FORMULATION AND IN VITRO EVALUATION OF NIFEDIPINE IMMEDIATE AND SUSTAINED RELEASE ENCAPSULATED MINI TABLETS

[1]Heena Tasneef, [2]Dr. SYED ABDUL AZEEZ BASHA

[1]M. Pharmacy, [2]Professor
Department of Pharmaceutics
Deccan School Of Pharmacy, Darussalam, Aghaphura, Hyderabad, Telangana, India.

***Abstract*: Solid oral dosage forms are most acceptable dosage forms especially tablets are most generally accepted by people of various age groups. Mini tablets are tablets with a diameter adequate to or smaller than 2–3 mm. Mini tablets are multiple unit dosage forms and are advantageous than pellets or the other oral dosage forms as they're easy to manufacture and stability problems are less(1). Many types of mini tablets are there like bio adhesive mini tablets, pH responsive mini tablets, gastro retentive mini tablets, paediatric mini tablets, oral disintegrating mini tablets. These mainly reduce the variation among subjects. The review emphasises on advantages of mini tablets, types, methods of manufacturing and modes of administration and evaluation of mini tablets.of the present study was to develop Bilayered tablets of Nifedipine which is used for treatment of Angina pectori. Bilayered tablet contains two layers. We can formulate first layer into immediate release and second layer into sustained release for desired action. Nifedipine have half-life 2hrs make the drug suitable for immediate release.In this formulation using material Nifedipine, Sodium starch glycolate, Lycoat, Crosspovidone, Carbopol, Guar gum, HPMC K4M ,Microcystalline cellulose, Magnesium stearate Talc.and method of prepartion are used as dircet compression method for both immediate and sustain release.(2).The post and pre ompression evaluation as been done and then compared with marketed formulation.**

***Keywords*: Mini tablet, Angina pectori, Direct compression.**

I. Introduction:-

Mini-tablets are flat or slightly curved small tablets as given by Lennartz and Mielck (1998) a tablet with a diameter between 1 and 5mm is considered as mini tablet. The weight of a mini-tablet is generally between 8 and 60 mg, depending on the size of the mini-tablet. Mini-tablets (coated or uncoated and Single or multiple-unit systems) are mainly developed as patient-friendly systems for pediatric and geriatric patients and also for personalized medicine because they offer improved swallowing and flexible dosing, combining various release kinetics, doses and active compounds in only one System. Mini tablets are more acceptable in children and elderly people as they are easy to swallow. Mini tablets are effective and alternative solutions for single unit dosage forms. Several mini-tablets can be placed into a capsule,Which later disintegrates and releases these sub-units. MP formulations generally have a more reliable in vivo dissolution performance when compared to a single unit dosage form, resulting in more uniform bioavailability and clinical effect [1]. The first development of industrial scale mini-tab production of Panzytrat (pancreatic), enteric-coated mini-tabs, was conducted in 1985 by Nordmark Arzneimittel GmbH [6]. Butler et al. [8] Compared the

GI transit of 3.8 mm mini-tabs with that of a traditional multiparticulate system (drug-layered and subsequently coated pellets) under fasted and fed conditions. Currently liquids are the most frequently used pediatric
Formulations. They are simple to administer, and the dose can easily be changed. However, they have major disadvantages such as chemical, physical, and microbial instability, palatability of the solution, inaccuracy of dosing, lack of controlled release, and elevated Toxico- logical risks [12–15]. Various typesof mini tablet

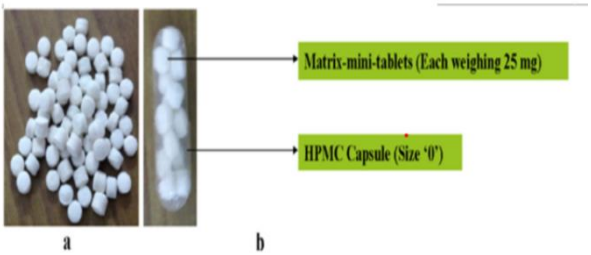

Fig No: 1 A-Mini Tablets b-Enclosed mini tablets

Types of mini Tablet:

