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FORMULATION AND EVALUATION OF FLOATING CONTROL RELEASE TELMISARTAN TABLET ON TREATMENT OF HYPERTENSION

[1]Yashraj A Patil, [2]Sneha P kamble, [3]Pritam A Salokhe, [4]Jaya R Kamble, [5]Dr. N.B. Chougule

[1]Student, [2]Student, [3]Assistant Professor, [4]Assistant Professor, Principal Pharmaceutics,

[1]Ashokrao Mane Institute of Pharmacy, Ambap, Kolhapur, India

ABSTRACT: The main objective of this research is to design development and evaluate floating control releases tablet of an antihypertensive drug in order to achieve therapeutic efficacy and patient compliance. The present research work discuses about the floating control release tablet which suitable for enhance its bioavailability (It is useful for achieving controlled plasma level as well as improving bioavailability) and prolonged residence time in the stomach. Gastro retentive drug delivery system is an approach to prolong gastric residence time of tablet, thereby achieving targeting and site specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Several gastro retentive drug delivery approaches being designed and developed, including high density (sinking) system that is retained in the bottom of the stomach, low density (floating) system that cause buoyancy in gastric fluid, mucoadhesion system that cause bio adhesion to stomach mucosa, and also unfoldable, extendible, or swellable system are involved.

Keywords: floating, gastrointestinal tract, control drug release, therapeutic efficacy, gastrointestinal tract

I. INTRODUCTION Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of 19th century and their popularity continues. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer. Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.[1, 2, 3]

Floating drug delivery systems (FDDS) are specialized drug delivery systems designed to release drugs in a controlled manner in the stomach, with the objective of improving the therapeutic efficacy of drugs that are unstable, insoluble or poorly soluble in water.[4] These systems work on the principle of buoyancy, where the drug-containing dosage form is formulated to have a density less than that of the
Gastric contents, thereby enabling it to float on the gastric contents for an extended period of time.[5] this provides the drug with prolonged contact with the gastric mucosa, resulting in better drug absorption and bioavailability. FDDS can be formulated in various forms such as tablets, capsules, beads, or microspheres, and can be designed to release the drug immediately, or after a predetermined lag time. The mechanism of drug release from FDDS can be either diffusion-controlled or erosion-controlled, depending on the nature of the dosage form.[6, 7]

Gastroretentive drug delivery systems (GRDDS) are specialized drug delivery systems designed to prolong the residence time of a drug in the stomach, with the objective of improving the therapeutic efficacy of drugs that have a narrow absorption window in the upper gastrointestinal tract. These systems work by taking advantage of the anatomical and physiological properties of the stomach to retain the drug for an extended period of time.[8]

The development of GRDDS has gained significant interest in recent years due to its potential to improve drug therapy by providing sustained drug release, reduced dosing frequency, increased bioavailability, and improved patient compliance. Furthermore, GRDDS has shown potential in treating various gastrointestinal disorders such as gastro esophageal reflux disease, gastric ulcers, and irritable bowel syndrome.[9]

The aim of study is to formulate and evaluate of control release floating tablet of Telmisartan. To study the effect of polymers on the release of Telmisartan, different polymers are used to attain floating control drug release and give maximum therapeutic effect for prolonged period of time when taken orally. To design the formulation of solid dosage of Telmisartan tablets with better stability of high product quality.

Hypertension:
Hypertension in adults is defined by World Health Organization (WHO) as a systolic pressure equal to or greater than160mmHg (21.3kPa) and a diastolic pressure (fifth phase) equal to or greater than 95 mmHg (12.7kPa).Hypertension results from increased peripheral
Resistance and reduced capacitance of the venous system. Although many of these individuals have no symptoms, chronic hypertension-either systolic or diastolic- can lead to CHF, MI, renal damage, and cerebrovascular accidents. Heart rate and blood pressure are increased in
the early morning hours (morning or A.M. surge). The blood pressure declines form midafternoon and is minimum at midnight. In most hypertensive patients, there is a rather marked rise in blood pressure upon awakening that is called the morning or “a.m.” Systolic
Blood pressure rises approximately 3mm Hg/hour for the first 4-6 hours post-awakening, while the rate of rise of diastolic blood pressure is approximately 2mm Hg/hour. Hypertension has been classified as "primary or essential hypertension" where definite cause for risk in
Blood pressure is not known and "secondary hypertension" which is secondary to renal, endocrine and vascular lesions. Hypertension, particularly essential or primary hypertension is wide spread and a major risk factor for stroke and to some extent ischemic heart diseases.[10,11]

