IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF COMBINATION TABLET OF ANTIHYPERTENSIVE AND DIURETIC DRUGS

Nikita Guleria[1], Harkomalpreet Kaur[2], Kulpreet Kaur[3], Dr. Afshan Ara [4], Daiwakshi Sandil[5]

Student[1], student[2], Student[3],Teacher[4],Teacher[5]

[1, 2, 3, 4,5] L.R. INSTITUTE OF PHARMACY

Affiliated to HPU/ HPTU, Approved by AICTE and PCI

Jabli-Kyar, P.O. Ochghat(Sultanpur Road), Solan(H.P.) Pin-173223

ABSTRACT:

The aim of this investigation was to develop a formulation of telmisartan and hydrochlorothiazide for the treatment of hypertension. Oral drug delivery systems are the most convenient and easiest route of administration. The goal of drug delivery systems is to provide a therapeutic amount of the drug to the proper site in the body to achieve a prompt result and then maintain the desired drug concentration. Single-dose combination antihypertensive therapy is an important option because it combines effective blood pressure reduction and a low side effect profile with convenient once-daily dosing to improve compliance. There is strong consideration of combination therapy for the treatment of various diseases and disorders requiring long-term therapy, such as hypertension and diabetes. Combining telmisartan (an angiotensin II receptor) and Hydrochlorothiazide (HCTZ), a diuretic, has been shown to have a cumulative antihypertensive effect. The addition of diuretics to angiotensin II receptors increases the action of angiotensin receptor blockers. This formulation was prepared by using low-substituted disintegrants. The tablets were prepared by the wet granulation method, and different excipients were added, like binders, lubricants, and disintegrants. The prepared formulations were evaluated with various parameters like tablet size and thickness, hardness, disintegrant testing, weight variation, and friability.

Keywords: Telmisartan, Hydrochlorothiazide, Low substituted disintegrants, Hypertension, Diuretics.

INTRODUCTION

The oral route of drug administration is one of the most important route of administrating drug for systemic effects of drugs that are orally administered. Oral routes of the drug administration had wide acceptance up to 50-60% of total dosage form.[1] A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. Oral route for the administration of therapeutic agents is the most convenient route because of low cost of therapy and ease of administration which leads to higher level of patient compliance.[2]

Tablets are one of most challenging of all the pharmaceutical products for designing and manufacturing. According to Indian Pharmacopoeia IP, tablets are solid, flat or biconvex dishes, unit dosage form. They are prepared by compressing a drug or mixture of drug, with or without diluent. Tablet is defined as a compressed solid dosage form that contain medicaments with or without excipients.[3]

TYPES OF TABLETS

Oral Tablets for Ingestion

1. Standard Compressed Tablets
2. Multiple Compressed Tablets
- Compression Coated Tablets-

a) sugar coated

b) film coated tablets

c) gelatin coated tablets

d) enteric coated tablets Layered tablet

3. Targeted Tablets –
   a) Floating Tablet,
   b) Colon Targeting Tablet
4. Chewable tablets
5. Dispersible tablets

Tablets used in the Oral Cavity

1. Lozenges and troches
2. Sublingual tablet
3. Buccal tablet
4. Dental cones
5. Mouth dissolved / rapidly dissolving tablets.[4]

Oral Drug Delivery:

Three categories of oral drug delivery systems are distinguished according to the intended therapeutic goals.

1. Immediate-release preparations: The main goal of these preparations is to achieve a rapid start of action. Benefits of making immediate release preparations include

- Improved oral bioavailability via pregastric and transmucosal administration absorption.
- Convenience in drug administration to dysphasic patients. Granules and fast-disintegrating tablets with effervescent mixtures like sodium carbonate, sodium bicarbonate, citric acid, and tartaric acid, as well as super disintegrants like sodium starch glycolate, croscarmellose sodium, and crospovidone, are examples of conventional IR formulations.

