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Formulation and Evaluation of Mouth Dissolving Tablets of Naproxen Sodium

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Abstract

Naproxen sodium is an analgesic NSAIDs (Non Steroidal Anti-Inflammatory Drugs) 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. So the rational of this investigation was to develop mouth dissolving tablets of Naproxen sodium using various polymers which offers quick onset of action of drug and minimizes the problem of gastric discomfort associated with it. Thus improves patient's compliance, generates rapid response, enhances bio-availability and also reduce the dose of drug. Mouth dissolving tablets of naproxen sodium were prepared from wet granulation method. The tablets were evaluated for thickness, friability, hardness, weight variation, wetting time, disintegrating time and in vitro dissolution studies.

Keywords: Naproxen, NSAIDs, Mouth dissolving, bio-availability

Introduction

For the past one decade, there has been an enhanced demand for more patient friendly and compliant dosage form. As a result, the demand of developing of new technologies has been increasingly annually.[1]Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden and patient who do not have easy access to water. The benefits in terms of terms of patient compliance, rapid onset of action, increased bio-availability and good stability make these tablets popular as a dosage form of choice in the current scienario.[2-3] The fundamental principle used in the development of the fast dissolving tablet is to maximize its pore structure. Researchers have evaluated spay-dried materials[4] and plastic materials[5] for development of such tablets. Vacuum drying[6-11] and freeze drying techniques[12] have been tried by researchers to maximize the pore structure of the tablet matrix. Therefore, a wet granulation technique was adopted in the present investigation after addition of a sublimating agent to increase porosity of the tablets. It is likely that s porous hydrophilic matrix will be easily picked up the disintegrating and breaks quickly. In the present, an attempt was to made to develop mouth dissolving tablets of Naproxen sodium and to investigate the effect of subliming agent on the release profile of drug.

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Material 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 gift sample from Wockhardt Research Centre, Aurangabad, India. All other chemicals used were of Analytical grade.

Preformulation study: Micromeritic properties (like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose), solubility and melting point of the drug were determined. Standardization of the drug was carried out using phosphate buffer pH 6.8 by UV spectrophotometer. Identification and authentication of drug were done by IR and UV Spectroscopy.

Preparation of Mouth Dissolving tablets of Naproxen sodium by sublimating agent: This technique involves the incorporation of a salt which is of volatile nature to the components of the tablet followed by their mixing together to form a mixture which is homogenous. Then, the volatile salt is volatilized to create pores in the structure of tablet. As a result, the tablet thus formed undergoes rapid disintegration as soon as kept in the oral cavity. Volatile salts such as urea, hexamethylenetetramine, ammonium bicarbonate, camphor, naphthalene etc. can be employed for this purpose. Table 1 shows the composition of different trials, which were taken for formulating mouth dissolving tablets.

Evaluation of formulating tablets

Thickness of tablets

An instrument known as micrometer employed for the measurement of thickness of individual units. The thickness should be within ±5 % of the standard value. Vernier calipers was employed for the measurement of thickness.

Hardness

The hardness was tested by Monsanto tester. The force was recorded in Kg/cm^2. The test was performed on three tablets and the average of the results was determined.

Weight variation

This test was performed according to IP. Twenty tablets were taken and individually weighed. Average weight of the tablets was calculated and the individual weights were compared with the average weight. According to IP, the maximum no. of tablets that can be outside the limit is 2 and those which can be outside two times the limit is 0.

Friability

Roche friabilator was employed for the assessment of friability. Ten tablets were taken and their total weight was determined. They were than place in the apparatus which was allowed to rotate for 4 mins. at a speed of 25rpm. Each revolution of the chamber causes the tablet to fall from a height of 6 inches. After 100 revolutions, the tablets were collected, dusted off, re-weighed and the loss in weight, if any, was noted down.

