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FORMULATION AND INVITRO CHARACTERISATION STUDIES OF CONTROLLED RELEASE TABLETS OF TELMISARTAN BY USING NATURAL POLYMERS

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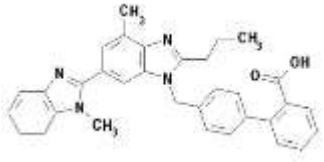
Abstract : The purpose of present study was to develop optimized and controlled release formulation for oral drug delivery of Telmisartan in order to ensure maximum controlled drug release. Telmisartan is an angiotensin 2 receptor antagonist (angiotensin receptor blocker) used in the management of hypertension. In this preparation the natural disintegrants are Banana powder, pectin from orange peel, and mucilage from isapgol seeds are used.The present research aims to enhance the dissolution profile of telmisartan through formulation of its fast disintegrating tablets using a super natural disintegration.Matrix tablets are an interesting option and new break through when developing an oral controlled release drug delivery system. Various controlled release drug delivery system have different mechanism to control the drug release rate such as osmotic pump, ion exchange resin and matrix systems.All the prepared formulations were evaluated for thickness, weight variation, hardness, friability, drug content and in vitro dispersion time and dissolution profile are found satisfactory.

Key words : Controlled release, matrix tablets, telmisartan, natural polymers, superdisintegrants.

I. INTRODUCTION

Telmisartan belongs to angiotensin receptor blockers (ARBs) and is prescribed for the treatment of high blood pressure, reducing the risk of heart attack, stroke, or death from cardiovascular causes.Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects.

Chemical Structure of Telmisartan:



Telmisartan is poorly water soluble drug with low bioavailability (about 45%). The decreased bioavailability of Telmisartan is mainly due to extensive first pass hepatic metabolism. Telmisartan has the longest biological half life (24 h) compared to any other ACE inhibitor and dosing frequency once in day makes it an ideal candidate for sustained release dosage form. From the literature survey it was found that the formulation and evaluation of telmisartan immediate release tablets using superdisintegrants such as sodium starch glycollate was reported for drug release up to 8 h. But for the treatment of hypertension, prolonged effect of drug is required which can maintain the concentration of drug in the body for long period of time.Hydrophilic matrix tablet is the simplest method for formulating an extended release tablet. Most of the synthetic polymers are toxic,bioincompatible and also

include high cost of production. To overcome these limitations, natural polymers have been exploited as safe alternatives in the preparations.

Isapgol mucilage:The mucilage of isabgol consist pentosan and aldobionic acid which hydrolysis yield arabinose, galactose, galactouronic acid and rhamnose. The gel forming fraction of the alkaliextractablepolysaccharides is composed of arabinose, xylose and traces of other sugars.It is widely used from the times of ayurveda as laxative to relive constipation. It also used for the treatment of diarrhea, crohns disease (inflammatory bowel ulcerative colitis disease), colon cancer, obesity in children and adolescents high cholesterol and diabetes. Psyllium seed husk has been successfully evaluated as binder and superdisintegrant.

Pectin: Pectin is a structural heteropolysaccharide contained in the primary cell walls of terrestrial plants. It was first isolated and described in 1825 by Henri Braconnot. It is produced commercially as a white to light brown powder, mainly extracted from citrus fruits, and is used in food as a gelling agent, particularly in jams and jellies. It is also used in dessert fillings, medicines, sweets, as a stabilizer in fruit juices and milk drinks, and as a source of dietary fibre.

Uses of pectin:

II. The main use for pectin (vegetable agglutinate) is as a gelling agent, thickening agent and stabilizer in food.

III. In medicine, pectin increases viscosity and volume of stool so that it is used against constipation and diarrhoea. Until 2002, it was one of the main ingredients used in Kaopectate a medication to combat diarrhoea, along with kaolinite. It has been used in gentle heavy metal removal from biological systems. Pectin is also used in throat lozenges as a demulcent.

IV. In cosmetic products, pectin acts as stabilizer. Pectin is also used in wound healing preparations and specialty medical adhesives, such as colostomy devices.