2. Controlled release preparation: Diffusion-controlled, solvent-activated, and chemically controlled systems are the three types of controlled release technologies presently available for oral medication delivery systems. Systems with diffusion control are reservoir devices that are monolithic. The drug's rate-limiting step in this process is its diffusion through a polymer matrix or polymeric membrane. Systems operated or activated by solvents can be regulated by swelling of the polymer or by osmoticism.

3. Targeted released preparation: Site-specific release Oral drug delivery involves placing a device at a specific location within the gastrointestinal tract. While a device can be targeted to specific parts of the GI tract, achieving site-specific delivery in the oral cavity and rectum require less effort than the stomach and small and large intestines. It is important to overlook both longitudinal and transverse GI constraints for the small, large intestine, and stomach. [5]

Hypertension Hypertension, high blood pressure, is a very common disorder particularly past middle age. It is an important risk factor for cardiovascular mortality and mobility. Blood pressure (BP) is measured by systolic and diastolic pressure. At Normal blood pressure, systolic range is 100-140mmHg and diastolic is 60-90mmHg. Risk appears to be increase even above 120/80 mmHg.[6] Hypertension is one of the most common preventable risk factors for cardiovascular disease (which includes coronary heart disease, heart failure, stroke, myocardial infarction and peripheral artery disease), chronic kidney disease and cognitive impairment.[7] High Blood pressure or hypertension is a force that a person's blood exerts against walls of the blood vessels. This pressure is depended upon the resistance of the blood vessels and hard the heart has
to work. Almost half of the adults in the United States have high blood pressure problem, but many are not aware of this.[8]

Diuretics Diuretics also known as Natriuretic are drugs that cause a net loss of Na+ and water in urine. Diuretics drugs are most widely prescribed drugs. Diuretics have been the standard antihypertensive drug as they do not lower BP in normotensives.[9] Diuretics are involved in the management and treatment of oedematous and various non-edematous illness conditions; diuretics are a type of drug. Diuretics are a type of medication. This activity discusses the benefits, side effects, and contraindications of using diuretics to treat heart failure, hypertension, ascites, and other conditions, as needed. Drugs called diuretics pharmacologically bias the kidney's ability to regulate fluid balance in favour of excreting water and electrolytes.[10] Among the most often prescribed drugs are diuretics. They are characterized as medications that aid in the kidneys' excretion of water and electrolytes, hence accelerating the flow of urine. Standard pharmacology textbooks state that diuretics are used to treat Edema, heart failure, or high blood pressure.[11]

Therapeutic action Telmisartan is an angiotensin II receptor blocker (ARB), acting on the AT1 subtype receptor and shown to be effective in the treatment of hypertension but Telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD).[12] Hydrochlorothiazide diuretics are among the most commonly used antihypertensive medications. Thiazides act as a diuretic by inhibiting the Na+/Cl−cotransporter (NCC) in the renal distal convoluted tubule. The NCC facilitates sodium absorption from the distal tubules to the interstitium, accounting for roughly 7% of total sodium reabsorption.[13] Thiazide use causes acute fluid loss to urine by decreasing sodium reabsorption, resulting in decreased extracellular fluid and plasma volume. This volume loss causes reduced venous return, increased renin release, decreased cardiac output, and lower blood pressure.[14]

Fixed dose combination The ARB telmisartan and the thiazide diuretic hydrochlorothiazide are two antihypertensive drugs with well-established clinical efficacy in the treatment of hypertension. However, as is common in the treatment of essential hypertension, many patients are not adequately controlled with telmisartan or hydrochlorothiazide alone, either at the time of diagnosis or later in their follow-up. Angiotensin receptor blockers' effects will be amplified when diuretics are added to angiotensin II receptor blockers. As a result, fixed-dose combinations of telmisartan and hydrochlorothiazide have been developed to improve telmisartan efficacy while also promoting compliance in patients who would otherwise require the administration of two drugs. Telmisartan and hydrochlorothiazide can be combined in three different doses: 40 mg/12.5 mg, 80 mg/12.5 mg, and 80 mg/25 mg. [15]