***In-vitro* dispersion time test**

In order to determine this, 6 ml of de-mineralized water was taken in a measuring cylinder of 10 ml capacity. In this cylinder, a tablet was dropped and the time taken by the tablet to disperse completely was noted.

Wetting time

For this test, a Petri dish having a diameter of 10 cm was taken and in it were placed 5 tissue papers having a diameter of 10 cm. To this, 10 ml of a water-soluble dye (Eosin) was added. A tablet was then placed carefully on tissue paper's surface and the time taken by water to reach tablet's upper surface was noted.

Water absorption ratio (%)

To a small Petri dish, 6 ml of water was added. in it was placed a twice folded tissue paper's piece. On this paper, a pre-weighed tablet was placed and the time taken by the tablet in getting wet completely was noted. Re-weighing of the wetted tablet was performed and the ratio was determined using:

Content Uniformity

Powdering of 5 tablets was done and an amount of powder equivalent to 100 mg drug was taken. This powder was then dissolved in PBS (pH= 6.8), filtered, and suitably diluted. Absorbance at 230 nm was noted and drug content was determined.

Disintegration time

The U.S.P. device employed for this test consists of six tubes made up of glass and having a length of 3 inches, with their top being open and bottom end supported against a screen of 10 mesh. This together forms the basket rack assembly. Each tube received a single tablet and then basket was suspended in a beaker consisting of 1 liter of

distilled water maintained at 37±2°C. The test was performed and the time taken by the tablets to disintegrate completely was noted down.

***In-vitro* drug release study (Dissolution study)**

USP Type-2 i.e. paddle type apparatus was employed for this purpose. In the dissolution chamber, 900 ml of the simulated fluid was filled and maintained at 37±0.5°C. Rotation speed was set at 50 rpm for 120 mins. samples were collected at different intervals of time, namely 5, 10, 20, 30, 40…… and 120 minutes. Sink condition was maintained by replacing the collected sample with same volume of fresh media. Suitable dilution of the collected sample was carried out and their absorbance was determined at 230 nm. The amount of drug dissolved at different time intervals was calculated.

Results and Discussion

Formulation of Mouth Dissolving Tablets has been done by superdisintegrant addition method. Three superdisintegrant Cros Carmellose Sodium, Crospovidone, and Sodium starch glycolate are used to prepare nine batches of Mouth Dissolving Tablets of Naproxen Sodium by direct compression and sublimation method. Tablets prepared from crospovidone shows best results out of all batches of tablet formulated that is prepared by using sublimating agent urea. Optimum tablets such pass in general appearance, Thickness 4.1±0.004, Avg. of weight 221 mg, Hardness 2.7±0.412, Friability 0.603%, Content uniformity 97.34±0.768, Wetting Time 45 sec, Water Absorption Ratio 85%, Disintegration time 16 sec, In-vitro Dispersion Time 23 sec. Optimized Formulation (F9) of Naproxen Sodium shows very better release in 2-60 min in comparison conventional tablets of Naproxen Sodium that comes in market.

Table 1: Composition of mouth dissolving tablets using different super disintegrants

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Naproxen Sodium	100	100	100	100	100	100	100	100	100
Urea	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Microcrystalline Cellulose	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Croscarmellose Sodium	5	7.5	10	--	--	--	--	--	--
Sodium starch glycolate	--	--	--	5	7.5	10	--	--	--
Crospovidone	--	--	--	--	--	--	5	7.5	10
Aspartame	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	220	220	220	220	220	220	220	220	220

Identification of Drug:

UV- Spectrophotometric study

UV- spectrophotometric study was carried out for the determination of λ_{max} and observed λ_{max} was found to similar with literature value. Absorbance observed at about 230 nm is 0.280 for a solution of 10µg/ml

Characterization of Blend:

The dried blends of different formulations were subjected for evaluation for micrometric properties i.e. Bulk density, Angle of repose, Tapped density, % compressibility, Hausner ratio. The results are given in table 2.