1. Pediatric mini tablet
2. Floatiing or Gastro retentive mini tablet
3. Bio adhesive vaginal mini tablet

4. pH responsive mini tablet
5. Bi phasive mini tablet
6. Oral disintegrating mini tablet

Angina pectoris:

Angina pectoris or angina is temporary pain or discomfort as a results of decreased blood flow to the guts muscle. It refers to a pressure-like substernal chest discomfort that is precipitated by physical or emotional stress Angina is not a heart attack, but it is a sign of increased risk for heart
Attack. Sustained drug delivery systems significantly improve the therapeutic efficacy of drugs. Drug-release-retarding polymers are the key performers in such systems. 1 Sustained release Delivery systems **are able to do** an extended duration of activity for drugs with half-life 2-4 hrs, decreased Toxicity, reduction of required dose, optimized therapy, and better patient compliance. Matrix tablets are widely accepted for oral sustained release (SR) as they're simple and straightforward to formulate. Nifedipine is a 1,4-dihydropyridine calcium channel blocker. It is used for the treatment of angina pectoris, Hypertension, and Raynaud's phenomenon. Nifedipine has a half-life of 2 hrs5. With a view to reducing the dosing frequency and the side effects.

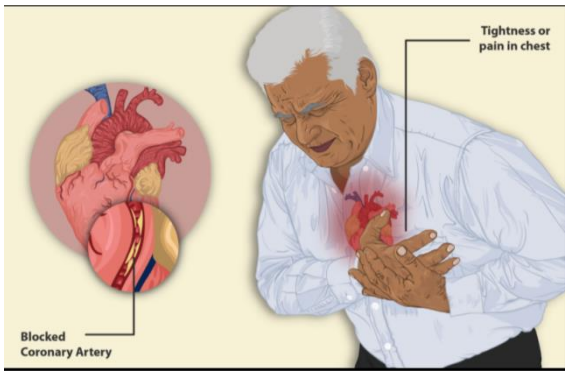

Fig no:2 Angina Pectoris

CAUSES OF ANGINA

Angina, which is also known as angina pectoris, occurs when the flow of blood through the coronary arteries to the heart muscle is insufficient to meet the heart's oxygen demands, such as during physical activity.

TYPES OF ANGINA

1. **STABLE:** doesn't typically change in frequency and it doesn't worsen over time.

2. **UNSTABLE: is** chest pain that occurs at rest or with exertion or stress. The pain worsens in frequency and severity.

3. **VARIANT ANGINA:-** (Prinzmetal's angina): Usually happens when you're resting Is often severe May be relieved by angina medication

II.MATERIALS AND METHOD

MATERIALS:

Nifedipine was supplied with Yarrow Chem Products, Mumbai. Sodium starch glycolate, Super disintegrant Signet Chemical Corp., Mumbai, Lycoat Super disintegrant Signet Chemical Corp., Mumba, iCrosspovidone Super disintegrant Signet Chemical Corp., Mumbai, Carbopol Polymer BMR chemicals, Hyderabad, Guar gum Polymer Green Pharma Hyderabad, HPMC K4M Hydrophilic polymer Drugs India Mahaveeray Hyderabad,Microcystalline cellulose Binder Otto Chemie Pvt Ltd, Mumbai. Magnesium stearate is used as lubricant, S.D. Fine Chem Limited Mumbai. Talc-Glidant,Lubricant S.D. Fine Chem Limited Mumbai.

METHOD:

Preparation of Immediate release mini tablets (IRMT)

Nifedipine immediate release mini-tablets were prepared by direct compression technique. Tablet ingredients were accurately weighed as mentioned in the table. All powders were then passed through #20 mesh sieve. After screening, the powdered ingredients

were blended in a large size poly bag by tumbling action. Finally, magnesium stearate was added and again mixed for 5 minutes, so that particle surface was coated by lubricant evenly. The blend was Then compressed into mini tablets weighing about 50 mg using 4 mm shallow biconcave punches in rotary tablet punching machine to a hardness of 3-4 kg/cm2. The prepared mini tablets were used for further evaluation studies

