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Method of Preparation of Fast Disintegrating Tablet Using Solid Dispersion Technique with Direct Compression for Hypertension

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ABSTRACT- Nisoldipine is a drug used in hypertension. the objective of this work was to study the oral route of fast disintegration tablet of nisoldipine SD formation increased the dissolution rate compared to pure drug with the corresponding physical mixtures failing to provide the same dissolution enhancement.. SD with polymer like HPMC and PVP were selected for preparation of fast disintegrating tablets. Nisoldipine is a calcium channel blocker mainly used for the treatment of hypertension, but its oral bioavailability is limited because of its low aqueous solubility and extensive metabolism. Solid dispersion and micronized formulations have been tested to improve its oral bioavailability. There should be proper physical characterization (DSC, XRD, and FT-IR) and no interaction between nisoldipine and the excipients was involved in any of the formulations.

Keywords: Solid Dispersion, Hypertension, Direct compression Method, Solubility.

I. INTRODUCTION-

Hypertension:

Hypertension (HTN or HT), also known as high blood pressure (HBP), is the medical term for persistently elevated blood pressure in the arteries. High blood pressure usually does not cause symptoms. However, long-term high blood pressure is a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, vision loss, chronic kidney disease, and dementia.[1]

High blood pressure is classified as primary (essential) hypertension or secondary hypertension. About 90-95% of cases are primary, defined as high blood pressure due to non-specific lifestyle and genetic factors. Lifestyle factors that increase risk include excess salt in the diet, excess body weight, smoking and alcohol consumption. The remaining 5-10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause such as chronic kidney disease, narrowing of the renal arteries, an endocrine disorder, or the use of birth control pills.

Blood pressure is expressed in two measurements, systolic and diastolic pressure, which are the maximum and minimum pressures. For most adults, normal resting blood pressure is between 100–130 millimeters of mercury (mmHg) systolic and 60–80 mmHg diastolic. In most adults, high blood pressure is present when resting blood pressure is consistently at or above 130/80 or 140/90 mmHg. Different numbers apply for children. 24-hour ambulatory blood pressure monitoring appears to be more accurate than office blood pressure measurement.[2]

CAUSES OF HYPERTENSION:[3]

You may be more at risk if:

- You are overweight.
- Eat too much salt and not enough fruit and vegetables.
- Don't exercise enough.
- Drink too much alcohol or coffee (or other caffeinated beverages).
- Smoke.
- You do not sleep very often or have disturbed sleep.
- They are over 65 years old.
- You have a relative with high blood pressure.
- Are of black African or black Caribbean descent.
- Live in a run-down area.

SYMPTOMS FOR HYPERTENSION:[4]

High blood pressure or hypertension rarely has noticeable symptoms. However, if left untreated, the risk of serious problems such as heart

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attacks and strokes increases. Around a third of adults in the UK have high blood pressure, although many are unaware of it. The only way to know if your blood pressure is high is to have it measured.

TREATMENT OF HYPERTENSION:

Several oral and parenteral medications are available for the treatment of hypertension.

Beta-blockers-Beta-blockers (beta-adrenergic blockers) work by reducing sympathetic nerve input to the heart. So the heart beats less often per minute and with less force. Subsequently, the heart reduces its work and blood pressure decreases. Beta blockers include propranolol, metoprolol, atenolol and many others.[5]

Diuretics-Diuretics cause the body to excrete water and salt. This leads to a decrease in plasma volume, which in turn lowers systemic blood pressure. Diuretics include furosemide, hydrochlorothiazide, and spironolactone.[5]

Angiotensin-converting enzyme (ACE) inhibitors: Angiotensin-converting enzyme (ACE) inhibitors work by preventing the body from producing angiotensin II, a hormone that normally causes blood vessels to narrow. As a result, blood vessels remain wider, which lowers blood pressure. Angiotensin II also normally stimulates the release of another hormone called aldosterone, which is responsible for retaining sodium in the body. Thus, in addition to creating wider blood vessels, ACE inhibitors mimic the effect of diuretics to some extent. As a result, the blood vessels are exposed to less pressure and the heart does less work. Examples of ACE inhibitors include enalapril, captopril, and lisinopril. [6]

