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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF NAPROXEN AND DOMPERIDONE

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ABSTRACT:

Today it is the need of fast results for paediatric as well as geriatric patients for minor as well as major disorders. So, MDT's (Mouth Dissolving Tablets) are preferred currently. Naproxen which is NSAID's for the treatment of inflammations. The other one is Domperidone which is used for treating Nausea and Vomiting and to increase gastric peristalsis. So, these are the tablet formulations which are necessary and demanding according to fast results. MDTs are rapidly dissolved in saliva due to their property of rapid disintegration (DT). The above drugs in fast dissolving form can be marketed globally.

Keywords: Mouth Dissolving Tablet, Non-Steroidal Anti-Inflammatory Drugs, Disintegration.

INTRODUCTION:

Fast Dissolving Drug Delivery System (FDDDS) is a approach by which MDTs is derived. It is a newer concept which involves the benefits of both liquid as well as solid preparations. It gives benefits over conventional dosage forms. The oral formulations or dosage forms are widely preferred over other medicated stuff, due to their easy handling low cost in comparison to other dosage forms. But these forms can have drawbacks like dysphasia (difficulty in swallowing). But again, due to the formulation development the researchers have modified the forms for better bioavailability via oral cavity which directly takes the formulation in the systemic circulation. According to Indian Pharmacopoeia the ideal timing for "Oral Dispersible Tablet (ODTs) is 2-3 minutes when placed in oral cavity".

STEPS IN FORMULATION DEVELOPMENT:

Naproxen:

Naproxen is structurally [(S)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid] its action has non-steroidal anti-inflammatory medicine that shows both antipyretic and analgesic behaviour. The mechanism of action of naproxen is believed to related with cyclooxygenase activity inhibition (COX-1) while COX- 2 inhibition is anti-inflammatory. The practically observed in curable half-life is almost 15 hours.

Domperidone:

On another hand the Domperidone which is a selective antagonist of dopamine D2 and D3 receptor. It can be administered orally, rectally or by I.V (Intravenous) route. These drugs are used to relieve nausea and vomiting and increase peristalsis of GIT. These drugs are available in the form of tablet, ODTs and suppositories.

FORMULATION DEVELOPMENT:

Formulation development is the process of utmost important as it involves developing and adequate preparation and form of a drug which both stable and acceptable to the patient. Drug formulation is also known as pharmaceutical formulation/ is the process through which a variety of substance are combined with the drugs active pharmaceutical ingredient to finally produce a drug product for the patient.

A critical part of the drug formulation planning stage is deciding what physical form the medicinal product should have. Stability and bioavailability are common challenges in early phase drug development programs. A compound might have deficient stability in a solution and need to be combined with another substance

1. Tablets (Mouth Dissolving Tablets):

a)Drug: The ultimate characteristics of a drug for dissolution in the mouth and pre gastric absorption from MDTs include:

- ✓ Free from bitter taste
- ✓ Dose lower than 20 mg
- ✓ Small to Moderate molecular weight
- ✓ Good solubility in saliva
- ✓ Ability to permeate through oral mucosal tissue

b)Bulking materials:

Bulking materials are significant in the formulation of fast-melting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

c)Emulsifying agents:

Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulphates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

d)Lubricants:

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

e)Flavours and sweeteners:

Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients

f)Selection of super disintegrants:

Although super disintegrants primarily affect the rate of disintegration, but when used at high levels they can also affect mouth feel, tablet hardness and friability. Hence, various ideal factors to be considered while selecting an appropriate super disintegrants for a particular

Formulation should-

•Produce rapid disintegration, when tablet comes in contact with saliva in the mouth/oral cavity.

•Be compactable enough to produce less friable tablets.

•Produce good mouth feel to the patients. Thus, small particle size is preferred to achieve patient compliance.

•Have good flow, since it improves the flow characteristics of total blend.

Various manufacturing of MDDS include:

- Lyophilization
- Moulding
- Direct Compression
- Cotton Candy Process
- Spray Drying
- Sublimation
- Mass Extrusion
- Nanonization
- Fast Dissolving Films

FORMULATION OPTIMIZATION:

Design of experiment plays a crucial role in the optimization process of formulation development. The process, equipment, and technology for developing and manufacturing oral solid-dosage forms are well defined. Nonetheless, designing a drug product formulation that achieves the desired properties of the target profile both in magnitude and robustness is a multi- dimensional, and generally, constrained optimization problem, observes Aaron Goodwin, principal investigator, Research and Development, Capsugel. The ultimate goal in formulation development is to deliver the drug to the right place, at the right time, in the right concentration so that a beneficial therapeutic effect is achieved, John McDermott, executive director, Drug Product Optimization, Quotient, explains. For a simple immediate-release tablet that is wet granulated, key optimization parameters for formulation would be granulation end-point, blend particle size distribution, granulating media volume, blend moisture content, and granule size distribution. Key process parameters for optimization would be the mixing time, granulation time, and drying.