MATERIAL AND METHOD

List of materials:[16]

Sr. No	Materials
1.	Telmisartan
2.	Hydrochlorothiazide
3.	CMC
4.	KOH
5.	Ascorbic Acid
6.	Titanium Dioxide
7.	Water
8.	Talcum Powder
9.	Aerosil
10.	Crospovidone
11.	Magnesium Stearate
12.	Pollacriline potassium

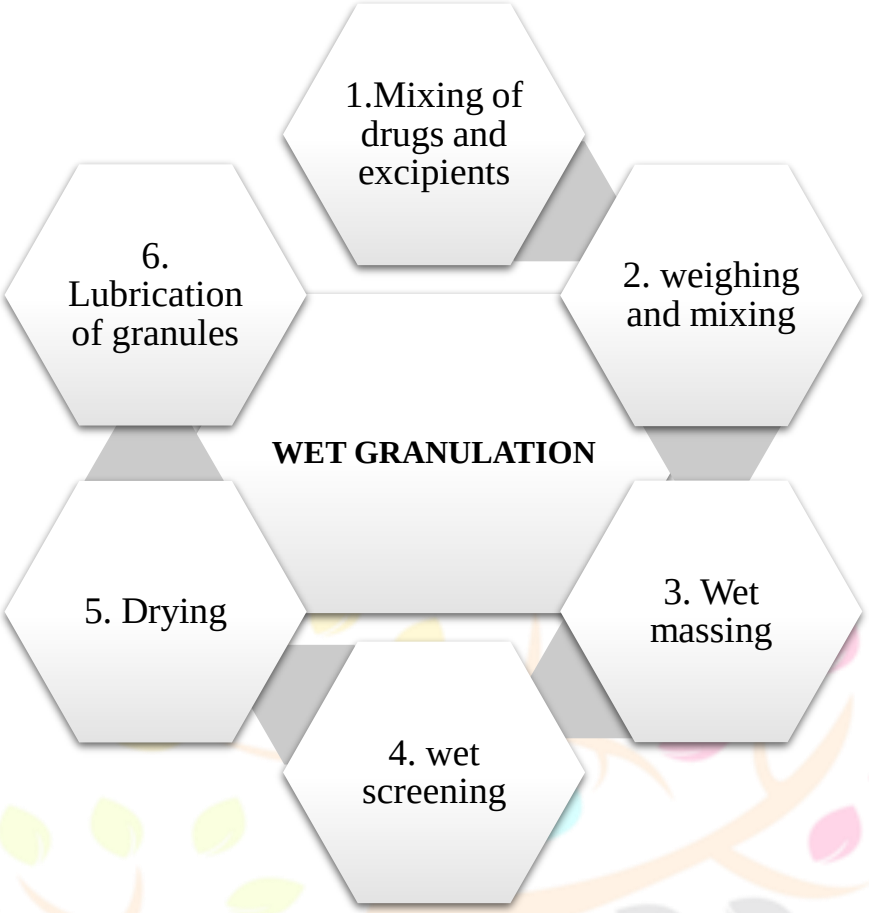
Method of formation of tablet

The production of tablets entails a few clearly defined procedures, which are as follows:

- Mixing
- Granulation
- Compression
- Coating (if required)

Mixing: Since particles of different sizes will separate during mixing, the various solid or powder materials are reduced to the same particle size in this step. A variety of machinery, including a roller mill, hammer mill, cutter mill, and fluid energy mill, is necessary to break apart the big chunks.

