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DEVELOPMENT OF RAPIDLY DISINTEGRATING NAPROXEN TABLETS BY HOLE TECHNOLOGY

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ABSTRACT

The conventional dosage form like tablet and capsule has wide acceptance. Research has done to prepare Naproxen fast dissolving tablets of Naproxen by Hole Technology. Once these fast- dissolving tablets contact with gastro intestinal fluids, the fluid can enter the hole within the tablet and immediate disintegration of tablets will takes place. Fast dissolving tablets of Naproxen was designed with a view to provide a quick onset of action. Here fast dissolving tablets were prepared by direct compression by using super disintegrates such as Sodium Starch Glycolate and Croscarmellose Sodium etc. This quick disintegration of tablets is additionally influenced by the formation of latest absolute space. The ready FTDs were subjected to numerous pre and post formulation studies. Its disintegration and dissolution rates were compared. Evaluation parameters like hardness and friability indicates that the tablets were mechanically stable in all formulations. Among the four formulations, F3 exhibited the highest drug release 98.29% in 30 minutes and was identified as the optimum formulation. The findings confirm that Hole Technology is an effective approach to increase tablet porosity, thereby improving drug solubility and dissolution. Naproxen fast dissolving tablets prepared by hole technology using camphor as a sublimating agent shows excellent drug release from the tablet so it shows that this method increases the porosity of the tablet and it is the one of the best methods used for the preparation of fast dissolving tablets.

KEYWORDS: Fast Dissolving Tablets, Naproxen, Sodium Starch Glycolate, Croscarmellose Sodium, Hole technology.

INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to its convenience, cost-effectiveness, and high patient compliance. The conventional dosage form like tablet and capsule has wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today due to high patient compliance, cost-effectiveness, less sterility constraints, flexibility in the design of dosage form, ease of production and it can be delivered in accurate dose. However, conventional oral dosage forms such as tablets and capsules often present challenges for pediatric, geriatric, and dysphagic patients who have difficulty swallowing solid dosage forms.[1] Some of the drugs administered through oral route have several limitations such as low aqueous solubility, limited targeting ability, low bioavailability and short retention time in gastrointestinal tract which lowers the therapeutic efficacy of the drug. To overcome these problems many advancements in oral drug delivery system are developed, one such technique is Fast Drug Delivery System (FDDS). Fast Dissolving Tablets (FDTs) have emerged as an innovative drug delivery system, designed to disintegrate rapidly in the oral cavity without the need for water, thereby improving patient adherence and therapeutic outcomes.[2, 3]

The faster the drug goes into the solution, quicker the absorption and onset of therapeutic action. The target population of these fast-dissolving forms have generally been pediatric, elderly who have difficulty in swallowing, preferred also in case of sudden unbearable acute pain and bedridden or disabled patients. Patients with persistent nausea, who are travelling or who have

no access to water are also good candidates for FDTs.[4] In the present study an attempt has been made to increase the solubility and formulation into rapid disintegrating tablets using Hole Technology. This technology is a novel approach to decrease the disintegration time and increase the patient compliance. The main principle involved in hole technology is sublimation. By using this technology absolute surface area of the tablet increases due to hole formation. Immediate breaking of the tablet takes place due to the fluid enters into the hole formed in the tablet. The tablets prepared with hole technology showed all the parameters like hardness, friability, weight variation within the limits.[5,6] Several technologies were developed to enhance the disintegration time but the tablets prepared by hole technology have increased surface area due to formation of hole and increased pore structure. It has been also shown to improve pharmaceutical properties like bioavailability, stability even palatability without affecting their intrinsic lipophilicity or pharmacological activity.[6]