II EXPERIMENTAL METHODOLOGY:

Method for extraction of Plantago ovata mucilage:

Seeds of Plantago ovata(Isapgol) were soaked in water for at least 48 hrs, subsequently mucilage was released into the water completely With the help of the muslin cloth the mucilage was squeezed out and separated from seeds. The mucilage was collected and precipitated using 3 times of 95% ethanol. Collected mucilage was dried in the oven at 50-55°C. Dried mucilage was scraped and powdered using pestle and mortar. Powder was sieved using mesh no.60.

Fig 1.Isapgol seeds soaked in water

Fig 2.mucilage collected from isapgol seeds

Extraction of orange peel pectin powder :

Ripped orange peel was obtained from local fruit shop. Peel was carefully washed and dried under shade for 24 h, further dried at 60 °C in a hot air oven. Dried fruit peel was cut into pieces and powdered by electric grater. Powdered peel was further passed from sieve No. 20.Peel powder, 200 g of was dissolved in 1 L of water and 1 g of citric acid was added to maintain acidic pH 2.This solution was subjected to reflux condensation at 70 ºC for 6 h to extract pectin. Dried fruit peel was cut into pieces and powdered by electric grater. Powdered peel was further passed from sieve No. 20.Peel powder, 200 g of was dissolved in 1 L of water and 1 g of citric acid was added to maintain acidic pH 2.This solution was subjected to reflux condensation at 70 ºC for 6 h to extract pectin. Hot acid extract was pressed in a cheese cloth bag and the concentrated juice was cooled to 4 ºC. Pectin was precipitated by ethanol: water (2:1 v/v) treatment followed by continuous stirring for 15 min and allowed to stand for 2 h. Pectin coagulate was filtered through cheese cloth, washed with 95 % alcohol and pressed. Pressed pectin was further dried to constant weight at 35 –45 ºC. Hard pectin cake was ground and passed through sieve No.60, stored in desiccators for further use.

Fig 3.Orange peel dried in hot air oven.

Fig 4.Refluxing of orange peel solution

Fig 5:pectin extract

fig 6: Pectin

BANANA POWDER:

Fresh banana was collected and it was peeled off.Skin peeled banana were dipped in ethanol for 5mins .These bananas were weighed and squeezed to paste.Citric acid 2-3% was added to the banana paste. Then the mass was subjected to centrifugation for 4-6 mins. Water is separated from the pulp and the settled down mass was taken.Processed mass was subjected to slight drying (tray drying) and dried substances were milled and it was screened through sieve no. 80 to get fine powder.

Fig 7. Squeezed banana

fig 8. Banana powder.

Tablet Manufacturing Method:

Table.1.Formulation of tablets by Direct Compression Method

S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Telmisartan	0.8	0.8	0.8	0.8	0.8	0.8
2	Pectin	0.5	0.4	0.6	---	---	---
3	Banana Powder	0.9	1.2	1.4	1.4	1.4	1.2
4	Isapgol mucilage	---	---	---	0.4	0.5	1.0
5	Lactose	0.6	---	0.5	---	0.4	---
6	Mannitol	---	0.3	---	0.3	---	0.2
7	HPMC	0.4	0.5	0.3	0.4	0.3	0.3
8	Eudragit	0.7	0.7	0.3	0.6	0.5	0.5
9	Talc	0.5	0.5	0.5	0.5	0.5	0.5
10	Magnesium stearate	0.6	0.6	0.6	0.6	0.6	0.6

Telmisartan controlled release tablets were prepared in 6 formulations from F1 to F6 using the ingredients mentioned in the Table. Telmisartan tablets were prepared by using natural polymers like orange peel pectin and Plantago ovata to formulate the tablets. All the ingredients with drug except talc and magnesium stearate were taken in the mortar. The powder blend was then mixed well by using mortar and pestle for 15 to 30 min, and then each mixture was passed through # 80 sieve. Finally magnesium stearate and talc was added as a lubricant and mixed thoroughly.

Tablets were prepared using 8 mm round flat-faced punch of the rotary tablet machine compression force was kept constant for all formulations.

CHARACTERISATION STUDIES:

Physical Properties

Angle of Repose:

Angle of repose is defined as maximum angle varied between the surface of the pile of powder and the horizontal aircraft. The frictional pressure in a unfastened powder or granules can be measured by using angle of repose.

$$\text{Tan } \Theta = h/r$$

$$\Theta = \tan^{-1}(h/r)$$

Where,

'Θ' is the angle of repose his height of pile

'r' is radius of the base of pile.