Table 2: Result of Preformulation Study

Formulation Blend	Angle of Repose	Bulk Density	Tapped Density	% Compressibility	Hausner Ratio
F1	28.002+_0.623	0.540 0.004	0.822 0.002	30.30%	1.53
F2	30.034 0.765	0.535 0.007	0.852 0.006	31.20 %	1.4
F3	27.056 0.543	0.561 0.002	0.857 0.003	34.53 %	1.52
F4	26.074 0.645	0.583 0.006	0.845 0.008	31.00%	1.44
F5	25.02 0.456	0.545 0.007	0.801 0.012	31.96%	1.46
F6	24.17 0.234	0.562 0.002	0.834 0.004	32.01%	1.47
F7	27.45 0.342	0.540 0.015	0.869 0.008	29.85%	1.60
F8	26.74 0.368	0.535 0.005	0.823 0.003	34.99%	1.53
F9	28.65 0.356	0.540 0.356	0.846 0.007	29.17%	1.56

(values are mean SD, N=3)

Evaluation of physical parameters

The Prepared Mouth Dissolving Tablets of Naproxen Sodium were subjected to a variety of physical parameters as discussed below. The results are given in table 3.

Table 3: Characteristics of Mouth Dissolving Tablets of Naproxen sodium

Formulation Code	Thickness (mm)	Weight variation	Hardness (kg/cm^2)	Friability	Content Uniformity (%)
F1	**4.1 0.004**	**PASS**	**3.0 0.267**	**0.679 0.135**	**96.27 0.654**
F2	**4.1 0.003**	**PASS**	**2.7 0.345**	**0.826 0.245**	**97.65 0.576**
F3	**4.0 0.008**	**PASS**	**2.8 0.567**	**0.606 0.541**	**99.01 0.634**
F4	**4.2 0.007**	**PASS**	**3.0 0.654**	**0.755 0.326**	**95.67 0.234**
F5	**4.1 0.001**	**PASS**	**2.8 0.734**	**0.687 0.256**	**97.45 0.276**
F6	**4.0 0.005**	**PASS**	**3.0 0.437**	**0.823 0.412**	**98.45 0.134**
F7	**4.0 0.005**	**PASS**	**2.5 0.437**	**0.954 0.264**	**97.60 0.463**
F8	**4.1 0.002**		**2.6 0.649**	**0.755 0.321**	**96.00 0.865**
F9	**4.2 0.004**		**2.7 0.412**	**0.603 0.348**	**97.34 0.0768**

Evaluation of other parameters

Table 4: Other evaluation tests of tablets

Formulation Code	Wetting time (sec)	Water absorption ratio (%)	Disintegration Time (sec)	*In-vitro* Dispersion time (sec)
F1	**85**	**69**	**28**	**75**
F2	**79**	**71**	**26**	**70**
F3	**75**	**81**	**25**	**68**
F4	**65**	**73**	**23**	**48**
F5	**60**	**75**	**22**	**46**
F6	**60**	**73**	**22**	**40**
F7	**52**	**80**	**19**	**30**
F8	**48**	**92**	**17**	**25**
F9	**45**	**85**	**16**	**23**

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***In-vitro* release study:**