Angiotensin II antagonists: Relatively new to the world of blood pressure treatment, angiotensin II antagonists are primarily used in patients who develop cough as a side effect of taking ACE inhibitors. This drug antagonizes angiotensin II, thereby inhibiting its effects. Examples include losartan and valsartan.[6]

Calcium channel blockers: Calcium channel blockers prevent calcium from entering the muscle cells of the heart and blood vessels. The heart and blood vessels relax, allowing the blood pressure to drop. Some calcium channel blockers are nisoldipine, nifedipine, verapamil and diltiazem.

Alpha-blockers: Alpha-blockers (alpha-adrenergic blockers) target the nervous system to relax blood vessels, allowing blood to pass more easily. Examples of alpha-blockers are doxazosin, prazosin, and terazosin.

Alpha-Beta-blockers: Alpha-beta-blockers (alpha- and beta-adrenergic blockers) have the same effect as combined alpha-blockers and beta-blockers. They target the nervous system to relax blood vessels and also work to slow the heart rate. As a result, less blood is pumped through the wider vessels, reducing overall blood pressure. Alpha-beta blockers include labetalol and carvedilol.[7]

Vasodilators: This category of drugs works by relaxing the muscle in the blood vessel wall. Hydralazine and minoxidil are generic forms of vasodilators.

METHODS OF SOLID DISPERSION PREPARATION

Solvent Evaporation Method: In this method, the drug and polymer are diffused in different proportions in a common solvent, and the solvent is evaporated under vacuum pressure to form a physical mixture. A scientist named tachibechi and nakumara first dissolved the drug and polymer or carrier (β-carotene and PVP carrier) into a solvent system, and after evaporation, a solid dispersion was formed. As a solvent, an alcohol such as ethanol, methanol and dichloromethane is basically used.[8]

A co-solvent can be used because a large amount of common solvents and evaporation is required for absolute dissolution and diffusion of the drug and polymer. The main characteristic of this method is the thermal decomposition of drug molecules or carriers can be removed thanks to the low temperature, which is favorable for the evaporation of solvents.

The disadvantages of this method are expensive, ecological and difficult to find common and removable solvents, the difficulty of completely removing the liquid solvent, the difficulty of reproducing the crystalline form.

Fusion method: According to this method, a physical mixture is prepared by adding drug and polymer in different proportions and heated to melt. The polymer used should be water soluble or hydrophilic in nature. After melting, the solution should be cooled in an ice bath and stirred vigorously to solidify. After solidification, the remaining mass was macerated, crushed, crushed and sieved. This sieved particle helps improve drug solubility and bioavailability. At high temperature, many drugs can degrade.[9]

Hot Melt Extrusion (HME) Method:[10] In this method, a new material known as extrudate is created by applying it through a hole in a controlled

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manner and with controlled parameters such as temperature, mixing speed, injection amount and pressure. This method differs from simple extrusion in which all excipients are mixed with the drug in molten form, but no solvent is required for the granulation process.

Utilization of HME

Use of HME

- These methods help to improve and enhance the water solubility and bioavailability of a BCS Class II hydrophobic drug.
- This process does not require any solvent and water to complete the process and to improve dissolution.
- This process required less money so it was economical, reliable and time consuming process with easy step and operation procedure.
- In this process, homogeneous particles of fine size are obtained.
- After applying this method, the stability of the product is maintained under different conditions of pH and humidity.
- This method is safe and effective for humans because it is insoluble in water in nature.

Using the method:

1. This method helps mask the bitter taste of active pharmaceutical ingredients or other solutes.
2. This method is applicable for the development of dispersions, it helps to improve drug solubility and dissolution rate.
3. It helps to improve the formation of controlled drug release in which the implants are included.
4. It helps create a targeted drug release system.

