Review Article

Solid oral drug delivery system:A mini review

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Abstract

The term "dosage form" describes the physical shape of a medication, such as a solid, liquid, or gas, that enables proper administration to certain body sections. Manufacturing has also benefited from coprocessed multifunctional ready-to-use excipients with shorter processing periods, especially for tablet dosage forms. To enhance the performance of products and processes, new advancements in granulation techniques have been created, such as reverse wet, thermal adhesion, steam, melt, freeze, foam, and moist and pneumatic dry granulation. Additionally, a variety of particle engineering methods, such as co precipitation, hotmelt extrusion, extrusion-spherization, have been used to create robust tablet formulations.

Keywords: solid,oral,delivery

Introduction

In orally administered dosage forms, tablets represent the preferred choice of class of product. Drug absorption from a solid dosage forms after oral administration depends on the release of the drug substance from the drug products, the dissolution or solubilisation of the drug under physiological conditions and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolutions may be relevant to the prediction of in vivo performance. Based on this general consideration, in vitro dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules Introduction The release of drug from the conventional tablet dosage form and its absorption from the GIT depends upon two main processes: First-the disintegration of tablet into granules and second dissolution of these granules through the GIT into the blood. Disintegration is the rate-limiting step in case of highly soluble drugs whereas dissolution is the rate limiting step in case of drugs with low solubility. The release of drug from an immediate release dosage form can be achieved by placing the drug in a layer or coating that is sufficiently thin to allow fast penetration by gastrointestinal fluid which then leaches the drug at a rapid rate. Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Super disintegrant improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants. Traditionally, starch has been the disintegrant of choice in tablet formulation, and it is still widely used. For instance, starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrant .[1-4] Hypertension, commonly referred to as “high blood pressure”, is a medical condition where the pressure is chronically elevated, is one of the commonly found diseases, affecting most of the populations in the world. So, for treating hypertension effectively is main criterion of this study. For treating hypertension, commonly used drugs include angiotensin receptor blockers, ACE inhibitors, α blockers, β blockers, calcium channel blocker, diuretics and combination of any of these categories in immediate action required. The advantage of this combination therapy for hypertension include better blood pressure control by synergistic combination of angiotensin II receptor blocker with calcium channel blocker

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Classifications of solid drug delivery system :

- Tablets
- Capsules
- Powder
- Pill
- Catches

TABLETS

1. Tablets are a unit dosage form where a single standard dose of the medication is precisely measured and deposited. Tablets are solid pharmaceutical dosage forms that can contain pharmacological substances with or without appropriate diluents. They are often made by molding or compression techniques. Tables are produced by the use of punches and dies to compress regular amounts of powders or grains under high pressure. The particles that need to be compressed are made up of one or more medications, either with or without auxiliary ingredients like glide ants, lubricants, binders, disintegration agents, and compounds that can alter how the medications behave in the digestive systems.[2] These compounds have to be safe and therapeutically inactive at the concentrations that are present.
2. A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tableting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.[4,5]

Advantages of the tablet dosage form

1. They come in single units.
2. They offer the greatest capabilities of all oral dosage forms for the best dose precision.
3. Cost is the lowest
4. Lighter and compact.
5. Easiest and cheapest to be packed as strips.
6. Easy to swallow.

7. Best chemical and microbial stability overall oral dosage form.

Disadvantages of tablet dosage form

1. Children and unconscious patients feel it is hard to take.
2. Drugs with poor wetting, slow dissolution properties, and optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
3. Some drugs resist compression into dense compacts, owing to amorphous nature, and low-density character.
4. Bitter and objectionable odour tablets are hard to intake which may require coating[6-10]

OVERVIEW ON TYPES AND CLASS OF TABLETS:

Oral tablets for ingestion

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exceptions are chewable tablet and oral dispersible tablets. Standard compressed tablets this class includes tablets like, Multiple compressed tablets, compression coated tablet, layered tablet, modified release tablet etc.