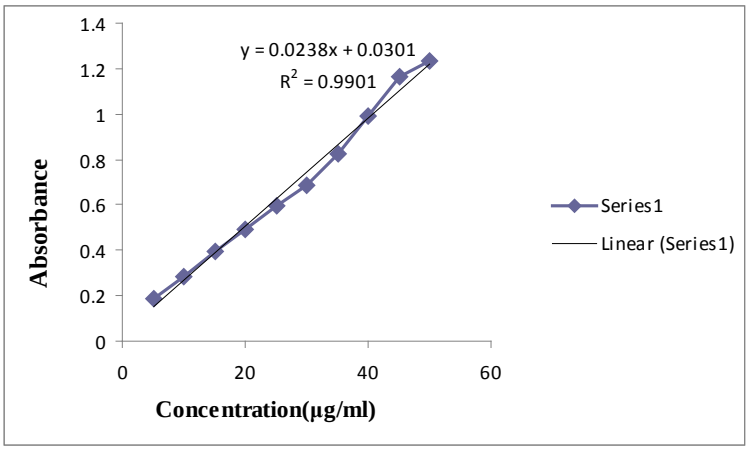

Figure 1: Calibration Curve of Naproxen Sodium in pH 6.8 Phosphate Buffer

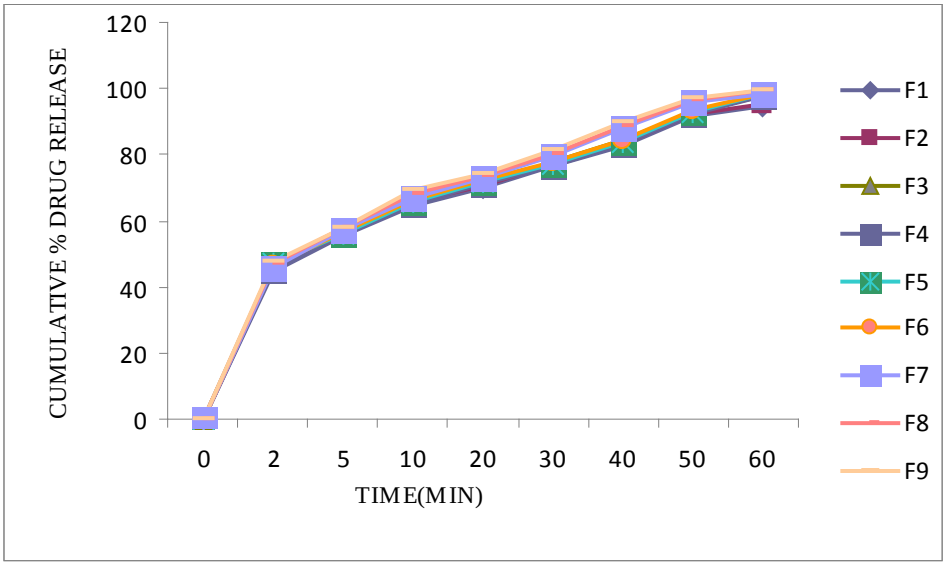

Figure 2: Drug release study of the MDT in simulated salivary fluid pH 6

Conclusions

Naproxen sodium is an analgesic NSAID intended for the treating fever, pain,stiffness, as well as inflammation which may have multiple causes such asdysmenorrhea, gout,migraine, rheumatoid arthritis,osteoarthritis, and juvenile arthritis. However, the drug is known to cause gastric discomfort leading to poor compliance amongst patient with the conventional dosage form. Hence, it was thought worthwhile to developorodispersible tablet of naproxen sodium, which serves the dual function of quickening the onset of action and minimizing the gastric issues associated with it so that patient compliance can be improved,bio-availability can be enhanced and drug's dose can be reduced.

Formulation of Mouth Dissolving Tablets has been done by superdisintegrant addition method. Three superdisintegrant Cros Carmellose Sodium, Crospovidone, and Sodium starch glycolate are used to prepare nine batches of Mouth Dissolving Tablets of Naproxen Sodium by direct compression and sublimation method. Tablets prepared from crospovidone shows best results out of all batches of tablet formulated that is prepared by using sublimating agent urea. Optimum tablets such pass in general appearance, Thickness 4.1±0.004, Avg. of weight 221 mg, Hardness 2.7±0.412, Friability 0.603%, Content uniformity 97.34±0.768, Wetting Time 45 sec, Water Absorption Ratio 85%, Disintegration time 16 sec, In-vitro Dispersion Time 23 sec. Optimized Formulation (F9) of Naproxen Sodium

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