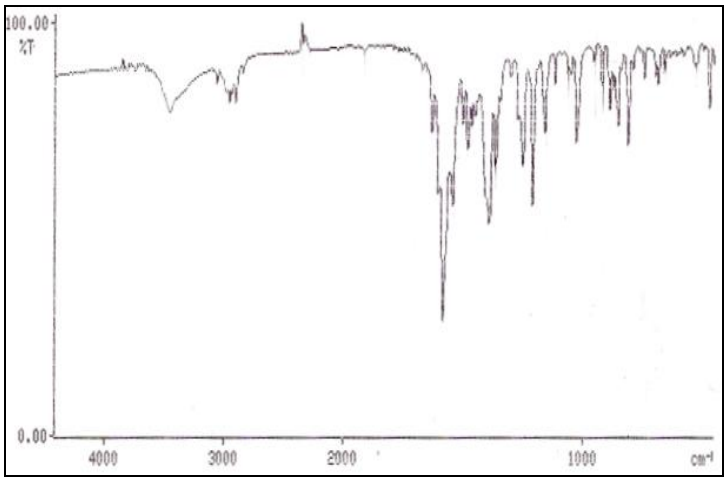

FIG. 2: IR SPECTRUM OF PURE DRUG

The drug sample showed characteristic functional group peaks at 1244 cm^{-1} due to C-O stretching (acid), 1586.02 cm^{-1} due to COO- stretching, 1641.31 cm^{-1} due to C-C aromatic skeletal stretching, 2835.16 cm^{-1} due to C-H aliphatic stretch. IR characteristics mentioned for sample drug were found to be in compliance with that reported for pure naproxen sodium.

DSC identification analysis of drug sample was done. DSC thermogram of drug (**Fig. 3**) depicts the prominent and sharp endothermic peak at 255.05°C, which represents melting point of drug and complies with the reported value of it for naproxen sodium. Thus, sample was authentified and identified as naproxen sodium.

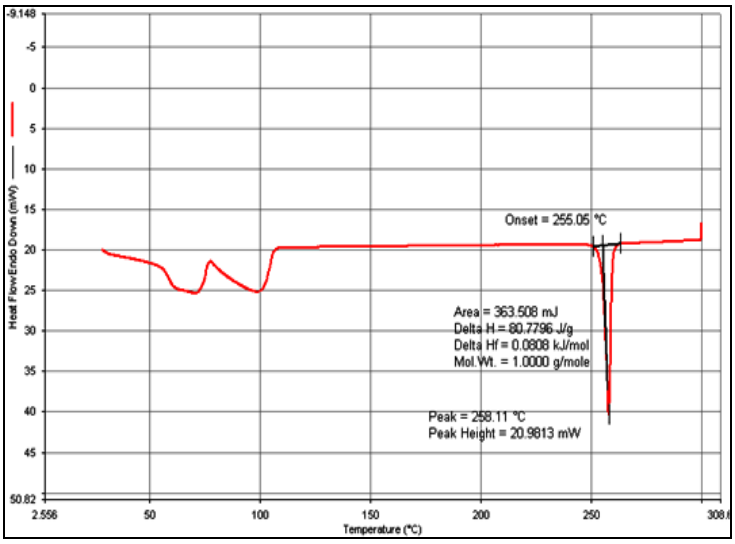

FIG. 3: DSC THERMOGRAM OF PURE DRUG

Drug excipient compatibility study was performed by IR and DSC analytical techniques. IR spectrum of drug-excipients (three superdisintegrants) combination sample **[Fig 4(a)]** showed characteristic functional group peaks as reported for naproxen sodium.

DSC thermogram of combination sample **[Fig. 5(a)]** exhibited an endothermic peak in the range of 255-257°C, which encloses the value of melting point reported for naproxen sodium. This shows no change in drug moiety and also its compatibility with excipients. The DSC thermogram of drug and excipients combination sample shows the suppression of endothermic peak, which is due to the dehydration of drug at high temperature during DSC analysis. **Figure 4(b) and 5(b)** are the IR spectrum and DSC thermogram of naproxen sodium respectively.