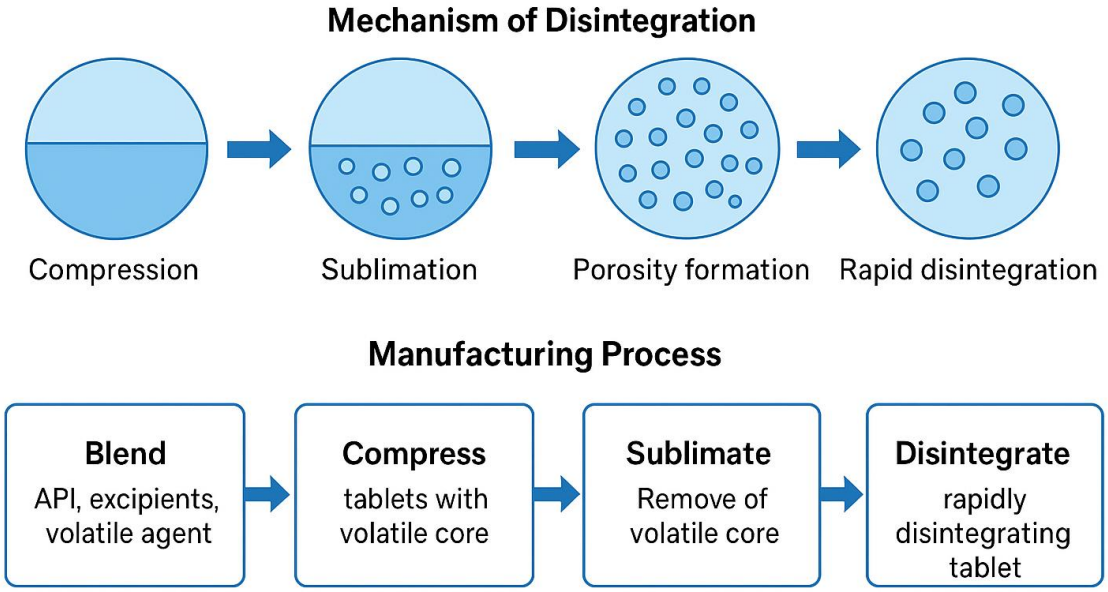

Fig. 01: Mechanism formulation and Disintegration.[5]

Naproxen is a member of propionic acid derivative related to the aryl acetic acid group of nonsteroidal 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. It is considered as the first-line treatment to treat acute pain, menstrual cramps (dysmenorrhea), acute gouty arthritis, inflammation, musculoskeletal pain, tendonitis and pain related to rheumatoid arthritis etc. Naproxen exerts its therapeutic effects by inhibiting the cyclo-oxygenase (COX) isoenzymes, COX-1 and COX-2 that catalyzes the first step in the synthesis of prostaglandins from arachidonic acid and other precursor fatty acids. Furthermore, the naproxen drug belongs to BCS class II i.e., drug having low solubility and high permeability. Hence, naproxen tablets can be formulated using novel hole technology. [7-10] In this study, an attempt has been made to enhance the solubility and disintegration rate of Naproxen tablets using Hole Technology. The formulated tablets are evaluated for key pharmaceutical properties to determine their suitability for rapid therapeutic action.

MATERIALS AND METHODS

Materials

Drug: Naproxen, Super disintegrants: Croscarmellose sodium, sodium starch glycolate, Filler: Lactose, mannitol, talc, magnesium stearate, Sublimating agent: Camphor

Methods

Preceding to dosage form development, pre-formulation studies of drug molecules conducted

Organoleptic properties: The colour, odour of Naproxen was recorded using descriptive terminologies.

Determination of λ_{max} of Naproxen in PBS pH 6.8 and Determination of Standard Curve of Naproxen[9]

The standard solution of Naproxen was scanned in the wavelength region of 200 - 400 nm. A stock solution of Naproxen was prepared by dissolving 100mg of drug in phosphate buffer pH 6.8 and final volume was made up to 100 ml (stock A). From stock A take 10 ml and final volume was made up to 100 ml with pH 6.8 phosphate buffer to make a concentration of 100 mg/ml (stock B). From this prepare 10, 20, 30, 40, 50 µg/ml dilutions. Standard calibration curve was plotted by taking absorbance vs concentration of solutions.

Derived properties of granules Angle of repose, Bulk Density, Tap density, Carr's index or % compressibility, Hausner's Ratio were determined.[11,12]

Preparation of FDTs by Hole Technology[5, 6, 13]

Accurately weighed quantities of Naproxen**,** Sodium Starch Glycolate**,** Croscarmellose Sodium**,** Lactose**,** and Mannitol were mixed uniformly in a clean dry container. Separately, plain camphor tablets (100 mg) were prepared by compressing camphor granules using direct compression. Talc and Magnesium Stearate, previously passed through sieve #60, were then added to the initial blend and thoroughly mixed to ensure uniform lubrication. During final compression, a portion of the prepared blend was placed into the die cavity, followed by placing the pre-compressed camphor tablet at the centre. The remaining blend was then added, and the contents were compressed to form the final Naproxen tablets containing a camphor tablet within (i.e., tablet-in-tablet structure). Post-compression, these tablets were placed in a hot air oven at 60°C until complete sublimation of camphor occurred. The removal of camphor resulted in the formation of a hole on the tablets, thereby increasing the porosity and surface area.

Fig. 2: Prepared tablets of Naproxen.

Table No. 1: Formulation chart for tablet.

Ingredients (mg)	F1	F2	F3	F4
Naproxen	250	250	250	250
Croscarmellose Sodium	8	16	-	-
Sodium Starch Glycolate	-	-	8	16
Lactose	46	46	46	46
Mannitol	92	84	92	84
Talc	2	2	2	2
Magnesium stearate	2	4	4	4
Camphor	100	100	100	100
Total	500	500	500	500

Post Formulation studies[13-22]

Weight variation: 20 tablets were selected randomly and weighted individually to check for weight variation. Weight variation specification as per I.P is shown in Table No. 2

Table No. 2: Weight Variation Specification as per IP.