Tablets used in the oral cavity

The tablets under this group are aimed to release active pharmaceutical ingredient in the oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity. This class includes tablets like lozenges and troches, sublingual tablet, buccal tablet, dental cones, oral dispersible tablet etc.

Tablets administered by other routes

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application. This class includes tablets like vaginal tablet, implants etc.

Tablets used to prepare solution

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used. This class includes tablets like effervescent tablet, hypodermic tablet.

DRUG PROFILE

Amlodipine Besilate: Amlodipine is a long acting calcium channel blocker (dihydropyrridine class) used as an anti hypertensive and in the treatment of angina. Like other calcium channel blocker, amlodipine act by relaxing the smooth muscles in the arterial bone, decreasing total peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscles.

PHARMACOKINETICS AND METABOLISM

Amlodipine is well absorbed following oral administration with peak blood concentration occurring after 6 to 12 hours. The bioavailability is about 60 to 65% this is due to high first pass metabolism. It has a prolonged terminal elimination half life of about 35 to 45 hours. Amlodipine is extensively metabolized in liver and it is a complex process. Amlodipine like other dihydropyridines is oxidized to pyridine analogue. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound

PHARMACODYNAMICS

Mechanism of actions : An increased concentration of cytosolic Ca2+ causes increased contraction in cardiac and vascular smooth muscle cells. The entry of extracellular Ca2+ is more important in initiating the contraction of cardiac myocytes (Ca2+-induced Ca2+ release). The release of Ca2+ from intracellular storage sites also contributes to contraction of vascular smooth muscle, particularly in some vascular beds. Cytosolic Ca2+ concentrations may be increased by various contractile stimuli. Thus many hormones and neurohormones increase Ca2+ influx through so-called receptor-operated channels, whereas high external concentrations of K+ and depolarizing electrical stimuli increase Ca2+ influx through voltage-sensitive, or "potential operated," channels. The Ca2+ channel antagonists produce their effects by binding to the α1 subunit of the L-type Ca2+ channels and reducing Ca2+ flux through the channel.[11-14]

Chemical Name: 3-ethyl-5-methyl2-[(2-aminoethoxy)methyl1]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.

Table1:.Physicochemical Properties

Molecular formula	$C_{20}H_{25}CLN_2O_5$
Molar Weight	408.879
Melting Point	111 – 113
Solubility	Slightly soluble in water
Appearance	White to off white crystalline powder

PHARMACOLOGICAL PROPERTIES

Cardiovascular Effects. Actions in Vascular Tissue: An increase in cytosolic Ca2+ results in enhanced binding of Ca2+ to calmodulin. The Ca2+- calmodulin complex in turn activates myosin light-chain kinase, with resulting phosphorylation of the myosin light chain. Such phosphorylation promotes interaction between actin and myosin and contraction of smooth muscle. Ca2+ channel antagonists inhibit the voltage-dependent Ca2+ channels in vascular smooth muscle at significantly lower

Actions In Cardiac Cell: The mechanisms involved in excitation-contraction coupling in the cardiac muscle differ from those in vascular smooth muscle in that, a portion of the two inward currents is carried by Na+ through the fast channel in addition to that carried by Ca2+ through the slow channel. Within the cardiac myocyte, Ca2+ binds to troponin, relieving the inhibitory effect of troponin on the contractile apparatus and permitting a productive interaction of actin and myosin leading to contraction. Thus Ca2+ channel blockers can produce a negative isotropic effect. Although this is true for all classes of Ca2+ channel blockers, the greater degree of peripheral vasodilatation seen with the dihydropyridines is accompanied by a sufficient baroreflex-mediated increase in sympathetic tone to overcome the negative isotropic effect.

Hemodynamic Effects: All the Ca2+ channel blockers approved for clinical use decrease coronary vascular resistance and increase coronary blood flow. The dihydropyridines are more potent vasodilators in vivo and in vitro. The hemodynamic effects of these agents vary depending on the route of administration and the extent of left ventricular dysfunction. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. The precise mechanisms by which Amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with Exertional angina, Amlodipine reduces the total peripheral resistance (after load) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in-vitro. This inhibition of coronary spasm is responsible for the effectiveness of Amlodipine in vasospastic (Prinzmetal's or variant) angina.