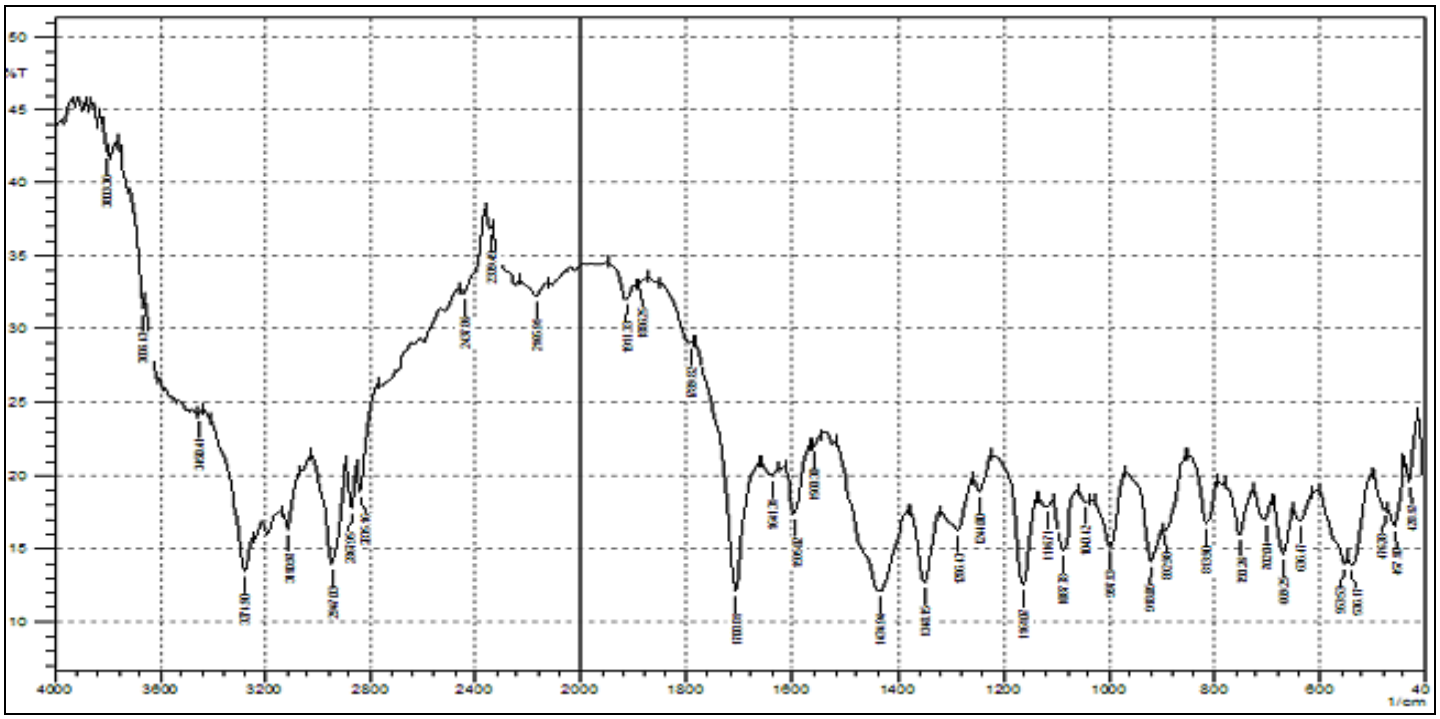

FIG. 4(A): IR SPECTRUM OF DRUG + CROSCARMELLOSE SODIUM (CCS) + SODIUM STARCH GLYCOLATE (SSG) + CROSPOVIDONE (CP)

