Nimesulide mouth dissolving tablets: evaluation

ABSTRACT

Mouth dissolving tablets has number of advantage viz., faster onset of action, elegance, ease of administration, ease of manufacturing, ease of storage and transport. A novel attempt has been made to develop mouth dissolving tablets of Nimesulide by including clove oil as flavouring and local anesthetic agent on taste buds. The tablets were prepared by direct compression method. The formulated tablets were evaluated for Pre formulation and post formulation parameters and they were found to be satisfactory. The formulated mouth dissolving tablets possessed good drug releasing property, good mouth feel and improved drug availability with better patient compliance.

Keywords: Mouth dissolving tablet, Nimesulide, direct compression method, superdisintegrants.

INTRODUCTION

Pediatric and geriatric patients, have difficulty in swallowing solid dosage forms. These patients are unwilling to take these solid preparations due to a fear of choking. In order to assist these patients, several mouth dissolving drug delivery systems has been developed. Mouth dissolving tablets can be prepared by direct compression, wet granulation, moulding, spray drying, freeze drying or sublimation methods (Biradar SS., 2006). Mouth dissolving tablets dissolve rapidly in the saliva without the need for water, releasing the drug (Kaushik D., 2004). Some drugs are absorbed from the oral cavity as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form (Seager H., 1998).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed for inflammatory disorders. NSAIDs exert their effect through inhibition of cyclooxygenase-II, the main form of isozyme associated with inflammation. But the simultaneous inhibition of cyclooxygenase-I and the resulting gastric and renal dysfunction limit their frequent use (Wallace JL. 1992). Nimesulide, a model active pharmaceutical ingredient acts specifically on cyclooxygenase-II and does not affect cyclooxygenase-I. (Singla AK et al., 2000) Hence, Nimesulide exerts its anti-inflammatory action while showing a marked increase in gastrointestinal tolerability and minimal incidences of renal dysfunction. Because of its additional action of inhibiting respiratory burst of phagocytosing neutrophils, nimesulide is also well tolerated by asthmatic patients (Dapino P et al 1994) Thus, it is one of the most commonly prescribed NSAIDs for the treatment of various inflammatory conditions such as tonsillitis, pharyngitis, stomatitis, rheumatoid arthritis, osteoarthritis, low back pain, etc. Nimesulide results in poor bioavailability when administered in the form of conventional tablets because of its high hydrophobicity and poor aqueous solubility (Piel G et al., 1997) Complexation and cosolvency techniques have been useful in improving the dissolution characteristics of nimesulide (Nalluri BN et al., 2003)

The main criteria for mouth dissolving tablets is to disintegrate/dissolve rapidly in oral cavity with saliva in 60 sec, without need of water and should have pleasant mouth feel(Sharma S., 2008). It has been reported that Nimesulide possess bitter taste hence the primary objective is to mask the bitter taste and further developing the drug into mouth dissolving tablets.

MATERIALS AND METHODS

Materials

Nimesulide was a gift sample from Waksman SelmanPvt Ltd, Anantapur, India. Stevia leaf powder was obtained from the medicinal garden of Sri Krishnadevaraya University, Anantapur, India and authenticated by the Botany department of Sri Krishnadevaraya University, Anantapur, India. Mannitol, Clove oil, talc, micro crystalline cellulose, Cross carmellose sodium, Cross Povidone, magnesium stearate and talc were purchased from S. D. Fine Chemicals, Mumbai, India. All other chemicals, solvents and reagents were used of either pharmacopoeial or analytical grade.

Methods

Preparation of Mouth Dissolving Tablets: (Kuchekar B. S., 2003)

All the ingredients were passed through sieve No. 60. Nimesulide, mannitol, Micro Crystalline Cellulose and stevia leaf powder were triturated in a glass mortar. Superdisintegrants were incorporated in the powder mixture and finally magnesium stearate and talc were added as lubricant. The powder mix was weighed individually and compressed with 10mm flat face surface punches using hydraulic press single tablet punching machine. The formulae of various mouth dissolving tablets were shown in Table 1.

Evaluation of the prepared tablet: (Avari, N. G., 2004, USP 24/NF 19, 2000))

Pre-compression parameters

Compatibilities study

Fourier Transform Infra-Red (FT-IR) spectral analysis:

Fourier-Transformed Infrared (FT-IR) spectrums of formulated tablets were obtained on a Fourier-Transform Infrared (FT-IR) spectrophotometer, (Perkin Elmer, spectrum-100, Japan using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm-1 and the resolution was 1cm-1. This spectral analysis was employed to check the compatibility of drugs with the polymers used.

Pre compression parameters

The powdered blend was evaluated for flow properties viz., Angle of repose, loose bulk density (LBD), tapped bulk density (TBD), Carr’s compressibility index and hausner’s ratio.

Post compression parameters:

Thickness

The thickness of the tablets was determined using a thickness screw gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used and average values were calculated.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and analyzed for hardness. The mean and standard deviation values were also calculated.