Adverse effects : The most common adverse effects of Amlodipine are associated with its vasodilatory action and often diminish on continued therapy. General: allergic reaction, back pain, hot flushes, malaise, pain, myalgia, rashes, hyperglycemia, thirst.

Precautions :

General - Since the vasodilation induced by Amlodipine Besylate is gradual in onset, acute hypotension has rarely been reported after oral administration.

Patients with Hepatic Failure - Since Amlodipine Besylate is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Amlodipine Besylate to patients with severe hepatic impairment

Hydrochlorothiazide

Hydrochlorothiazide, abbreviated HCTZ, HCT, or HZT, is a diuretic drug of the thiazide class that acts by inhibiting the kidneys' ability to retain water. This reduces the volume of the blood, decreasing blood return to the heart and thus cardiac output and, by other mechanisms, is believed to lower peripheral vascular resistance. Hydrochlorothiazide is a calcium-sparing diuretic, meaning it can help the body get rid of excess water while still keeping calcium.

Pharmacokinetics and metabolism :Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.[15-20]

Pharmacodynamics

Mechanism of action : Hydrochlorothiazide belongs to the thiazide class of diuretics. It reduces blood volume by acting on the kidneys to reduce sodium (Na) reabsorption in the distal convoluted tubule. The major site of action in the nephron appears on an electro neutral Na+-Cl- co-transporter by competing for the chloride site on the transporter. By impairing Na transport in the distal convoluted tubule, hydrochlorothiazide induces a natriuresis and concomitant water loss. Thiazides increase the reabsorption of calcium in this segment in a manner unrelated to sodium transport. Additionally, by other mechanisms, HCTZ is believed to lower peripheral vascular resistance. Acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

Chemical name :6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7sulfonamide1,1-dioxide

Table2:.Physicochemical Properties

Molecular formula	$C_7H_8CLN_3O_4S_2$
Molar Weight	297.739
Melting Point	237 – 275
Solubility	Slightly soluble in water , soluble in acetone
Appearance	white crystalline powder

Adverse Effect : Hypokalemia,Hypomagnesaemia ,Hyperuricemia, Gout, High blood sugar,Weight gain, Nausea/vomiting, Pancreatitis, Dosage And Administration

Adults: The usual initial diuretics oral dose of Hydrochlorothiazide is 12.5 mg once daily with a maximum dose of 25 mg once daily. Small, fragile, or elderly individuals or patients with hepatic insufficiency may be started on 7.5 mg once daily.

Hypertension

Hypertension, commonly referred to as “high blood pressure” is a medical condition in which the blood pressure is chronically elevated. While it is formally called arterial hypertension, the word “Hypertension” without a qualifier usually refers to arterial hypertension.

Raised blood pressure is a common and quantitatively important cardiovascular risk factor. Over 50% of over 65’s in industrialized countries may be considered to have hypertension1 and 50% of people in this age group go on to die a cardiovascular death such as myocardial infarct or stroke. Studies have clearly demonstrated the benefit and safety of an aggressive strategy of blood pressure lowering with targets of below 140 mm Hg systolic and 90 mm Hg Diastolic. Hypertension-induced stroke appears to be largely preventable and a significant reduction is seen in hypertension-attributable ischemic heart disease when the above targets are achieved.

Normal Blood Pressure less than 120/80

Pre-Hypertension 120-139/80-89

High Blood Pressure (Stage 1) 140-159/90-99

High Blood Pressure (Stage 2) higher than 160/100

Blood Pressure

High Blood Pressure Causes

In 90% of people with hypertension, the cause of high blood pressure is not known and is referred to as primary or essential hypertension. While the specific cause is unknown, there are risk factors that can contribute to developing high blood pressure. Raised levels of blood pressure result from the complex interplay of environmental and genetic factors leading to the activation or suppression of one or more of a host of physiological systems involved in blood pressure regulation . The complexity of blood pressure control mechanisms.