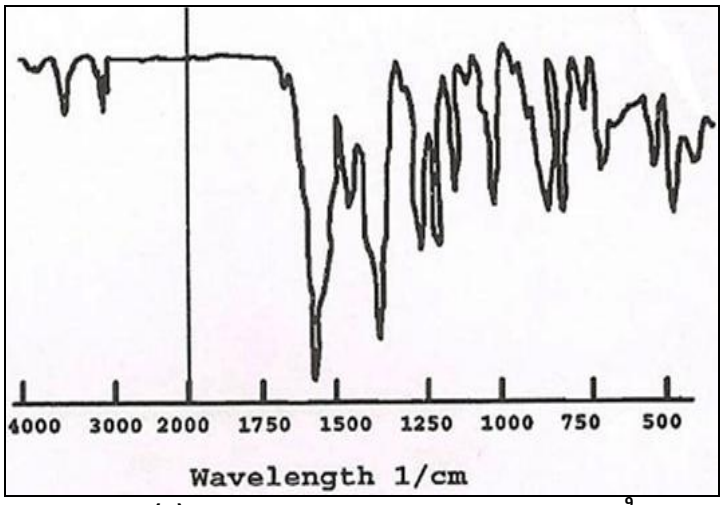

FIG. 4(B): IR SPECTRUM OF NAPROXEN SODIUM [9]

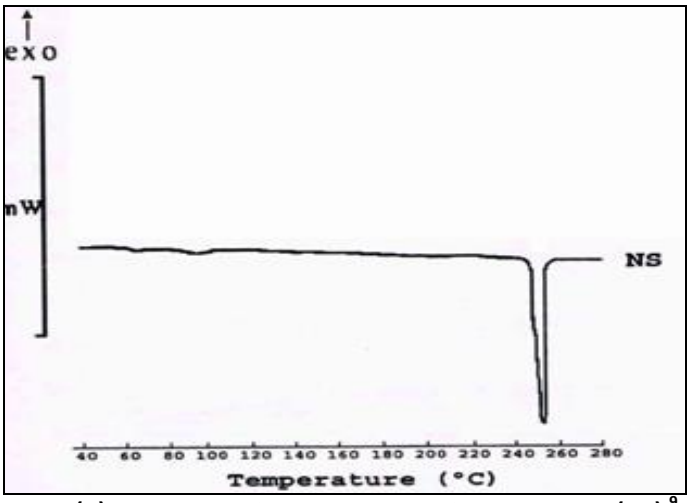

FIG. 5(B): DSC THERMOGRAM OF NAPROXEN SODIUM (NS) [9]

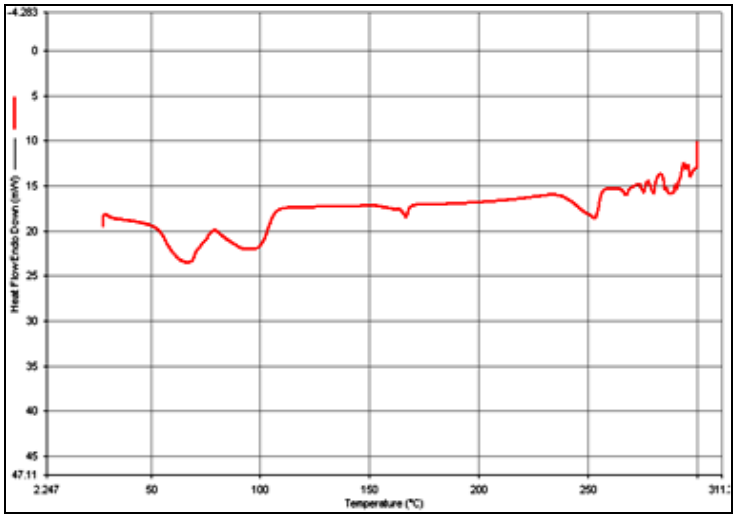

FIGURE 5(A): DSC THERMOGRAM OF DRUG + CCS + SSG + CP

For the preparation of ODTs of naproxen sodium, formulae were suitably designed by selecting appropriate ingredients in appropriate concentrations and the concentrations of superdisintegrants were optimized thereafter. Formulations F1-F9 were prepared to achieve an optimized concentration of a single superdisintegrant and the most efficacious one among the three superdisintegrants incorporated to prepare ODTs as shown by the **table 1**. Among the formulations containing SSG (F1-F3), F1 exhibited the lowest wetting time, dispersion time, disintegration time and highest % cumulative drug release as revealed by **table 2 and 3**. This might be due to the reason that SSG swells in 3D and at higher levels serve