Hypertension, commonly known as high blood pressure, is a major health concern worldwide, affecting millions of people. Telmisartan is an effective antihypertensive drug that has been widely used in the treatment of hypertension. However, its short half-life and poor bioavailability make it difficult to maintain a therapeutic concentration in the blood, leading to poor patient compliance and treatment
Outcomes. Floating controlled-release tablets are a promising drug delivery system that can help overcome these challenges. These tablets are designed to float on top of the gastric contents and release the drug in a controlled manner over an extended period of time. This can enhance drug absorption and reduce the dosing frequency, thereby improving patient compliance and treatment outcomes. The formulation and evaluation of floating controlled-release tablets of Telmisartan for the treatment of hypertension is a challenging task that requires careful consideration of various factors such as drug solubility, release kinetics, and tablet properties. In conclusion, the development of a floating controlled-release tablet of Telmisartan for the treatment of hypertension requires a multidisciplinary approach that integrates formulation, evaluation, and regulatory compliance. Successful development of such a product can significantly improve the treatment outcomes for patients with hypertension and contribute to the advancement of pharmaceutical science.[12]
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II. Material and method:

2.1Pre Formulation Studies: [13, 14]

Drug- Excipients in- Compatibility Studies: Drug was mixed with excipients. About 5gms of blend was prepared, which were kept in
10 ml white colored glass vials and packed properly. These vials are exposed to room temperature and 40 0 c±2 0 C/75±5% RH. Observations for physical appearance were made at zero weeks to 1 month, and then the samples were withdrawn for analysis of appearance. The drug excipients interaction was investigated by FT-

IR

FT-IR- Spectroscopy: Drug and excipients compatibility study is done by Fourier Transform Infrared Spectroscopy [FTIR]. FT-IR Spectra were obtained by using an FT-IR Spectroscopy- (PERKINELMER). The samples (pure drug) was previously ground and mixed thoroughly with KBr, an infrared transparent matrix at (sample/KBr) ratio respectively. the KBr discs were prepared by the compressing the powders at a pressure of 5 tons for 5min in a hydraulic press (40 scans were obtained at a resolution 4cm -1 from 4600-300cm -1). The compatibility studies provide the frame work for the drugs combination with the excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets.

2.2Formulation Development:

The active ingredient i.e. Telmisartan and each single polymer (HPMC E15) (HPMCK15) and also mixture of two polymers, filler (MCC), lubricant (Magnesium stearate) glidant (Talc) Floating (sodium bi carbonate and citric acid)were blended together by dry mixing in a laboratory mixer (polybag) for 10 minutes. The mixture was compressed by using 8mm standard flat round punch and die set at compression force 4-6 ton.

Table no 1: Formulation of Telmisartan Tablet

INGREDRDIENTS	C1	C2	C3	C4	C5
Telmisartan	50	50	50	50	50
HPMC(E15)	--	--	200	200	200
HPMC (K15)	50	200	--	--	--
Microcrystalline cellulose	201	51	51	65	75
Sodium bi carbonate	30	30	30	20	10
Citric acid	5	5	5	5	5
Talc	7	7	7	5	5
Magnesium Sterate	7	7	7	5	5
Total weight	350	350	350	350	350

2.3. Pre Evaluation Compression Parameter [15, 16, 17]

2.3.1 Angle of repose:

The angle of repose of powder blend was determined by the funnel method. The accurately weigh powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. Where, - h and r are the height and radius of the powder cone.

Tablet no 2: Comparison between angle of reposes and flow properties

Angle of repose (θ)	Flow
< 25	Excellent
25 – 30	Good
30 – 40	Moderate (addition of 0.2% glidant required)
> 40	Poor

2.3.2 Bulk density:

Both bulk density (BD) and tapped density (TD) was determined. A quantity of 10 gm. of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 50 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. Bulk density (BD) and Tapped density (TD) were calculated using the following equations.

Table no 3: Flow ability according to Hausner's ratio

Hausner's ratio	Flow character
1.0-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
> 1.60	Very, very poor

2.3.3Compressibility index (Carr's Index): Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20% has good flow property.

.Table no 4: Properties of compressibility index

% Comp. Index	Properties
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely Poor

2.4Post Compression Evaluation Parameters:12The tablets were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight variation, hardness, friability, assay, and drug content.

2.4.1Physical appearance:

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. the control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour presence or absence of odour, taste, surface texture and constituency of any identification of marks.

2.44.2Thickness:

10 tablets were measured for their and diameter with a vernier caliper. Thickness and diameter were calculated.

2.44.3Weight variation:

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the table.