Table No: 1 Formulation of immediate release mini tablets

Ingredients	IR1	IR2	IR3	IR4	IR5	IR6
Nifedipine	10	10	10	10	10	10
Sodium starch glycolate,	1.5	3	-	-	-	-
Lycoat	-	-	-	-	1.5	3
Mcc	37.5	36	37.5	36	37.5	36
Magnesium streate	0.5	0.5	0.5	0.5	0.5	0.5
Sunset yellow fef	qs	qs	qs	qs	qs	qs
Talc	0.5	0.5	0.5	0.5	0.5	0.5
Total	50	50	50	50	50	50

Preparation of Sustained release mini tablets:

Nifedipine sustain release mini-tablets were prepared by direct compression technique. Tablet ingredients were accurately weighed as mentioned in the table. All powers were then passed through #20 mesh sieve. After screening, the powdered ingredients were blended in a large size poly bag by tumbling action. Finally, magnesium stearate was added and again mixed for 5 minutes so that particle surface was coated by lubricant evenly. The blend was then compressed into mini tablets weighing about 50 mg using 4 mm shallow biconcave punches In rotary tablet punching machine to a hardness of 5-6 kg/cm2 . The prepared mini tablets were used for further evaluation studies.

Table No: 2 Formulation of sustain release mini tablets

Ingredients	SR1(mg)	SR2(mg)	SR3(mg)	SR4(mg)	SR5(mg)	SR6(mg)
Nifidipine	20	20	20	20	20	20
Carbopol 940	7.5	15	-	-	-	-
HPMC K4M	-	-	7.5	15	-	-
Guar Gum	-	-	-	-	7.5	15
PVP K30	2.5	2.5	2.5	2.5	2.5	2.5
MCC	19	11.5	19	11.5	19	11.5
Magnesium Sterate	0.5	0.5	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5	0.5	0.5
Total	50	50	50	50	50	50

III.EVALUATION OF MINI TABLETS:

PRE FORMULATION STUDIES:

Solubility

Solubility of Nifedipine was determined in Ethanol, Acetone, pH1.2, pH6.8 and pH7.4 phosphate buffers. Solubility studies were performed by taking excess amounts of Nifedipine in different beakers containing the solvents. The mixtures were shaken for 24hrs at regular intervals. The solutions were
Filtered by using whattmann's filter paper grading. 41. The filtered solutions were analyzed spectrophotometrically at 238 NM.

UV method development for estimation of drug:

Standard Stock:10 mg of model drug was taken and added to the respective media in a 10 ml volumetric flask and volume was made up to 10 ml, resulting in a standard stock solution of 1000 µg/ml. Working Stock – For the above standard stock solution 1 ml was taken and added to respective buffer media in a 10 ml volumetric flask and volume was made up to 10 ml to get 100 µg/ml solution. From the working stock dilutions were prepared using respective media

EVALUATION OF PRE COMPRESSION BLEND

Determination of absorption maxima:

10 µg/ml solution was taken to determine absorption maxima. The initially blank buffer solution was kept and scanned in the region of 200-400 NM. Then the sample was kept for analysis and scanned in the same region.

Calibration curves of nifedipine:

Nifedipine standard graphs are determined by UV, visible spectrophotometer. Spectro photometric estimation of nifedipine was conducted in 0.1 N HCl, and 6.8 pH phosphate buffer.

Preparation of standard stock solution in 0.1 N HCl, and pH 6.8 phosphate buffer:

Accurately weighed 10 mg of nifedipine and dissolved in 10 ml of 0.1 N HCl, pH 6.8 phosphate buffer respectively. From this solution 1 ml was withdrawn and diluted to 10 ml with 0. 1N HCl, and pH 6.8 phosphate buffer to produce a standard stock solution of nifedipine (10µg/ml).

Preparation of sample solution in 0.1 N HCl, and pH 6.8 phosphate buffer:

From the stock solution, 0.5, 1, 1.5, 2.0, 2.5, 3.0 ml were withdrawn and diluted to 10 ml With 0.1 N HCl, pH 6.8 phosphate buffer to yield a concentration of 5, 10, 15, 20, 25, 30 µg/ml respectively. The observance was observed at 238nm respectively, using a UV visible spectrophotometer. Then Calibration curve of nifedipine was plotting the graph between absorbance values (NM) on the Y- axis and Concentration (µg/ml) on X –axis.