as sustain release matrix. Therefore, as the concentration of SSG increases from 3% to 5%, wetting time, dispersion time, disintegration time extends beyond 1 minute and a decline in drug release is seen. Among the formulations containing CCS (F4-F6), F5 exhibited lowest dispersion time, disintegration time and highest % cumulative drug release. Among the formulations containing CP (F7-F9), F9 depicted lowest dispersion time, disintegration time and highest % cumulative drug release. Thus the optimized concentrations of superdisintegrants were found to be 3% SSG, 5% CCS and 7% CP. On the whole, among the 3 superdisintegrants, CP came out to be the most efficacious superdisintegrant to prepare ODT of naproxen sodium as indicated by **fig. 9**, which exhibits the dissolution profiles of optimized concentration of each superdisintegrant. This might be attributed to the low swelling efficiency, high water uptake capacity and spongy nature of CP, which yield porous tablets that disintegrate in fractions of second. While CCS swells in 2D to about 4-8 folds in less than 10 seconds and SSG swells in 3D to about 7-12 folds in less than 30 seconds. The results of all evaluation tests have been depicted in **table 2 and 3**, indicating the successful development of ODT of naproxen sodium by direct compression method using superdisintegrants. **Figures 6, 7 and 8,** exhibit dissolution profiles of formulations F1-F3, F4-F6, F7-F9 respectively.

TABLE 2: EVALUATION PARAMETERS OF PREPARED ODTS

Evaluation Parameters							
Formulations	**Hardness (Kg/cm^2)**	**Friability (%)**	**Weight variation**	**Wetting time (sec)**	**Dispersion time (sec)**	**Disintegration time (sec)**	**Drug content uniformity (%)**
F1	3.1 ± 0.1	0.828 ± 0.017	Pass	58.81 ± 0.62	53.72 ± 1.52	49.78 ± 1.47	97.88 ± 0.477
F2	3.0 ± 0.2	0.839 ± 0.022	Pass	84.44 ± 2.16	70.02 ± 1.91	58.98 ± 2.08	96.25 ± 0.499
F3	3.1 ± 0.26	0.825 ± 0.025	Pass	127.75 ± 4.91	104.24 ± 4.18	83.43 ± 3.83	98.01 ± 0.570
F4	3.06 ± 0.15	0.832 ± 0.018	Pass	55.58 ± 2.5	48.68 ± 2.75	41.21 ± 2.30	96.50 ± 0.550
F5	3.2 ± 0.1	0.805 ± 0.026	Pass	41.9 ± 1.51	38.26 ± 0.32	35.31 ± 0.63	99.27 ± 0.515
F6	3.13 ± 0.05	0.823 ± 0.036	Pass	50.31 ± 1.78	43.45 ± 2.02	38.55 ± 2.43	97.48 ± 0.496
F7	3.1 ± 0.2	0.825 ± 0.038	Pass	41.25 ± 2.62	33.97 ± 0.25	29.30 ± 1.31	97.12 ± 0.539
F8	3.0 ± 0.17	0.843 ± 0.027	Pass	34.56 ± 1.9	30.39 ± 2.18	76.98 ± 2.12	95.33 ± 0.477
F9	3.15 ± 0.05	0.822 ± 0.03	Pass	25.85 ± 0.92	23.35 ± 0.55	21.50 ± 1.81	98.79 ± 0.488

SD ± (n = 3)

TABLE 3: DISSOLUTION PROFILE OF PREPARED ODTS

Time (min)	% Cumulative drug release of different formulations								
	Formulations incorporating SSG as superdisintegrant			Formulations incorporating CCS as superdisintegrant			Formulations incorporating CP as superdisintegrant		
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
2	15.078±3.691	16.456±1.037	13.405±1.772	51.594±3.691	70.393±2.657	63.208±4.727	79.251±2.657	83.287±3.842	85.354±2.806
4	59.074±1.920	60.550±4.577	55.137±2.806	78.365±2.229	89.192±1.037	81.712±1.626	95.393±3.842	96.574±2.972	98.542±1.036
6	77.676±0.743	72.263±3.396	62.617±6.498	97.460±0.742	98.346±0.742	97.854±0.886	98.444±1.352	99.034±0.781	99.527±0.681
8	96.771±1.193	83.779±1.921	74.330±1.037	-	-	-	-	-	-
10	-	93.326±3.397	89.782±1.921	-	-	-	-	-	-

SD ± (n = 3)