Super Critical Fluid Method (SCF):[12-13] This method for dispersing solids requires a fluid at a given temperature and pressure. SCF has the property of liquid and vapor above the critical temperature. It is an ecological, green synthesis that is more efficient and safe and cost-effective. The main parameters for SCF formation are temperature and pressure. SCF gains more area to compress

Inclusion complexes:[14] This method is applied by encapsulating a non-polar compound or a hydrophobic molecule in a second group. No interaction bonds or forces are involved, hence it is known as no bond compound or complex. The main component of the inclusion complex is cyclodextrin (CD). It has a cyclic structure of oligosaccharides generated by starch degradation. Cyclodextrin is available in different forms, depending on glucopyranose units with 6, 7 and 8 glucose ring and is known as α, ß and γ-CD. Cyclodextrins contain a hydrophilic outer and a hydrophobic inner cavity.

As with all methods, this method is used even more to improve or increase solubility in water. Drug dissolution rate and drug absorption rate. One compound is the host and the other is the guest, and the host molecule engulfs the guest molecule to improve the solubility and bioavailability of the hydrophobic drug. They are crystalline, hydrophilic and cyclic oligosaccharides that have glucose monomers embedded in a bucket-shaped ring with a hydrophobic cavity and a water-loving outer surface. Three naturally occurring CDs are α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin.[15]

CDs and its different types are basically applied in complexation process. Complex are form between drug and polymer. Derivatives of R-cyclodextrin with increased water solubility (e.g. hydroxyl propyl cyclodextrin are most commonly used in pharmaceutical formulation.[16]

1. The exclusion of high energy water from the cavity,
2. The release of ring strain particularly in the case of -CD,
3. It involves Van Der Wal's Forces
4. There are involvement of Hydrogen and hydrophobic bindings.[17]

Direct Compression Tablets Manufacturing Technique-[18]

Direct compression is considered to be the most preferred, standard, low-cost method of tabletting with less time-consuming. This method of making tablets is preferred by both academics and pharmaceutical manufacturers. Most pharmaceutical companies use conventional manufacturing equipment and routinely readily available ingredients.[19]

The following direct compression methods are commonly used:[20]

a. Composite components
b. Sieve mixes
c. Mix the mixture/lubrication
d. Compressed Mixtures

Direct compression method can be useful in the production of FDT by choosing the right

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combination of drug: excipients ratio. This proper ratio of drug to excipients will provide rapid disintegration with good physical resistance. A technique based on sugar-products as bulking agents has been widely accepted in the preparation of FDTs. It is widely accepted due to its high and fast solubility with sweet taste in aqueous or water. The sweet taste is pleasant in the mouth and masks the bitter taste of the medicine. To mask the taste of the drug, most ready-made formulations of FDTs are incorporated with sugar or some sweetener as a formulation excipient.[21]

Direct compression has a good compressibility and compact ability. The addition of superdisintegrants increases the rate of disintegration and drug dissolution in the simplest, most profitable process of tablet manufacturing. Due to its simple and convenient preparation method of tablets, which mainly require excellent characteristics of powder? Powder features in various characteristics like excellent powder flow in the body.**22**