Table no 5: Weight variation limits

Average weight of tablet (mg)	Maximum % difference allowed
130 or less	10
130-324	7.5
>324	5

.2.4.4Tablet hardness: The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm 2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

2.4.5Friability: Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.[18]

IV. RESULT AND DISCISSION:

Table No 6: Preformulation

SR. NO	EXPERIMENT	RESULT
1.	Physical Properties a) Colour b) Odour	a) A white to off-white crystalline powder b) odourless
2	Solubility a) Sparingly soluble b) Slightly soluble c) Practically insoluble	a) Dichloromethane b) Methanol c) Water
3	Melting Point	The reported melting point of Telmisartan is in the range of 265°C-272°C the observed melting point is 270^0c.

Preformulation is the first step in rational development of any Pharmaceutical dosage form of a new drug. Preformulation study focuses on Physiochemical Property of new drug compound that can affect drug performance and development of effective dosage form.

The reported melting point of pure drug Telmisartan is the range of 265°C-272°C and the observed melting point at 270°c. It confirmed that given powdered drug is in pure in nature and it confirmed that given power is Telmisartan.

4.1 THERMAL ANALAYSIS: Differential Scanning Calorimetric (DSC) Study:

Fig No 1. : Thermal Analysis Graph

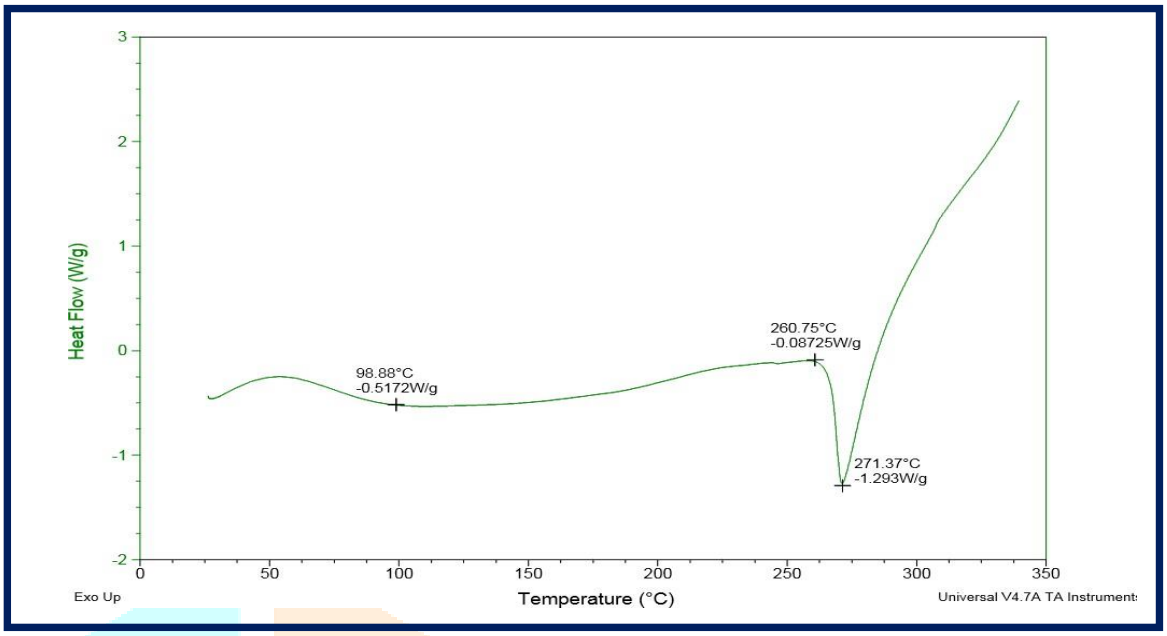
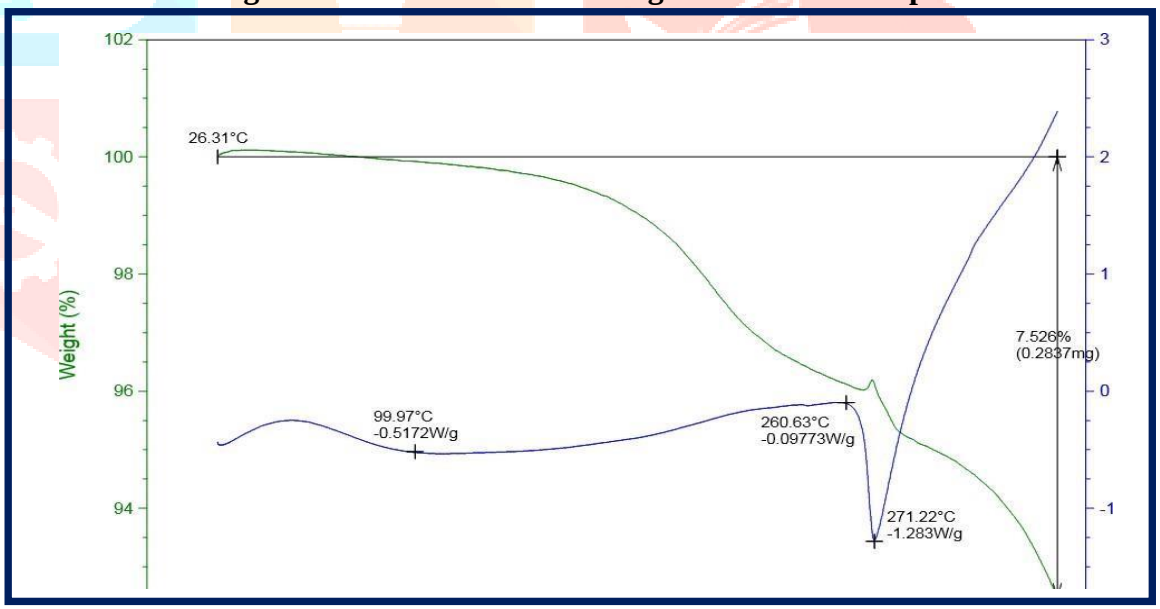


