IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

DEVELOPMENT AND EVALUATION OF TELMISARTAN EFFERVESCENT TABLETS BY DIRECT COMPRESSION METHOD.

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ABSTRACT- The therapy of essential hypertension is advised for telmisartan, a strong, long-acting, nonpeptide antagonist of the angiotensin II type-1 (AT1) receptor. The primary objective of this study was to develop, construct, and physico-chemically assess effervescent Telmisartan tablets as they are simple to deliver and oral dosage forms can be challenging for the elderly and young. Croscarmellose, sodium starch glycolate, and cross povidone are examples of superdisintegrants that are used to boost the effectiveness of solid dosage forms. The rapid disintegration may be caused by the rapid uptake of water from the medium, swelling, or burst effect, which increases bioavailability.

Methods 20mg effervescent tablets were created using direct compression techniques. Wet granulation was used to analyse the powder mixture and granule mixture for various pre- and post-compression parameters**.**

KEY WORDS - Super dissolving agents, Fast absorption, Direct compression method, moist granulation process, effervescent tablets

INTRODUCTION –

Angiotensin II Type 1 (AT1) receptor antagonist telmisartan, sold under the brand name Micardis, is authorised for the treatment of hypertension. both on its own and in combination with other antihypertensive medications. Telmisartan's prolonged elimination half-life (24-hour dose interval) ensures that the medication effectively lowers blood pressure (BP). In a wide range of hypertensive patients, including the elderly and those who already have type 2 diabetes mellitus, telmisartan is well tolerated and provides long-term antihypertensive efficacy when used alone or in combination with other hypertensive agents, according to extensive evidence from well-designed clinical trials. For instance, Telmisartan alone (once daily 40 or 80mg) for 8 weeks produced greater antihypertensive efficacy in patients with mild-to-moderate hypertension than monotherapy with losartan or valsartan. Telmisartan, an anti-hypertensive medication, Therefore, the goal is to create and test a quick-release formulation of telmisartan employing hydrophilic polymers like PEG 4000 and PEG 6000.

Since effervescent pills are uncoated and contain medications designed to dissolve quickly in water. They are the dose forms that must be taken by dissolving the medication in water before being taken internally. The effervescent tablet's key benefit is that the solution may be prepared quickly and easily. Consequently, excipients like water-soluble. Formulations with friability of 1% (or 0.5–1%) or less showed that the mechanical resistance of the tablets was good. The percentage of drugs was discovered to be between 98 and 102%, which is within acceptable levels. The tablet's hardness was determined to be between 3 and 4kp. Effervescent tablets can be absorbed quickly because they have already begun to dissolve by the time they reach your stomach. In order to boost the bioavailability and stability of active compounds that are only moderately soluble in water in aqueous solution, cyclodextrine has mostly been utilised as a complexing agent.

lubricants (e.g. PEG 4000, 6000 and sodium benzoate) sweetners, flavouring water soluble colors are applied. PEG 6000 in small amount can be used as effective binder.

Nowadays, many super disintegrants are favoured because of their many benefits, including their wide availability, lower price, and non-irritating and non-toxic nature.

Due to a number of benefits, including a broad range of availability, lower cost, and a non-irritating and non-toxic nature, several super disintegrants are favoured nowadays.

Effervescence reaction equation

$$3NaHCO3\ (aq) + H3C6H5O7\ (aq) \rightarrow 3H2O\ (aq) + 3CO2\ (g) + 3Na3C6H5O7\ (aq).$$

MATERIALS AND METHODS –

In general, the selection of tablet production methods depends on a number of parameters, including:

- The ingredients utilised to create the product's excipients.
- The therapeutic agent's physical and chemical stability during manufacture.
- The accessibility of particular processing machinery.
- The price of the production process.

such as angle of repose, compressibility index, mean particle size and Hausner's ratio. The tablets were evaluated for post-compression features including weight variation, hardness, friability, drug content, dissolution time, carbon dioxide content, effervescence time, pH, Telmisartan is a ACE inhibitor antihypertensive drug. Hence, in the present work, Telmisartan