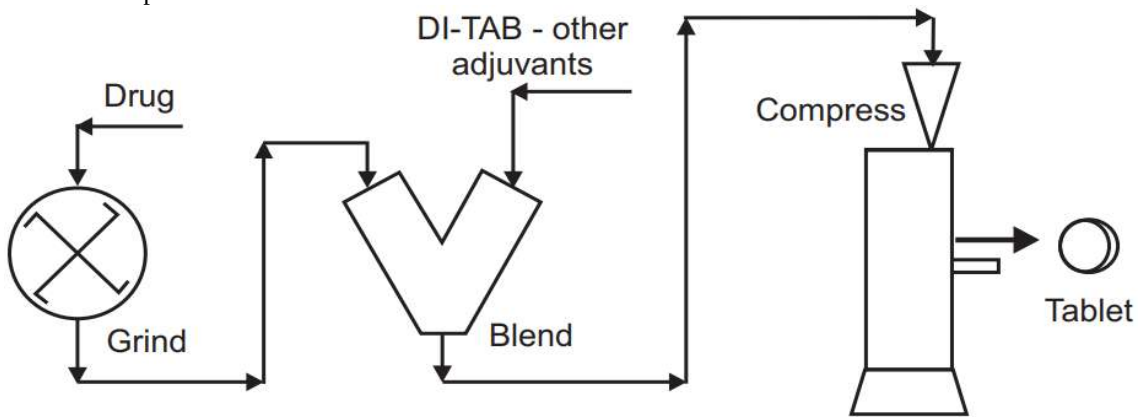

Figure- Process of Tablet Manufacturing (Direct Compression)

Fast disintegrating Tablet[23]

A drug delivery system is an efficient tool for enhancing the market, extending product life cycles, and creating opportunities. Drug delivery system (DDS) makes a significant contribution to global pharmaceutical sales through market segmentation and is moving rapidly.[24]

Despite tremendous innovations in drug delivery, the oral route remains the preferred route for the administration of therapeutic agents because of accurate dosage, low-cost therapy, self-medication, non-invasive method, and ease of administration leading to a high level of patient compliance.

The most popular dosage forms are conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is 'Dysphagia' or difficulty in swallowing for many patients; almost 50% of the population is affected by such a problem. Hence they do not comply with prescriptions, which results in a high incidence of non-compliance and ineffective therapy.[25]

Recently fast disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems because they are easy to administer and lead to better patient compliance.

In some cases such as motion sickness, sudden episodes of allergic attacks, or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty experienced by pediatric and geriatric patients. To overcome such problems, fast-disintegrating tablets or orally disintegrating tablets have emerged as an alternative dosage form recent advances in novel drug delivery systems (NDDS) aim for enhancing the safety of a drug molecule while maintaining its therapeutic efficacy to achieve better patient compliance. Pharmaceutical technologists have put in their best efforts to develop a fast-dissolving/ disintegrating drug delivery system (FDDTs).[25]

The Center for Drug Evaluation and Research (CDER), US FDA defined Fast dissolving/disintegrating tablets (FDDTs) are solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue. Recently European Pharmacopoeia also adopted the term Oro Dispersible Tablet defined as an uncovered tablet for the buccal cavity, where it disperses before ingestion Fast disintegrating tablets (FDT) are also known as fast dissolving mouth dissolving rapid-dissolve quick disintegrating orally

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disintegrating raiment fast melts or dispersible melt-in-mouth quick dissolving porous tablets EFVDAS or Effervescent Drug Absorption System. Fast disintegrating tablets are those when put on the tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva. When Faster the drug into solution quicker the absorption and onset of clinical effects. Some drugs are absorbed from the mouth pharynx and esophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth-dissolving dosage forms is increasingly being recognized in both, industry and academics. The basic approach in the development of FDT is the use of superdisintegrants like cross-linked carboxymethyl cellulose (croscarmellose) sodium starch glycolate (primogel, exploited), cross-linked polyvinylpyrrolidone (crospovidone), etc, which provide instantaneous disintegration of tablet after putting on the tongue, they are by release the drug in saliva. The bioavailability of some drugs may be increased due to the absorption of the drug in the oral cavity and also due to the pregastric absorption of saliva-containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first-pass metabolism is reduced as compared to the standard tablet. The target populations for diuretics, and anti-hypertensive in geriatrics. The combination choice depends on the disease state of the patient.[26]

Requirements of fast disintegrating tablets –[27]

The tablets should:-

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds. Allow high drug loading. Be compatible with taste masking and other excipients.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration
- Have sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature
- Be adaptable and amenable to existing processing and packaging machinery.
- Allow the manufacture of tablets using conventional processing and packaging types of equipment at low cost.