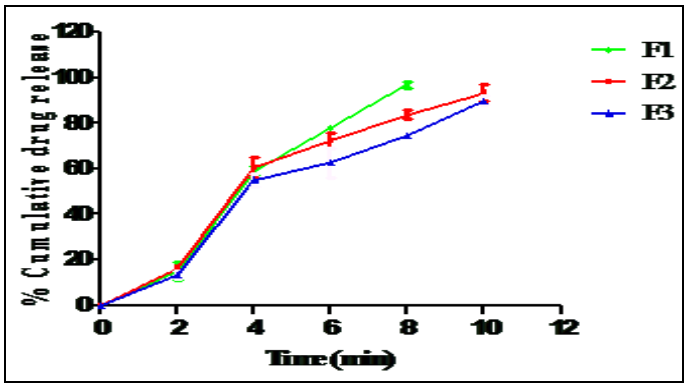

FIG. 6: DISSOLUTION PROFILES OF ODTS (F1, F2, F3)

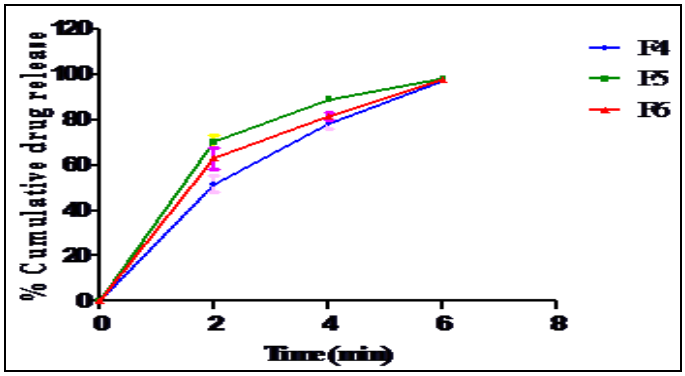

FIG. 7: DISSOLUTION PROFILES OF ODTS (F4, F5, F6)

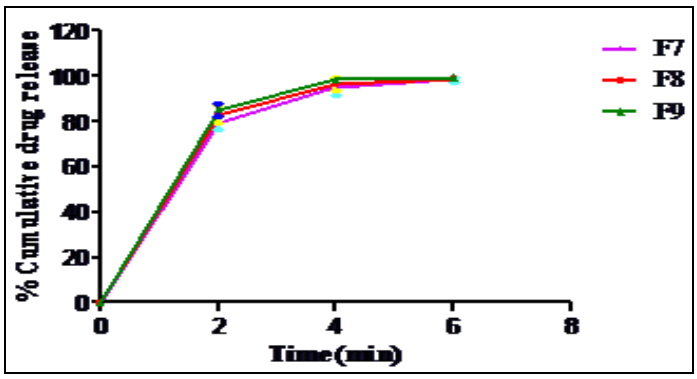

FIG. 8: DISSOLUTION PROFILES OF ODTS (F7, F8, F9)

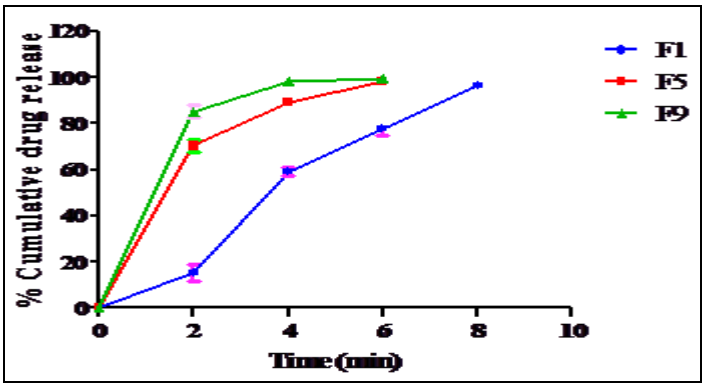

FIG. 9: DISSOLUTION PROFILES OF ODTS (F1, F5, F9)

The rapid drug release profile of ODT and pregastric absorption favoring characteristics of drug suggest generation of rapid response and minimization of gastric discomfort caused by the drug. Thus ODT of naproxen sodium appears to be more patient compliant alternative over commercially available conventional dosage forms of drug. On the basis of all the evaluation parameters formulation F9 came out to be the optimized formulation, which was further subjected to the stability study.