Factors that cannot be changed:

Age: the older a person is, the greater the likelihood that he or she will develop high blood pressure, especially elevated systolic readings. This is largely due to arterio-sclerosis, or “hardening of the arteries”.

Race: African Americans develop high pressure more often than Caucasians. They develop high blood pressure at a younger age and develop more severe complications sooner in life. Socioeconomic status: High blood pressure is found more commonly among the less educated and lower socioeconomic groups. Residents of the south-eastern United States, both Caucasian and African American, are more likely to have high blood pressure than residents of other regions.

Family History (Heredity): the tendency to have high blood pressure appears to run in families

Antihypertensive drug

Antihypertensive drugs are medications used to manage hypertension (high blood pressure) and prevent its associated complications, such as stroke, heart failure, and kidney failure. These medications work through various mechanisms to lower blood pressure and are categorized into several classes:

Classes of medicines for hypertension

1. Diuretics: These medications lower blood volume by assisting the body in getting rid of extra salt and water. Common varieties include loop diuretics like furosemide and thiazide diuretics like hydrochlorothiazide.
2. ACE Inhibitors: Angiotensin I is not converted to angiotensin II, a strong vasoconstrictor, by angiotensin-converting enzyme (ACE) inhibitors like lisinopril and enalapril.
3. Angiotensin II Receptor Blockers (ARBs): These drugs, which include losartan and valsartan, prevent angiotensin II from acting

at its receptor sites, resulting in blood pressure reduction and vasodilation.

4. Calcium channel blockers: Medicines such as nifedipine and amlodipine prevent calcium from entering the heart and blood vessel cells, causing the vessels to relax and enlarge.

5. Beta-blockers: These medications, which include atenolol and metoprolol, lower blood pressure by lowering heart rate and contraction force.

6. Renin Inhibitors Directly: One such medication is Aliskiren, which lowers blood pressure by blocking renin, an enzyme that is needed to produce angiotensin.

7. Vasodilators: These drugs cause blood vessels to relax directly, lowering blood pressure. Examples are minoxidil and hydralazine[21-25].

METHODS OF FORMULATION IMMEDIATE RELEASE TABLETS

In general, the choice of method for the manufacture of tablets is dependent on a number of factors like:

The physical and chemical stability of the therapeutic agent during the manufacturing process.

The availability of the necessary processing equipment

DIRECT COMPRESSION

The term direct compression is used to define the process by which tablet are compressed directly from powder blends of the active ingredient and suitable excipients which will flow uniformity into a die cavity and from into a firm compact. No pretreatment of the powder blends by wet or dry granulation necessary. The manufacture of tablets using wet granulation or dry granulation method is both time - consuming and potentially costly. The mechanism of particle-particle interaction in tablets produced by dry granulation. The advent of direct compression was made possible by the commercial of direct compressible tablet vehicles that possess both fluidity and compressibility.The simplicity of the direct-compression process is obvious. But direct compression should not be conceived as a simplified modification of the granulation process for making tablets. It requires a new and critical approach to the selection of raw materials, flow properties of powder blend and effect of formulation variable on compressibility. During the wet granulation process the original properties of the raw materials are, to a great extent, completely modified. As a result, a new materials are covered up during the granulation step. This is not true in direct compression and therefore the properties of each and every raw material and the process by which these materials are blended become extremely critical. Direct compression is often preferred because of its simplicity and relatively that less then 20 percent of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression.

WET GRANULATION METHOD

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems[21-25]

DRY GRANULATION METHOD

Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation equipment offers a wide range of pressures to attain proper densification and granule formation. Dry granulation is simpler than wet granulation, therefore the cost is reduced. However, dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules. At last powder lubricants are added..

PROBLEMS IN TABLET MANUFACTURE AND RELATED REMEDIES

Capping and Lamination-'Capping' is the term used to describe the partial or complete separation of the top or bottom crowns of a tablet from the main body of tablet. 'Lamination' is the separation of a tablet into two or more distinct horizontal layers

Chipping-'Chipping' is defined as the breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operations.