Average Weight of Tablet	% Deviation
80 mg or less	±10
80 - 250 mg	±7.5
250 mg or more	±5

Hardness: Hardness or tablet crushing strength. The force required to break a tablet in a diametric direction was measured using digital portable tablet hardness tester. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded.

Thickness: The thickness of six tablets was measured using Venire calipers. The extent to which the thickness of each tablet deviated from ±0.2 mm of the standard value was determined. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded.

Friability (F): Friability of the tablet determined using Friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dedusted and reweighed. The friability (F) is given by the formula.

F = (W initial - W final / W initial) x 100

Disintegration Test: The disintegration time was determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus and disc was added to each tube. The bath temperature-maintained 37±2°C. The time taken for the complete disintegration of the tablet with no palpable mass remaining in the basket was measured and recorded.

Dissolution Test: USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm. 6.8 Ph Phosphate buffer (500 ml) was used as a dissolution medium. Determination of amount of drug dissolved form tablets was carried by UV spectrophotometer at 238.8 nm. *In-Vitro* drug release studies details:

Table No. 3: Dissolution Parameters.

Apparatus used	USP II dissolution test apparatus
Dissolution medium	6.8 pH phosphate buffer
Dissolution medium volume	900 ml
Temperature	37±0.5℃
Speed of basket paddle	50 rpm
Sample withdrawn	5 ml
Absorbance measured	238.8 nm

RESULTS AND DISCUSSIONS

Pre-formulation Studies of Naproxen: The pre-formulation studies Table No 4 confirmed that Naproxen met the reported literature limits, indicating its suitability for direct formulation without the need for any modification.

Table No. 4: Organoleptic properties of Naproxen.

Properties	Reported	Result
State	Crystalline	Crystalline
Odor	Odorless	Odorless
Color	White to off-white	White
Melting Point	152-158℃	153.82℃
Taste	Bitter	Bitter
Solubility	Water- soluble Ether - soluble	Water-soluble Ether-soluble

Determination of λ_{max} of Naproxen in PBS pH 6.8

The spectrum of Naproxen (10 µg/ml) in buffer (pH 6.8) showed the peak at 238.8 nm. The absorption maxima (λ_{max}) of 238.8 nm was selected for the present study.

Determination of Standard Curve of Naproxen

The standard plot of Naproxen was obtained in the range of 10 to 50 µg/ml at the wavelength of 238.8 nm Table No 5 and Fig 3. It has shown good linearity with regression coefficient of 0.9994 (R^2 Value).

Table No. 5: Calibration data of Naproxen at 238.8 nm in PBs pH 6.8

Concentration (µg/ml)	Absorbance
0	0.000
10	0.072±0.008
20	0.140±0.011
30	0.213±0.007
40	0.282±0.013
50	0.363±0.010

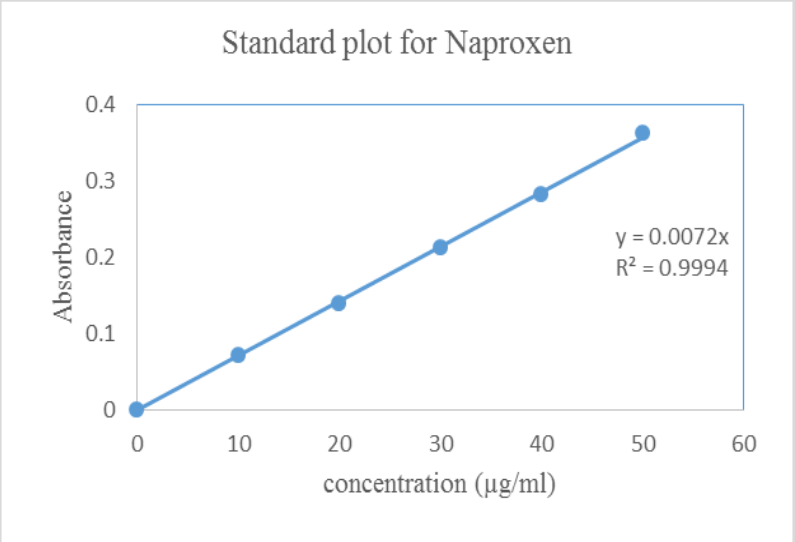

Fig. 3: Standard plot for Naproxen at 238.8 nm.

Results of Derived properties of granules: Angle of repose, Bulk Density, Tap density, Carr's index or % compressibility, Hausner's Ratio were determined.