Different ranges of flow ability in terms of angle of repose are given in Table.2

TABLE 2. Relationship between angles of reposes and flow properties.

ANGLE OF REPOSE (DEGREE)	FLOW:
<25	EXCELLENT
25-30	GOOD
30-40	PASSABLE
>40	VERY POOR

Method:

A funnel filled to the brim and then take a look at the sample which is allowed to waft easily through the orifice under gravity.

From the cone shaped heap on a graph sheet, measure the location of pile, the glide capability of the granules and the height of the pile can also be measured using the formula.

Bulk density:

Bulk density is described because the mass of a powder divided via the bulk volume. the majority density of a powder relies upon primarily on particle length distribution, particle shape, and the tendency of the particles to stick to one another.

Loose bulk density (LBD) and tapped bulk density (TBD) both were determined.

Method:

A quantity of accurately weighed powder (bulk) from every method, formerly shaken to interrupt any agglomerates formed become introduced into a 25 ml measuring cylinder. After the initial extent changed into observed, the cylinder is allowed to fall underneath its very own weight onto a difficult surface from the peak of 2.5cm at 2 sec. The tapping is endured until no addition exchange in extent was cited .

LBD and TBD were calculated using following formula;

TBD=Weight of powder Volume of packing

LBD= Weight of powder Tapped packing

Hausners Ratio:

The **Hausner ratio** is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner (1900–1995).

The Hausner ratio is calculated by the formula

$$\text{Hausners ratio} = \frac{tapped\ density}{bulk\ density}$$

Hausner ratio is not an absolute property of a material; its value can vary depending on the methodology used to determine it.The Hausner ratio is used in a wide variety of industries as an indication of the flowability of a powder. Hausner ratio greater than 1.25 is considered to be an indication of poor flowability. The Hausner ratio (H) is related to the Carr index (C), another indication of flowability. Both the Hausner ratio and the Carr index are sometimes criticized, despite their relationships to flowability being established empirically, as not having a strong theoretical basis. Use of these measures

persists, however, because the equipment required to perform the analysis is relatively cheap and the technique is easy to learn.

TABLE NO.3.Powder flowability based on hausners ration

Flow Character	Hausner Ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45
Very poor	1.46-1.59
Very, very poor	>1.60

COMPRESSIONAL PARAMETERS:

HARDNESS: Tablet hardness testing, is a laboratory technique used by the pharmaceutical industry to test the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage" The breaking point of a tablet is based on its shape. It is similar to friability testing, but they are not the same things.The Pfizer tester was used in our work and thiscompresses tablet between a holding anvil and a piston connected to a force-reading gauge when its plier-like handles are gripped.

FRIABILITY: Friability is the tendency for a tablet to chip, crumble or break following compression. This tendency is normally confined to uncoated tablets and surfaces during handling or subsequent storage. It can be caused by a number of factors including poor tablet design (too sharp edges), low moisture content, insufficient binder, etc. For obvious reasons, tablets need to be hard enough such that they do not break up in the bottle but friable enough that they disintegrate in the gastrointestinal tract. Based on an original design by Roche, the friability tester has now become an accepted standard throughout the pharmaceutical industry for determining the resistance of uncoated tablets to the abrasion and shock experienced in manufacturing, packing and shipping operations. Whilst the basic design remains unchanged, considerable advances have been made in terms of reliability and ease of usage which have now been incorporated into current units.

Method:

1. Select 20 tablets randomly, dedust and weigh (W_O).
2. Place the tablets in the Roche friabilator drum, switch on the apparatus adjusting the timer at 4 min. and the speed at 25 rpm.
3. At the end of this operation, remove the tablets from the friabilator, dedust and reweigh (W). (Any tablet that breaks up should be rejected before reweighing).
4. friability is expressed as a percentage loss in weight: i.e.,

$$\% \ loss = \frac{W_O - W}{W_O} x100$$

N.B.: if the value of friability (% loss) is less than or equal to 1%, the batch is accepted.