Stability study of optimized formulation (CP 7% ODT) was conducted for three months. The dissolution, drug content and disintegration behaviors of ODTs were tested after each month and the values of these evaluation parameters have been mentioned in **Table 4, figure 10 and 11** respectively. No significant change was found on comparing the values of evaluation parameters before and after the stability study. Thus, formulation was indicated to be stable.

Table 4: Stability study data of dissolution profile of optimized formulation

Optimized formulation	After 1 month		After 2 month		After 3 month	
	Time (min)	% Cumulative drug release	Time (min)	% Cumulative drug release	Time (min)	% Cumulative drug release
F9 (7% CP ODT)	0	0	0	0	0	0
	2	85.551 ± 2.867	2	85.255 ± 2.580	2	85.058 ± 2.545
	4	97.952 ± 0.451	4	97.853 ± 0.781	4	97.755 ± 0.451
	6	99.232 ± 0.614	6	99.133 ± 0.450	6	98.838 ± 0.451

SD ± (n = 3)

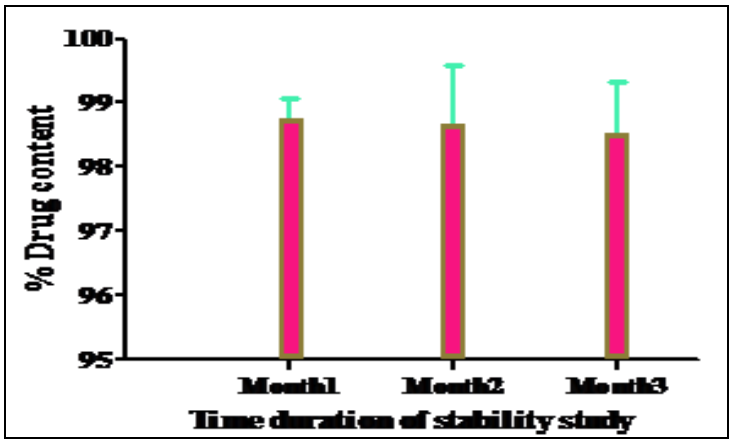

FIG. 10: STABILITY STUDY DATA OF DRUG CONTENT UNIFORMITY OF OPTIMIZED FORMULATION

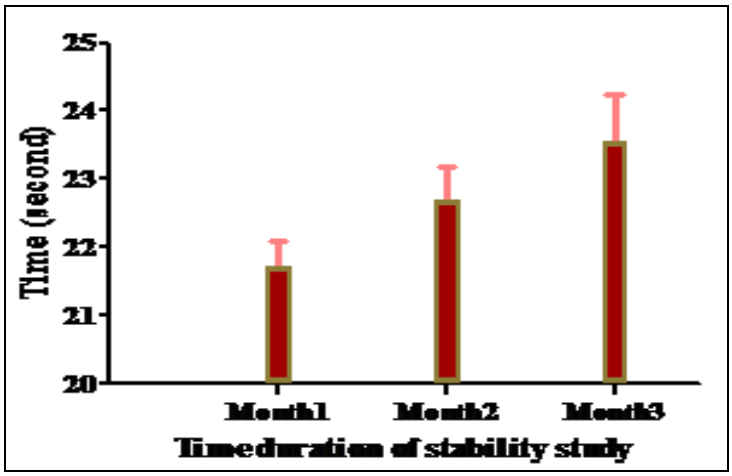

FIG. 11: STABILITY STUDY DATA OF DISINTEGRATION TIME OF OPTIMIZED FORMULATION

CONCLUSION: The present investigation successfully formulated orodispersible tablet of naproxen sodium with impressive drug release profile. Three different superdisintegrants in three different concentrations were incorporated to formulate ODTs. The results of evaluation parameters conclude that SSG at 3%, CCS at 5% and CP at 7% concentration were found to generate efficacious ODTs and comparatively among above mentioned superdisintegrants, CP at 7% concentration was found to be the most suitable. Thus ODT of naproxen sodium can be prepared by direct compression using superdisintegrants and can be regarded as novel and more patient compliant alternative over conventional dosage forms of drug available commercially in the market.

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