Different super dissolving agents will be used to make effervescent tablets. When compared to normal tablets and mouth-dispersing tablets, the amount of medication that is vulnerable to first pass metabolism is minimised. A wide range of pharmacological active substances from many therapeutic areas are included in effervescent tablets. Tablet that is effervescent and has high porosity, low density, and low hardness. The blend's pre-compressional characteristics were investigated. The pre-compression parameters' evaluated values fell within the set bounds and showed good free-flowing characteristics. All of the It was discovered that the in vitro dispersion duration was in the 70–150 sec range, with rapid in vitro dissolution occurring in under 3 min. There was no evidence of a chemical reaction between the medication and excipients. the direct medication release from the Telmisartan pill.

Advantages-

Since direct compression skips the soaking and drying steps and boosts the stability of active components, it is best suited for medications that are susceptible to heat and moisture.

• Because there are fewer unit operations, there are less validation and documentation needs.

• Equipment, space, and people savings.

• There is very little danger of microbiological contamination in tablets because there is no water in the granulation process.

• Tablets should not be swallowed.

• Improved tolerance due to good gut and stomach health.

They're portable, too.

• Increasing portability.

• Dosing acutely.

• Because they deliver a steady and sustained release of the medicine, they are the ideal dosage forms.

• Boost the palatability.

Disadvantages-

- Relatively expensive due to some excipients.
- Larger tablet would need different kinds of packaging material.

Rationale for Effervescent tablet-

Effervescent tablet are so popular due to the fact that they are dissolved in liquid such as water, and fruit juice meaning that they taste better than conventional tablets which dissolve

Effervescent tablets, in contrast, dissolve more rapidly, completely, and thus you receive the full benefit of the contents. This increases absorption rate. Once consumed, conventional tablets usually dissolve gradually in the stomach, but occasionally they only partially dissolve, which might cause irritation. The advantages of effervescent tablets are that they dissolve uniformly, preventing the localised concentration of the chemicals. This translates into greater taste, a lower risk of irritability, and an effective way to consume ingredients. Effervescent tablets improve fluid consumption while simultaneously providing the adequate nourishment desired. If you are dehydrated, this may be especially helpful.

MATERIALS-

The required Ingredients and their sources -

Acid & Base, additionally it also requires a Sweetener and a Binding agent.

Acids*:* Acids include citric acid (citrus fruit), Tartaric acid (grapes, apples, pineapple), Malic acid (mainly apples), Adipic acid (beet juice) and Fumaric acid (plant Fumaria officinalis).

Bases*:* Bases include Sodium bicarbonate (dissolved in mineral springs), Sodium hydrogencarbonate (natural mineral form is nahcolite).

Sweetener*:* Vanillin (eugenol or guaiacol), Mannitol (plant manna) Sucrose (sugarcane, sugar beets, sugar maple sap).

Disintegrating agent*:* Cross povidone (from cross-linking reaction of vinyl pyrrolidone), Sodium starch glycolate (corn or potato starch), Kappa carrageenan (species of seaweed called Euchema cottonii).

Lubricant: Mg. stearate (palm oil, coconut oil and vegetable oil), PEG 6000 (petroleum-based compounds).

Filler or Binder: Lactose monohydrate (alpha-lactose from cow's milk).

Complexing agent*:* Cyclodextrine (bacterial enzyme cyclodextrin glycosyltransferase).

Solvent: Ethanol (non-aqueous method) (source- distillation of fermented starch).

Sweetening agents are very important in these formulations. As sucrose is Hygroscopic (which absorbs water easily) it could be the major reason for the increase in the mass of the tablet, hence other sweeteners like Vanillin, aspartame, mannitol and sucralose are often used.