Compatibility study:

FTIR analysis:

The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, with reference to a salt (KBr; SD Fine Chem. Ltd., Mumbai, India) were mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr disc in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of 2 cm–1 using Happ-Genze lapodization.The characteristic peaks were recorded

EVALUATION OF PRE-COMPRESSION BLEND:

Angle of repose (h)

The angle of repose was determined by taking accurately weighed quantity of powder blend into the funnel. The blend was allowed freely to pass through the funnel onto the surface. The radius and height of the cone was measured. The angle of repose was calculated using the subsequent formula

Ø =Tan-1h/r

where h and r are the height and radius of the formed powder cone respectively.

Loose Bulk density (LBD) and Tapped Bulk density (TBD)

Weighed amount of the powder blend was taken and transferred to a measuring cylinder. Bulk volume of the blend is noted as per the reading on the measuring cylinder.

Bulk density is calculated using following formula.

Bulk density = Mass of the blend / Bulk volume of the blend

Hausners Ratio:

Hausners ratio specifies the flow properties of the powder blend and is measured by the ratio of tapped density to bulk density.

Hausners ratio = Tapped density/Bulk density
Values of Hausner ratio; 1.25: poor flow

If Hausner ratio is between 1.25-1.5, flow are often improved by addition of glidants.

POST COMPRESSION EVALUATIONS:

The compressed mini tablets were evaluated for the following parameters.

Weight Variation Test:

Weight variation test is conducted by using digital weighing balance. Twenty mini tablets were randomly selected and weighed individually and calculated average weight. And comparing the individual weights to the average weight. The percentage of weight variation was calculated using following formula:

% Weight Variation = Individual weight – Final weight/Final weight * 100

Hardness Test:Hardness test of all the formulations was measured using a Monsanto Hardness Tester. It is expressed in kg/cm2.Hardness of tablet defined as the force required to the break a tablet. Six mini tablets were randomly selected from each formulation and the mean and standard deviations are calculated.

Thickness Test:

The thickness test of ten randomly selected mini tablets from each formulation was individually Noted in mm using screw gauge and digital caliper. The mean and standard deviation values were Calculated. Tablet thickness is controlled to facilitate packaging.

Friability Test:

Twenty mini tablets are selected randomly from each formulation and their initial weight (W0) was noted and placed in a friabilitor. The friabilitor was rotated at 25 rpm for 4 minutes, after which the Mini tablets were removed.Mini tablets are weighed again (Wf).

The percentage of variability was calculated by using the following formula.

$$\% F = W_0 – W_f/W_0 * 100$$

Whereas, % F = Percentage of friability

W_0 = Intial Weight

W_f = Final weight

Disintegration Test:

The disintegration test for mini tablets was determined by using Disintegration Test Apparatus as per the specifications of Indian Pharmacopoeia. One mini tablet was placed in each of the six tubes of the basket. The apparatus was run using 900 ml of dissolution medium as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute in dissolution medium maintained at 370 C. Then note down the disintegration time for mini tablets.

Drug Content:

Ten tablets were weighed and powdered and 350mg equivalent weight of Nifedipine was accurately weighed and transferred in 100ml volumetric flask. It was dissolved and made up the volume with 0. 1N HCl, pH- 1.2. Subsequently the solution was filtered and suitable dilution was made and analyzed at 235 NM using UV-Visible spectroscopy.

In Vitro Dissolution Studies:

In vitro dissolution studies were carried out using USP dissolution type 1 (basket) apparatus. Mini tablets containing capsules placed in the basket and immersed completely in dissolution media. In order to stimulate the pH changes along with gastrointestinal tract three different dissolution media with a pH1.2, 6.8 buffers were used. The dissolution media were maintained at a 37 ± 0.5o C temperatures throughout the experiment and the ration speed of basket maintained at 50 rpm, .900 ml of dissolution medium was used at Each time.Nifedipine mini tablets in capsule system were placed the basket to prevent floating. When performing experiments, the 0.1 N HCL was used for first two hours because the average gastric emptying time is two hours, then the dissolution medium was removed and add a fresh dissolution medium at pH 6.8 phosphate buffer for the remaining rest of the time. A 5 ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were Analyzed by using a UV visible spectrophotometer and calculate the cumulative amount of drug release over the sampling

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