Table No. 6: Angle of repose, Bulk density, Tapped density, %Compressibility & Hausner ratio:

Formulation	Θ=Tan^{-1} h/r	Bulk Density (g/ml)	Tapped Density (g/ml)	% Compressibility	Hausner Ratio
F1	35.4 °	0.524	0.729	27.9%	1.391
F2	32.6 °	0.521	0.728	28.40%	1.397
F3	30.9 °	0.524	0.726	27.8%	1.385
F4	33.8 °	0.526	0.725	27.4%	1.378

Post Formulation Studies

Table No. 7: Weight variation, Hardness, Thickness and Friability.

Formulation	Weight Variation (mg) Avg.±%	Hardness (kg/cm^2)	Thickness (mm)	Friability (%w/w)
F1	499.5±0.023	3.0	4.31	0.62
F2	498.3±0.014	3.4	4.34	0.74
F3	498.8±0.019	3.2	4.28	0.84
F4	497.9±0.038	3.5	4.26	0.86

Disintegration Test

Table No 8: Disintegration Test.

Formulation Code	Disintegration Time (sec)
F1	113
F2	97
F3	70
F4	86

All the formulations showed disintegration within 86 to 113 sec. As shown in the Table No.08. Formulation F3 showed best disintegration time 70 sec.

Dissolution Studies

Table No. 09: Dissolution study data.

Sl. No	Time (min)	% Cumulative Drug Release			
Formulation		F1	F2	F3	F4
1	0	0	0	0	0
2	5	14.01±0.21	12.03±0.36	12.05±0.89	10.02±0.23
3	10	26.13±0.32	34.56±0.41	20.03±0.48	24.05±0.86
4	15	32.18±0.15	46.27±0.22	37.04±0.11	36.72±0.54
5	20	43.06±0.22	58.97±0.53	54.23±0.73	53.19±0.77
6	25	56.04±0.61	81.73±0.80	76.46±0.55	72.65±0.83
7	30	59.18±0.69	92.48±0.47	98.29±0.92	94.45±0.60

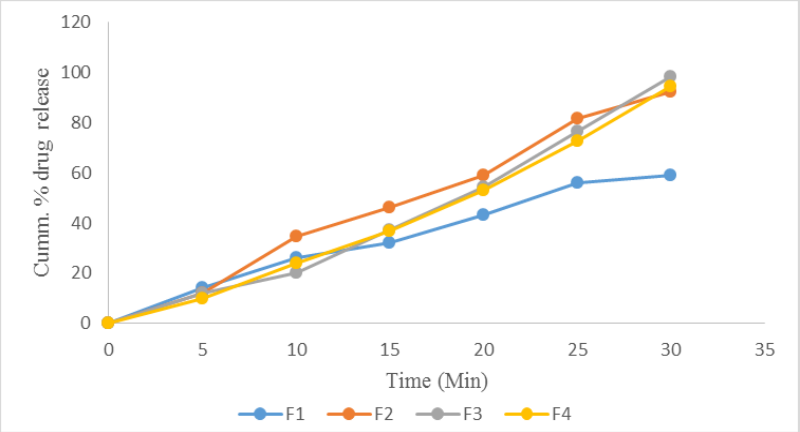

Fig. 04: *In-vitro* drug release study.

From the dissolution studies, it was observed that the release rate of drug from tablets varied. Table No. 9 and Fig no. 04 shows cumulative percentage drug release from formulation F1, F2, F3, F4 containing different concentration of super disintegrants at the end of 30 min was found to be 59.18%, 92.48%, 98.29%, 94.45%

respectively. In-vitro release studies showed that F3 shows better release compared to other formulation. Overall, the results confirm that Hole Technology, combined with the use of suitable superdisintegrants, significantly improves the disintegration and dissolution characteristics of poorly soluble drugs like Naproxen. The method offers a simple, cost-effective, and scalable approach for developing FDTs, and the optimized formulation (F3) could potentially lead to better therapeutic outcomes by providing faster onset of action and improved patient compliance.

CONCLUSION

The present study successfully demonstrated the formulation and evaluation of fast dissolving tablets of Naproxen using Hole Technology with camphor as a sublimating agent. Pre-formulation studies confirmed compliance with reported literature limits, and compatibility studies established no interaction between Naproxen and the selected excipients. The incorporation of camphor and superdisintegrants significantly enhanced the disintegration and dissolution rates of the poorly soluble drug. All formulations met pharmacopeial standards for hardness, friability, weight variation, and disintegration time. Among the four formulations, F3 exhibited the highest drug release (98.29% in 30 minutes) and was identified as the optimum formulation. The findings confirm that Hole Technology is an effective approach to increase tablet porosity, thereby improving drug solubility, dissolution, and overall performance in fast dissolving dosage forms.

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CONFLICT OF INTEREST: None

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