Excipients used in formulation of Effervescent tablet-

• To avoid interactions with the active ingredients, this necessitates a thorough understanding of the chemistry of these excipients. Another concern that formulators must deal with is how much these substances will cost. Except for specific actives that are needed as masking agents, excipients can typically be used for a wide range of activities.

a. Bulking agents:

• Texture-improving compounds accelerate the composition's disintegration in the mouth and stomach. Additionally, bulking agents lower the composition's active ingredient concentration. For increased aqueous solubility and good sensory perception, more sugar-based bulking agents are advised for this delivery system, such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose), and starch hydrolystate. In instance, mannitol has a high degree of water solubility and is well absorbed by the body. Bulking agents are incorporated into the final composition in amounts ranging from 10% to 90% by weight.

b. Lubricants:

They take away grit and aid in the movement of drugs from the mouth into the stomach. Lubricants are typically used to tablet formulations to lessen friction as the tablet is created between the grains and die wall. PEG 6000, for instance, in mg.

c. Emulsifying Agents:

Emulsifying agents are crucial excipients in the formulation of effervescent tablets because they promote quick disintegration and painless medication release. Emulsifying chemicals are also helpful in stabilising immiscible blends and improving bioavailability.

Certain lipid molecules and their metabolites have the power to cause gastrointestinal fluid changes that enhance medication absorption. At the point where two immiscible liquids and a stabilised system meet, agents form a film.

Additionally, a pharmaceutically acceptable emulsifier ought to be stable.

• Work well with additional components.

• Not be harmful.

• Have little flavour, colour, or odour; • Not affect the stability or effectiveness of the active substance.

d. Binding agents-

In order to give plasticity and boost the inter-particulate bonding strength inside the tablet, binders are added to the formulation of the tablet.

CLASSIFICATION ON THE BASIS OF THEIR APPLICATION:

*1.*Solution binders*:*

A solvent is employed to dissolve them (for example water or alcohol can be used in wet granulation processes). Examples include polyethylene glycol, gelatin, cellulose, cellulose derivatives, polyvinyl pyrrolidone, starch, and sucrose.

2. Dry binders*:*

These are included in the powder blend, either as part of a direct powder compression (DC) formula or after a wet granulation process. cellulose and methylcellulose are two examples.

TYPES OF NATURAL BINDERS:

Starch used as a binder

B. Binder: natural gums

C. The binding agent is dried fruit.

In the culinary and pharmaceutical industries, milk sugar is another name for lactose monohydrate.

It is readily available, highly inexpensive, has a long shelf life, and a mildly sweet flavour. Additionally, it blends well with a variety of components.

e. Disintegrating agent –

When tablets are made, a disintegrant is a chemical added to make them dissolve upon contact with moisture and release their medical ingredients. Tablets and capsules contain disintegrants and super-disintegrants to ensure quick disintegration into their basic components and facilitate the release of the active substances. Cross povidone, sodium starch glycolate, and kappa-carrageenan are three examples.

f. complexing agent-

Pharmaceuticals that are poorly soluble are routinely given a boost in stability, solubility, and bioavailability using cyclodextrins (CDs), a versatile complexing agent. Additionally, it is used to extend shelf life and mask food products' flavours. A -(1,4) link holds six or more glucopyranose units together to form cyclic oligosaccharides, or CDs. The chemical structures of the top three natural cyclodextrins (-, -, and -CDs).

METHODS –

Wet Granulation-

Wet granulation is the method that is most frequently used. The steps that make up the wet technique are weighing, mixing, and granulating; screening the damp mass; drying; dry screening; lubrication; and compression. The components are weighed first, sieved through sieve number 60, transferred to a quick mixer granulator, combined there for five minutes at a slow speed, and then a binder solution is added. The mixture is then churned ferociously for a further two minutes. After passing through a sieve, the mass is next dried in a tray dryer at 70°C. This is used to make tablets.

afterwards compressed. The excipients and API are wet massed with granulation liquid with or without a binder to create the granules, which is referred to as "wet granulation" in common usage.

Direct Compression-

To create tablets, the powdered mixture is instantly compressed at 8000–12000 lb of pressure. delivers the easiest, quickest, and most effective way to make tablets. By adding an API to the excipient and the lubricant before compression, the manufacturer can quickly process the product. There is no requirement for further processing steps.

Lower production costs for resources including capital, labour, and energy, as well as avoiding the use of water for granulation for medications with water sensitivity, are the key advantages of direct compression versus wet granulation.