Granulation: It is the method used to get the main powder particles to stick together to create substantial multistep entities. Size range: 0.2 mm – 4 mm. (between 0.2 and 0.5 mm)

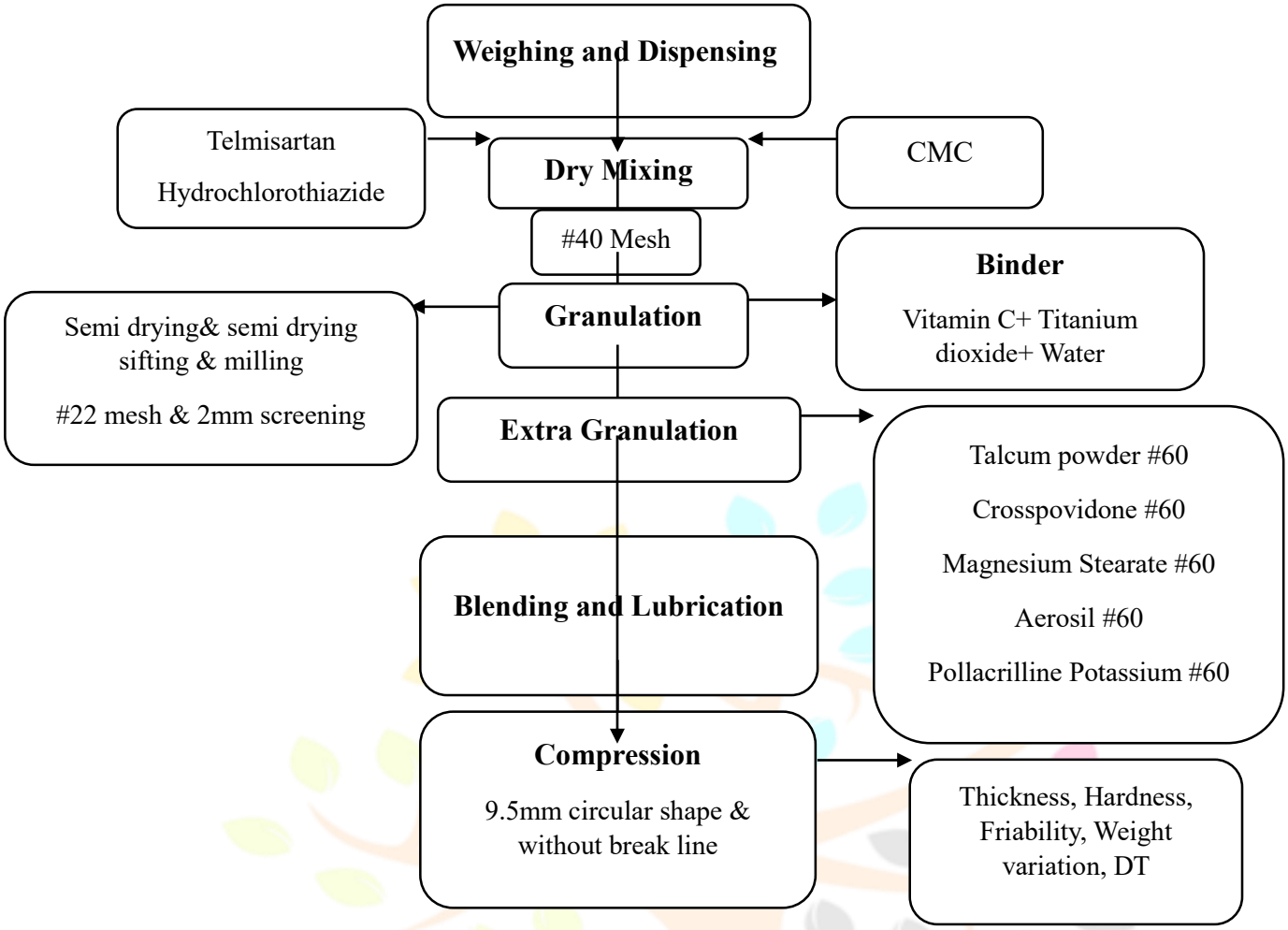


Wet Granulation

Method of Preparation

By Wet Granulation:

1. Mixing of drugs i.e., Telmisartan & Hydrochlorothiazide and excipients. (excluding the lubricants).
2. Preparation of binder dispersion.
3. Mixing of Binder solution with powder to form a coarse mass.
4. Coarse Sieving.
5. Drying of Moist granules.
6. Sieving of dried granules and mixing with disintegrants and lubricants.
7. Compression into Tablets.