THICKNESS:

The **thickness of tablets** is critical to their therapeutic effectiveness.All tablets, where the active ingredient comprises a major part of the tablet are required to meet a weight variation test. It is assumed that providing the weight of the tablet is kept within defined limits that the amount of active drug available to the user will remain the same.The weight of a compressed tablet is dependent on three factors: density, diameter and thickness. In theory, the density of the powder blend and the diameter of the resultant tablet (which is dictated by the die wall) should remain unchanged.

It follows that by monitoring the thickness of the tablets at regular intervals, potential problems relating to tablet weight and hence content uniformity can be detected at an early stage.

The **calipers** thickness **testers** are simple, easy to use instruments designed for use.

OFFICIAL TESTS:

WEIGHT VARIATION:

TABLE NO.4.Weight variation limits.

IP/BP	**Limit**	**USP**
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

CONTENT UNIFORMITY:

Uniformity of Content is a pharmaceutical analysis parameter for the quality control of capsules or tablets. Multiple capsules or tablets are selected at random and a suitable analytical method is applied to assay the individual content of the active ingredient in each capsule or tablet.

The preparation complies if not more than one (all within limits) individual content is outside the limits of 85 to 115% of the average content and none is outside the limits of 75 to 125% of the average content. The preparation fails to comply with the test if more than 3 individual contents are outside the limits of 85 to 115% of the average content or if one or more individual contents are outside the limits of 75% to 125% of the average content.

Content uniformity Limits:
IP**:** Active less than 10mg or 10%,
BP**:** Active less than 2 mg or 2%,
USP**:** Active less than 25mg or 25%.

- If in 10 tabs limit NMT 1 tab deviate 85 – 115% & none outside 75 – 125% of the average value/IP/BP/USP (Relative Standard Deviation less than or equal to 6%),
- If 2 or 3 individual values are outside the limits 85 – 115% of the average value, & none outside 75 – 125% repeat for 20 tabs.
- When 30 tabs NMT 3 of the individual values are outside the limit 85 – 115% of the average value, and none outside 75 – 125%.

DISSOLUTION:
A dissolution test is a means of identifying and proving the availability of active drug materials in their delivered form. A dissolution test simulates the availability of active substance and allows the prediction of the time for complete release of the material from the dosage form.

TABLE NO 5.Units Of Dissolution And Their Acceptance Criteria

STAGE	NUMBER UNITS	ACCEPTANCE CRITERIA
S1	6	Each unit is not less than Q* +5%
S2	6	Average of the 12 (S1+S2) units is ≥ Q and no uni is less than Q−15%
S3	12	Average of 24 (S1+S2+S3) units is ≥ Q and not more than 2 units are less than Q−15% and no unit is less than Q−25%

Where, Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

DISINTEGRATION TEST

Disintegration are agents added to tablet formulations to promote the breakup of the tablet into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. To pass the test all 6 of the tablets or capsules must have disintegrated.

RESULTS AND DISCUSSIONS:

TABLE NO 6.PHYSICAL PARAMETERS:

Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Tapped Density (g/cc)	0.8	0.81	0.8	0.8	0.81	0.82
Carr's Index (%)	7.4	7.3	7.4	7.4	7.4	7.4
Hansner Ratio	1.06	1.07	1.09	1.06	1.08	1.07
Angle of Repose	24.31	25.1	25.37	25.22	26.29	27.91

TABLE NO 7.COMPRESSIONAL PARAMETERS:

Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Hardness	4.06±0.11	4.02±0.05	3.98±0.14	4.10±0.15	4.08 ± .03	4.03 ± .12
Friability (%)	0.75±0.04	0.67±0.02	0.88±.01	0.74±.01	0.83±0.03	0.89 ± .04
Thickness	3.60 ± .03	3.54 ± .31	3.53 ± .15	3.52 ± .08	3.51 ± .14	3.36 ± 0.12
Content Uniformity	97.45 ± .31	99.74±.51	99.66± 43	98.21 ±58	99.28 ±. 3	97.45 ± .54
Disintegration Time	44	39	51	48	39	32
Dissolution	83.48±.17	84.59±.52	85.9±.23	84.92±.16	83.92±.2	99.43±.11

CONCLUSION:

From the data it was concluded that stable formulation can be developed by incorporating natural polymers in a definite proportion. The F6 formulation showed drug release of 99.43% which is selected to have optimum hardness, Friability and Disintegration time was good when compared to all other formulations.

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