Dry Granulation

No heat source or solvent are needed for dry granulation. The least utilised method for granulation is this one. Fibric is first compressed into a compact, and then the compact is milled to create granules. Dry granulation can be done in two different ways. Slugging, the most used method, is compressing the powder once more and grinding the resulting tablets or slug to create granules. An alternative method involves recompressing the powder with pressure rolls using a tool called a Chilosonator.

This inquiry was divided into two parts. The effects of various citric acid and sodium bicarbonate concentrations on the effervescent tablet were investigated in the study's first section. The process of making effervescent

Part 1*:* Formulation of Effervescent Tablet Using Different Percentages of Effervescent Agent.

Citric acid and sodium bicarbonate were the effervescent materials used in this experiment.

Weighed and combined for 15 minutes were the primary powder mixtures of lactose, microcrystalline cellulose, citric acid, and sodium bicarbonate. Following the creation of the primary powder combinations, magnesium stearate, a lubricant, was added and mixed with other components for 5 minutes. Using a single stroke tablet press machine and a 10mm concave surface punch, the powders were then directly compressed into effervescent tablets.

Examining the powder

The flowability of the powder was assessed before it was compacted into tablets. Granule flow measurement, Hausner Ratio, and angle of repose were the three techniques that were accessible.

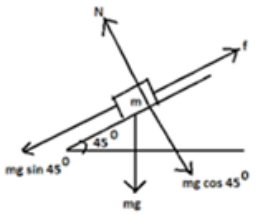
similar to Carr's Index The flowability of the powder had to be determined using these three methods in order to facilitate tableting.

- **Equation 1**

Angle of Repose- The maximum possible angle between the surface of the pile of the powder and the horizontal plane. Formula,

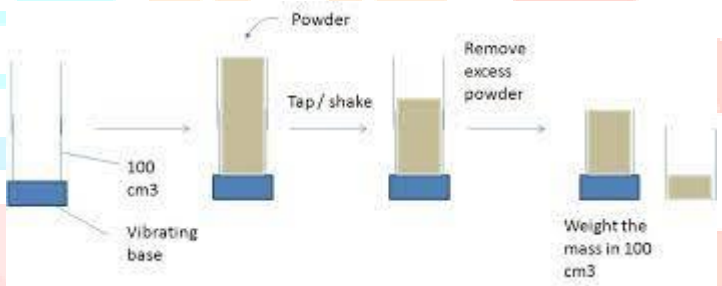
Θ= tan-1(2h/d) Θ = Angle of Repose

After manually tapping the cylinder twice on a flat tabletop, the bulk volume was calculated.



Bulk and Tapped Density-

After manually tapping the cylinder twice on a flat tabletop, the bulk volume was calculated. Bulk density was determined to be g/ml. After tapping with 250 drops per minute in increments of 500 and 750 taps, the tapped volume was calculated using the density tester. Following that, the tapped density was estimated as g/ml.



Formula,

Bulk density =Mass/bulk volume.

Tapped/true density = Mass/tapped(true)volume.

- **Equation 2**

Hausner Ratio and Compressibility Index

1. Hausner ratio expressed as the tap density divided by the bulk density,

Hr = taped density / bulk density. (Hr = ρtap/ρb)

ρtap- ρb/ ρtap × 100.

The flowability of a powder or granular substance is connected with a value called the Hausner ratio. It bears the engineer Henry H.'s name.

2.Index of Compressibility Compressibility is described as a powder's capacity to contract under pressure, while compactibility is the capacity of a powdered substance to be compressed into a tablet of a particular strength Formula,

- **Equation 3**

Carr's Index formula Characterization Tests Weight Variation

To investigate the weight variance, twenty tablets were chosen at random. Each tablet was weighed separately, and the results were recorded. The standard deviation and average weight were computed. The maximum weight variation allowed for tablets is 10% for weights up to 120 mg, 7.5% for weights between 120 mg and 300 mg, and 5% for weights greater than 300 mg.

a weight-variation formula

$$W_{avg} - W_{initial} / W_{avg} \times 100$$

Where, W_{avg} = average weight.

$W_{initial}$ =initial weight.