Cracking-Small, fine cracks observed on the upper and lower central surface of tablets, or very rarely on the sidewall are referred to as 'Cracking'.

Sticking/Filming-'Sticking' refers to the tablet material adhering to the die wall. Filming is a slow form of sticking and is largely due to excess moisture in the granulation.

Picking-'Picking' is the term used when a small amount of material from a tablet is sticking to and being removed off from the tablet-surface by a punch face. The problem is more prevalent on the upper punch face than on the lower ones.

Fixed-dose combinations

Pharmaceuticals known as fixed-dose combinations (FDCs) are formulations that include two or more active ingredients in a single dosage form, like a tablet or capsule. By lowering the number of pills, a patient must take daily, they are intended to increase therapeutic efficacy,improve patient compliance, and streamline treatment regimens.In the case of hypertension, Fixed-dose combinations (FDCs) of antihypertensive medicationsare increasingly recognized for their effectiveness in managing hypertension. These Combinations typically include two or more active agents in a single pill, which contrasts with free-equivalent combinations (FECs) where the drugs are taken separately. Combination antihypertensive agents are made up of pharmacologic classes such asangiotensin-converting enzyme (ACE) inhibitors and diuretics, beta-blockers and diuretics,angiotensin-II antagonists and diuretics, and calcium channel blockers and ACE inhibitors.By combining two or more medications that typically act at different sites to block multiple effector pathways, fixed-dose combination therapy effectively lowers blood pressure. Moreover, when two medications are taken together, the second one might prevent the firstone from activating the counter-regulatory system

Advantages of fixed-dose combinations

FDCs have various advantages, such as

Increased Compliance: FDCs assist patients in following their treatment plans by lowering the pill burden.

Synergistic Effects: Drug combinations that function through various pathways can increase overall efficacy.

Cost-Effectiveness: FDCs may lower distribution and packaging expenses, lowering patient costs.

Rationale for fixed drug combinations

The goal of fixed-dose combination therapy is to improve compliance by using a single tablet taken once or twice daily and to achieve improved blood pressure control by utilizing two or more antihypertensive agents with distinct modes of action.The clinical and metabolic effects of using the maximum dosages of each component of the combined tablet can also be reduced by using low doses of the two separate agents. Because of these possible benefits, some researchers have suggested starting combination antihypertensive therapy as the first line of treatment, especially for patients who have more severe initial levels of hypertension or damage to target organs. It has been established that the use of agents with complementary mechanisms of action—such as diuretics, calcium channel blockers, and renin-angiotensin-aldosterone systemblockers—in combination for patients needing three medications is sensible and efficient. Triple medication

combinations have been demonstrated in recent research to be extremely safe, effective, and well-tolerated by patients. Lately, the FDA approved three distinct fixed- dose triple-drug combinations to treat hypertension: hydrochlorothiazide, amlodipine besylate, and olmesartan medoxomil. Comparing triple-combination regimens to dual combination regimens, a higher percentage of patients were able to achieve BP control, with noticeably lower BP levels.[26-28]

Evaluation parameters

Pre-compression parameters of blend

1. Angle of repose: The term "angle of repose" refers to the greatest angle that can be formed between a horizontal plane and a powder pile that is floating freely. Utilizing the equation below angle of repose was ascertained,

2. Bulk density: The mass of a powder divided by the bulk volume is known as bulk density. Particle shape, particle size distribution, and particle adhesion tendency are the main factors influencing a powder's bulk density. A certain amount of precisely weighed bulk powder from every formula was transferred into a 25 ml measuring cylinder, shaken to break up any agglomerates, and the initial volume was noted.[29-33]

3. Tapped density: A weighed quantity of tablet blend was transferred into a graduated cylinder. The volume occupied by the powder mixture was noted down. Then measuring cylinder was subjected to 100, 200 and 300 taps in a tap density apparatus.

4. Carr's index: Another name for Carr's index is compressibility. It is connected to ohesiveness, particle size, and relative flow rate indirectly. This method of predicting the characteristics of powder flow is easy to use, quick, and well- liked

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