Friability test

The friability of tablets was determined using Roche Friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The % friability was then calculated by eq. 1.

F= Winitial – Wfinal / Winitial X 100 ..... (1)

F= friability (%), Winitial = initial weight, Wfinal = Final weight

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed according to the official method.

Drug content uniformity

Tablet containing 100mg of drug is dissolved in 100ml of 0. 1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1ml of filtrate was taken in 50ml of volumetric flask and diluted up to mark with 0. 1N HCl and analysed spectrophotometrically at 213 nm. The concentration of Nimesulide in mg/ml was obtained by using standard calibration curve of the drug. Claimed drug content was 100mg per tablet. Drug content studies were carried out in triplicate for each formulation batch.

Wetting time

The tablet was placed in a petridish of 6. 5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out six times and the mean value calculated.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using eq. 2

R = 10 X (Wa – Wb) ……. (2)

Wb

Where, Wb = weight of the tablet before water absorption

Wa = weight of the tablet after water absorption

Three tablets from each formulation were analysed performed and standard deviation was also determined.

In vitro dispersion time

Tablet was placed in 10 ml phosphate buffer solution, pH 6. 8±0. 5oC. Time required for complete dispersion of a tablet was measured.

In-vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I. P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6. 8 (simulated saliva fluid) maintained at 37±20C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6. 8 maintained at 37±20C. The time in

seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Mouth feel

To know mouth feel of the tablets, selected human volunteers were given placebo tablets and the taste sensation felt was evaluated.

In-vitro dissolution studies

In vitro release studies were carried out using tablet dissolution test apparatus USP XXIII. The following procedure was employed throughout the study to determine the in-vitro dissolution rate for all the formulations. The parameters in-vitro dissolution studies were tabulated in table 5.

Accelerated Stability studies:

The optimized formulation (F5) was tested for stability for a period of 3 months at accelerated conditions of a temperature 400C and a relative humidity of 75% RH, for their drug content as per ICH guidelines (Remunan C., 1992)

RESULTS AND DISCUSSION:

The FTIR spectrum of Nimesulide and formulation F5 were shown in Fig 1 and 2 respectively. The results obtained for angle of repose of the powdered blends was less than 300, the loose bulk density was ranged from 0. 55±0. 06 to 0. 59±0. 01 g/cm3, the tapped bulk density was ranged from 0. 64±0. 05 to 0. 68±0. 06 g/cm3, the percent compressibility was ranged from 15. 25 to 16. 36 %. All these values were represented in table 2. The mean thickness values were found in the range from 2. 99±0. 10 to 3. 08±0. 074 mm, the hardness of formulated tablets were found to be 5. 99±0. 21 to 7.

22±0. 16 kg/cm2, the loss in friability was ranged from 0. 44 to 0. 91, the weights of tablets were found to be from 299. 11±6. 25 to 300. 80±5. 66 g. The drug content in the formulations were ranged from 98. 59±0. 95 to 100. 65±0. 19 mg and these values were shown in table 3. The wetting time was ranged from 94 ± 1. 66 to 100 ± 0. 48 sec, the in-vitro disintegration time was ranged from 52±5. 01 to 70±4. 25 s, the mouth feel was palatable which were shown in table 4. The physical parameters of optimized formulation (F5) were shown in table 5.

The characteristic peaks in FTIR spectrum of formulation blend retained the peaks which were observed with the pure drug. The All formulations showed angle of repose within 300 which indicates good that showed little higher angle of repose above 300 indicating fair flow. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. This result helps in calculating the % compressibility of the powder. All formulations show good compressibility. The formulated tablets were eligent and almost uniform thickness. All the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness. The weight loss after friability test was found well within the approved range (<1%) in all the formulation, indicates the tablets possess good mechanical strength. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7. 5%. All formulations showed quick wetting, this may be due to ability of swelling and also capacity of absorption of water. All superdisintegrants have high water absorption capacity and cause swelling. All formulations showed disintegration time less than 95 seconds, indicates

the swelling of disintegration substance suggested mechanism of disintegration. The volunteers felt good taste in all the formulations. As the drug is not bitter and due to presence of stevia leaf powder, which is 400 times sweeter than sucrose and the Euginol in clove oil acts as both flavoring agent and local anesthetic agent to block the bitter taste of the drug on taste buds. In oral disintegration all the formulations showed rapid disintegration in oral cavity. By observing the above results use of cross cormilose sodium and cross Povidone, in direct compression method results in hydrophilicity and swelling which in turn causes rapid disintegration. Thus these disintegrants are suitable in preparing the rapidly disintegrating tablets. This rapid dissolution might be due to fast breakdown of particles of superdisintegrants. In all formulations the drug release was nearer to 100% within 12 minutes. The optimized formulation F5 was selected for accelerated stability studies and the tablets possessed the same parameters even after the stressed conditions, indicates good stability properties of formulation.