Angle of Repose	Carr's Index	Hausner's Ratio	Flow Properties
25-30	<10	1.00-1.11	Excellent
31-35	11-15	1.12-1.18	Good
36-40	16-20	1.19-1.25	Fair
41-45	21-25	1.26-1.34	Passable
46-55	26-31	1.35-1.45	Poor
56-65	32-37	1.46-1.59	Very Poor
>66	>38	>1.60	Very Very Poor

- **Equation 4**

Percentage deviation formula -

Thickness -Ten tablets from each formulation were selected randomly. Each tablet was being placed vertically on the spindle of hardness tester machine

Hardness-

Ten tablets were chosen at random from each batch of the formulation based on their hardness. The hardness tester machine's spindle and a tablet were placed in contact. The tablet was being pressed against. The pressure was then raised consistently until the tablet broke, at which point the machine read out the pressure needed to break the tablet and recorded it.

Friability - The 20 tablets from each formulation were weighed first, and then they were tested for 4 minutes at a speed of 25 rpm. After the friability testing, dusts and cracked effervescent tablets must be extracted and separated from the rest. The tablets were reweighed after the dusts were removed, and the following equation was used to determine the friability percentage:

$$\%F = W1 - W2 / W1 \times 100$$

%F = Percentage of Weight Loss
w1= weight at time zero
w2= weight after test

- **Equation 5**

Disintegration Test

Using the disintegration tester, the test was run on six tablets that were chosen at random. The disintegration medium was distilled water at 37°C 2°C, and it took the tablet exactly one second to completely dissolve. Gelatin disintegrated in 7 minutes whereas hypromellose (carrageenan) tablets took 8 minutes to break down in a fasting state.

Study of In-Vitro Release

Utilizing a six stage dissolution rate test USP Type 1 equipment at 100 rpm, 0.1N hydrochloric acid (pH 1.2) for the first two hours, and phosphate buffer (pH 6.8) for the final hour, in-vitro dissolution tests were conducted. For the study, a volume of 900 ml of the dissolving fluid was kept at 37 1° with a stirring speed of 100 2 rpm. At regular intervals, 5 ml aliquots of the buffer were removed and replaced with an equal volume of new buffer kept at the same temperature. Then, using a UV/Visible Spectrophotometer, absorbance was determined at about 262 nm. Equation derived from conventional NA curve was used to determine drug content. Three copies of each dissolution study were carried out.

Interaction between drugs and excipients

The interaction between drugs and excipients was examined using FTIR and the KBr pellet method. The Spectra were taken directly on the KBr window with Nujol as the solvent of choice.

- **Effervescent time –**

In a beaker with 200 mL of aquadest at 25°C, one pill was added. When a clear, particle-free solution was obtained, the effervescence was deemed to be finished. For each formulation, the mean value of the three measurements was recorded.

- **pH of the effervescent solution-**

One tablet was dissolved in 200 mL of 20 1 °C filtered water, and the pH was measured immediately after the tablet had completely dissolved. Three iterations of this experiment were run for each formulation.

- **pH-**

The varying effervescent mix concentrations may be the cause of pH value variations. However, all of the effervescent pill solutions' measured pH values fell within the normal range (5-6). A solution with a pH between 5 and 6 is not excessively acidic. As a result, it was determined that the effervescent preparation was safe to consume. Additionally, the little acidity can give food a crisp flavour when ingested.

Selection of Optimum Formulation

The best formulation from the first stage of the trials would be chosen to move on to the second step, which required incorporation of various super-disintegrant percentages. The most effective formulation was chosen based on the effervescent tablet's capacity for the quickest disintegration, as well as its ideal hardness and friability, homogeneous weight, and thickness.

Part 2: Formulation of Effervescent Tablet with Different Percentage of Superdisintegrant Using Optimized Percentage of Effervescent Agents.

For the second stage of this trial, different superdisintegrant percentages were added to each formulation. In this investigation, sodium starch glycolate (SSG), cross povidone, and carrageenan were all utilised as superdisintegrants.

Dissolution studies

The tablets were weighed and were dissolved at a temperature of 37 0.5 0C in a dissolution liquid (0.1 N hydrochloric acid). The time of dissolution was recorded, and test samples were collected and examined using ultraviolet-visible spectroscopy at regular intervals.