Advantages of fast disintegrating tablets-[28]

FDTs offers dual advantages of solid dosage forms and liquid dosage forms along with special features which include:

Accurate dosing: Being unit solid dosage forms provide the luxury of accurate dosing, easy portability, and manufacturing, good physical and chemical stability, and an ideal alternative for pediatric and geriatric patients.

Enhanced bioavailability: The bioavailability of drugs is enhanced due to absorption from the mouth, pharynx, and esophagus.

Rapid action: Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in the oral cavity.

Patient compliance: No need for water to swallow the dosage form. Hence, it is convenient for patients who are traveling and do not have immediate access to water

Ease of administration: Convenient to administer especially for geriatric, pediatric, mentally disabled, and bedridden patients who have difficulty swallowing.

Obstruction free: No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.

Enhanced palatability: Good mouth feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of the drug.

Simple packaging: No specific packaging is required. It can be packaged in push-through blisters.

Business Avenue: Provide new business opportunities in the form of product differentiation, line extension, uniqueness, and life cycle management. Cost-effective: Conventional processing and packaging types of equipment allow the manufacturing of tablets at a low cost.

Limitations of Mouth-Dissolving Tablets:[29]

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave an unpleasant taste and/or grittiness in the mouth if not formulated properly.
- Drugs with relatively larger doses are difficult to formulate into FDT e.g. antibiotics like ciprofloxacin with an adult dose tablet containing about 500 mg of the drug.

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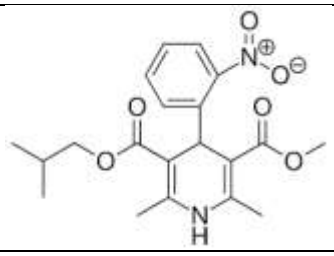
DRUG PROFILE[30]

Structure of Nisoldipine	
Chemical Formula	$C_{20}H_{24}N_2O_6$
IUPAC NAME	3-O-methyl 5-O-(2-methylpropyl) 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate
Synonyms	Nisoldipin ,Nisoldipina , Nisoldipino ,Nisoldipinum
Molecular Weight	388.4g/mol
Melting point	151-152(°C)
LogP	3.26
Solubility	5.77e-03g/L
Pharmacodynamics	Nisoldipine, a dihydropyridine calcium-channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. Nisoldipine is similar to other peripheral vasodilators. Nisoldipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes possibly by deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

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Mechanism of action	By deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum, Nisoldipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.
Protein binding-	99%
Metabolism	Pre-systemic metabolism in the gut wall and this metabolism decreases from the proximal to the distal parts of the intestine. Nisoldipine is highly metabolized; 5 major urinary metabolites have been identified. The major biotransformation pathway appears to be the hydroxylation of the isobutyl ester. A hydroxylated derivative of the side chain, present in plasma at concentrations approximately equal to the parent compound, appears to be the only active metabolite and has about 10% of the activity of the parent compound. Cytochrome P450 enzymes are believed to play a major role in the metabolism of nisoldipine. The particular isoenzyme system responsible for its metabolism has not been identified, but other dihydropyridines are metabolized by cytochrome P450 IIIA4.
Route of elimination	Although 60-80% of an oral dose undergoes urinary excretion, only traces of unchanged nisoldipine are found in urine.
Half-life	The reported elimination half-life of nisoldipine is 7-12 hours.

II. CONCLUSION:

Hypertension is the alarming problem in current scenario which effects every age group to overcome such problem in terms of novel concept fast disintegration oral tablets are designed which was found to be efficient in curing such ailments as compare to conventional approaches. Presently fast disintegrating drug delivery systems have extensively gaining importance and acceptance as new drug delivery systems due to their low cost therapy and enhanced bioavailability and palatability nature apart from this it also promotes patient compliance and other restricted measures which affects the oral route of administration.

In Recent Advances Pharmaceutical drug experts develops the system fast dissolving drug delivery system focuses on enhancing the drug safety while maintaining the therapeutic efficacy and rapid action in terms of novel drug delivery formulation development.

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