Manufacturing process of tablet

EVALUATION PARAMETERS

The chemical, physical, and bioavailability aspects of tablets must be quantitatively evaluated and assessed to develop tablets and thereafter monitor the quality of tablets produced. Physical and chemical factors are the two main categories into which tablets are evaluated. parameters.

Angle of repose: After determining the angle of repose, the flow property was ascertained. It is the greatest angle that can be formed between the powder heap's free-standing surface and the horizontal plan.

$$= \tan 1 (h/r)$$

h=height, r=radius

Tapped density and bulk density: 5g of the powder (W) from each formula were added to a 25-millilitre measuring cylinder. Following the observation of the initial volume, the cylinder was allowed to descend on its own weight, at intervals of two seconds, from a height of 2.5 cm onto a hard surface. The sound of the tapping was proceeded till the volume didn't vary any more. The following formulas were used to get the bulk density and the tapped density.

$$\text{Bulk density} = W / VO$$

$$\text{Tapped density} = W / Vf$$

Where, W = weight of the powder, VO = initial volume, Vf = final volume

Carr's index: One significant metric that may be derived from the bulk and tapped densities is the compressibility index. Theoretically, a material has greater flowability the less compressible it is. A substance is considered free flowing if its values are between 20 and 30 percent.

$$CI = 100 (VO – Vf)/V$$

Where, CI = Compressibility index, VO = initial volume, Vf = final volume.

Hausner ratio: The ratio of tapped density to bulk density is used to measure it and provides information about the powder's flow characteristics.

PHYSICAL APPEARANCE

Hardness: A tablet's hardness level reveals how well it can tolerate handling-related mechanical shocks. A Monsanto hardness tester was used to measure the tablets' hardness. Kilo Pascals are used to express it. The tablets' hardness was assessed after three were chosen at random.

Weight variation test: The average weight of twenty tablets was calculated after they were chosen at random. None of the individual weight's deviates from the average weight by more than twice the %, and no weight deviates from the average weight by more than two times the percentage.

Friability test: The Roche friabilator was used to assess the friability of tablets. It has a percentage (%) as its expression. Twenty pills were put into the friabilator after being weighed initially (w0 initial). The friabilator was run up to 100 revolutions or for 4 minutes at 25 rpm. The devices were weighted once more (w).

Next, the percentage friability was determined by.
Percentage of Friability = 100 (1-w/w0)
Percentage friability of tablets less than 1% is considered acceptable.

Disintegration test: Disintegration, the process of breaking down a tablet into smaller particles or granules, is an essential initial step toward a solution for most tablets. One of the crucial quality control tests for tablets of the disintegrating type is this one. We measure the disintegration time of six pills utilizing USP XXII equipment. The disintegration time of traditional release tablets with a disintegration type is tested.

CONCLUSION:

The stable robust qualities of telmisartan and hydrochlorothiazide conventional tablets are formulated. The formulated tablets are compared with the specifications of the innovator and the optimized formulation complies with the specifications. The disintegrant used in the formulation is Carboxymethylcellulose which is different from that of the innovator and even the binder differs from the innovator even though the specifications of the evaluation are compiled as per the specifications. Nowadays these tablets are gaining more importance in the enterprise targeting paediatrics, geriatrics and all age group. The ODTs have conceivable blessings over traditional dosage forms, with their elevated effect person compliance, bioavailability and rapid onset of action had drawn the interest of many manufactures over a decade.

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