RESULTS AND DISCUSSION-

The majority of oral medicinal dose forms, like regular tablets and capsules, are designed to be ingested whole or chewed. Children and the elderly frequently struggle to take these dose types. New effervescent or fast-dissolving effervescent tablets or capsules are used to treat these issues. The outcome demonstrates that the direct compression method has more flowability than the fusion method. As was already indicated, patients have a lot of trouble with the extremely bitter taste. The next step was to add flavour and sweeteners to the final product in order to improve the taste and increase patient acceptance. All formulations had effervescence times that were under 3 minutes and within the range noted in BP. Within 67 to 98 seconds, effervescence was visible in all of the formulations. Every formulation's drug content fell within the USP-specified range. Measurements of relative humidity in various formulations showed that the fusion process absorbed more moisture than the direct compression method did. One of the elements that might have contributed to the powder's good flowability was the amount of magnesium stearate utilised in all formulations, which serves as a lubricant and improves the powder's flowability. The disintegration time result indicates that the effervescent tablet dissolves more quickly the higher the percentage of effervescent agents used in the formulation. When the effervescent component comprises a sizable fraction of the formulation, the tablet disintegrates more quickly when the effervescent reacts. The key metrics to assess the consistency in the die fill and pressure used during tablet compression were the uniformity of weight and thickness of the effervescent tablets. In a single dose, a typical effervescent tablet (diameter 1 inch, weight 5 grammes) may contain more than 2,000 mg of water-soluble active components. The addition of sodium starch glycolate, a substance with a well-known ability to quickly absorb moisture from the environment, may have an impact on this. The flowability decreases when the moisture level in the powder bed rises because it promotes cohesion and condenses on the surface. The hardness of the tablet decreases with the amount of superdisintegrant employed in the formulation of effervescent tablets.

When the weight loss of the tablets was less than 1% from their initial weight, the friability result was deemed ideal. reported that a high superdisintegrant concentration would speed up disintegration. The capacity of sodium starch glycolate to quickly absorb moisture was its most well-known characteristic. The adhesiveness of the other chemicals in a tablet was overcome due to its interaction with water, and this caused the effervescent tablet to disintegrate. Accordingly, in this section of the investigation, the more sodium starch glycolate was utilised, the more forceful the swelling mechanism was, which decreased the time needed for disintegration. It has been hypothesised that the superdisintegrant's swelling and the carbon dioxide produced by the effervescent reaction that separates the tablets have a synergistic effect. Each tablet's thickness in each formulation must only vary from the mean thickness by 5% in order to pass the thickness test. Any armour that deviates from the thickness reading by more than 5% will be expelled. The homogeneity of the components employed in each formulation will have a direct impact on the thickness of the effervescent tablet's content. The material composition of each effervescent tablet may change depending on whether the variance in tablet thickness is greater than or less than 5%. It is possible to be sure that every effervescent tablet had a consistent material composition because every effervescent tablet produced for this section of the study passed the thickness test.

CONCLUSION-

Citric acid, sodium bicarbonate, and sweeteners (vanillin, which has flavor-enhancing properties) are used in this study to conceal the bitter taste of the medicine telmisartan and to boost the solubility of water-insoluble drugs like telmisartan. However, MCC does have some drawbacks, such as slow drug breakdown and lack of disintegration. To get around these drawbacks, kappa-carrageenan was researched as an alternative to MCC. In general, kappa-carrageenan pellets outperformed MCC pellets in terms of quick disintegration and quick drug release. Drugs containing PEG 6000 solid dispersions may be helpful to address a number of issues, including stability, solubility, dissolution, and bioavailability. Conclusion: The time required for an effervescent tablet to dissolve decreases with increasing sodium starch glycolate content.

The optimum formulation in terms of disintegration time, percentage of weight loss, and the crushing strength of the effervescent tablet was determined by the study's examination of the effects of effervescent agents. Superdisintegrant, which contained 40% of effervescent agent and 10% of superdisintegrant, was selected. Direct compression manufacturing was the approach adopted in this investigation. This technique was well recognised for being straightforward and for using inexpensive materials.

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