On the other hand, for a modified-release pellet coated with a polymer, the key optimization parameters for the formulation would be the film forming temperature, uniformity, and integrity of the film and its impact on drug dissolution and drug release. Key process parameters for optimization would be spray atomization, product temperature, and humidity control.

EVALUATION OF FORMULATION:

For Naproxen:

It is an odourless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water with a low pH (below pH 4), while freely soluble in water at 6 pH and above. Naproxen has a melting point of 153 degree centigrade.

It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is

1.6 to 1.8. Naproxen sodium USP is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

Solubility profile of naproxen: Bioavailability: In-vivo 95%

Protein Binding: Naproxen >99% albumin-bound. Half-life: 15 hours.

For Domperidone:

It is a white crystalline substance, lipid soluble, poorly water-soluble follows BCS class-II.

Domperidone is a dopamine antagonist with anti-emetic properties, Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary.

Solubility profile of domperidone:

It is practically insoluble in water (1 part in 50,000 part of water) and has a pka value of 7.9 so, it is a weakly-basic drug with a very poor dissolution rate at relatively high pH values.

Bioavailability: 13-17% by oral route, 90% by IM injection. Half-life: 7-9 hours.

Protein binding: 91-93% plasma protein bound.

Evaluation parameters:

For solid dosage forms:

1.Dissolution and disintegration test:

a)In-vitro dissolution studies:

Randomly selected 6 tablets were subjected to drug release studies using USP dissolution apparatus, in dissolution medium volume of 900 ml was used and a temperature of 37 ± 0.5oC was maintained. 5 ml of the sample was collected for every 5 minutes interval till 30 minutes and replaced with 5 ml of fresh buffer solution. The samples were filtered and suitably diluted and the drug assay was performed using UV spectrophotometer or HPLC system. The results were compared with standard values.

b)Disintegration time:

Disintegration time for randomly selected 6 tablets was measured using disintegration test apparatus. The average time required for disintegration was calculated and compared with standards.

2.Friability and hardness test:

a)Hardness test:

Hardness of the tablets was measured by using hardness testers like Monsanto hardness tester, Pfizer hardness tester etc. The pressure required to break the tablets is measured as a function of hardness (kg/ cm2). The values obtained must meet the standard value.

b)Friability:

Friability is to measure the extent of tablet breakage during physical stress conditions like Packing, transportation etc. A sample of randomly selected 6 tablets was evaluated for friability using Roche friabilator at 25 rpm for 4 minutes. The % weight loss is calculated by measuring the total weight of 6 tablets before and after operation.

Formula for calculating the % weight loss is given below:

% $Weight\ loss$=Total weight of tablet before − Total weight of tablets after Total weight of tablets × 100

iii) Weight variation and content uniformity:

a) Weight variation test:

Randomly selected 20 tablets were taken and their individual weights & the average weight of 20 tablets were determined. The deviation of each individual tablet from the average weight was calculated and compared with the standard values given in Pharmacopoeia.

The % weight variation of each individual tablet from the average weight is calculated by the given formula

% $WeightVariation$ = Individual weight of each tablet – Average weight of 20 tablets * Average weight of 20 tablets × 100

Labelling and packaging:

Types of packaging and packaging materials for solid dosage form:

i)Tamper – Evident containers are closed containers fitted with a device that irreversibly indicates if the container has been opened.

ii)Strip packages have at least one sealed pocket of material with each pocket containing a single dose of the product. The package is made of two layers of film or laminate material. The nature and level of protection which is required by the contained product will affect the composition of these layers.

iii)Blister packages are composed of a base layer, with cavities called blisters which contain the pharmaceutical product, and a lid. This lid is sealed to the base layer by heat, pressure or both. They are more rigid than strip packages and are not used for powders or semi-solids. In tropical areas blister packages with an additional aluminum membrane is used which provide greater protection against high humidity.

iv)Child Resistant Containers, commonly referred to as CRC's, are designed to prevent the child accessing the potentially hazardous product.

CONCLUSION:

Fast disintegrating tablet is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional dosage forms. The FDT dosage form had a good balance over disintegration time and mechanical strength. The prime objective of the study was to develop salbutamol sulphate fast disintegrating tablet by using commonly available excipients and conventional technology. From the study, it was concluded that by employing commonly available pharmaceutical excipients such as super disintegrants, hydrophilic and swellable excipients, and proper filler, a fast-disintegrating tablet of salbutamol sulphate can be developed which can be commercialized.

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