Fig No 2. : Differential Scanning Calorimetric Graph



DSC studies were performed using a Mettler DSC 1 (Mettler Toledo, Germany). The instrument was calibrated with an indium standard. Accurately weighed sample (5-10mg) were placed in closed, pierced, flat bottom aluminum pans. DSC scan were recorded at a constant heating rate of 10ºC/min from 30 to 350ºC. Nitrogen gas was pumped at a flow rate of 80ml/min. The melting points, peak maxima, appearance any new peak and change in peak shape were noted.

DSC was used to assess the thermal behaviour of the drug Telmisartan. In the fig. DSC Thermogram of Telmisartan shows a single sharp characteristic endothermic peak (T peak =271.37ºC) corresponding to the melting point of Telmisartan. And a single peak indicates that the drug sample is free from impurities.

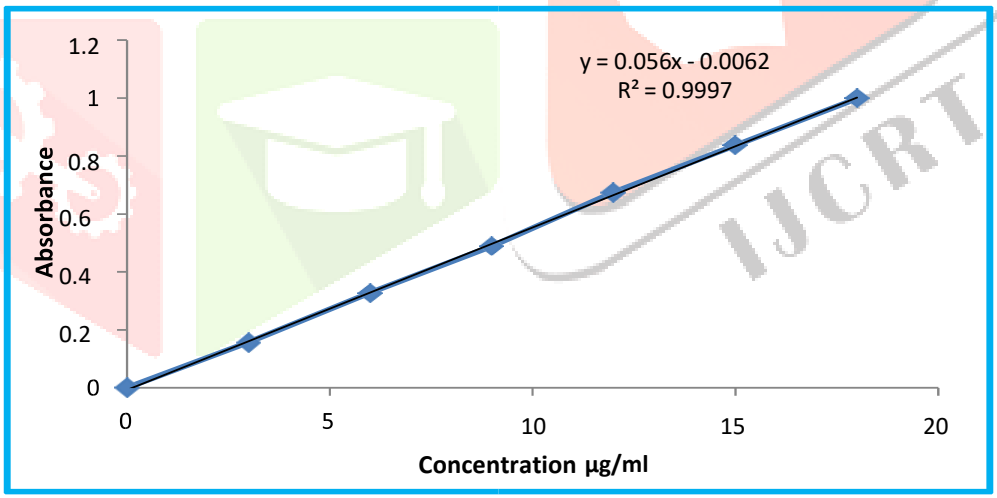
4.2 CALIBRATION CURVE OF TELMISARTAN:

Calibration curve of Telmisartan in phosphate buffer pH 7.5 was found to be linear in range of 3 to 18 µg/ml and coefficient was found to be 0.999.

Table No.7: Reading of Calibration Curve of Telmisartan In Phosphate Buffer Ph 7.5.

Sr. No	Concentration µg/ml	Absorbance
1	3	0.157
2	6	0.328
3	9	0.489
4	12	0.675
5	15	0.838
6	18	0.999

Fig No. 3: Calibration Curve of Telmisartan in Phosphate Buffer pH 7.5



The λ max of pure drug telmisartan was found to be 296nm. It indicates that given sample of drug is pure in nature and it confirmed that the given powder is Telmisartan. The calibration curve of telmisartan is as per beers law the slope was found 0.006 and R^2=0.999. Hence from calibration curve and λ max it is clear that given sample of powder drug is Telmisartan and it is pure in nature.

4.3 COMPATIBILITY STUDY:

FTIR SPECTRA OF PURE DRUG TELMISARTAN:

Fig. No.4: FTIR study Spectra of Pure Telmisartan.

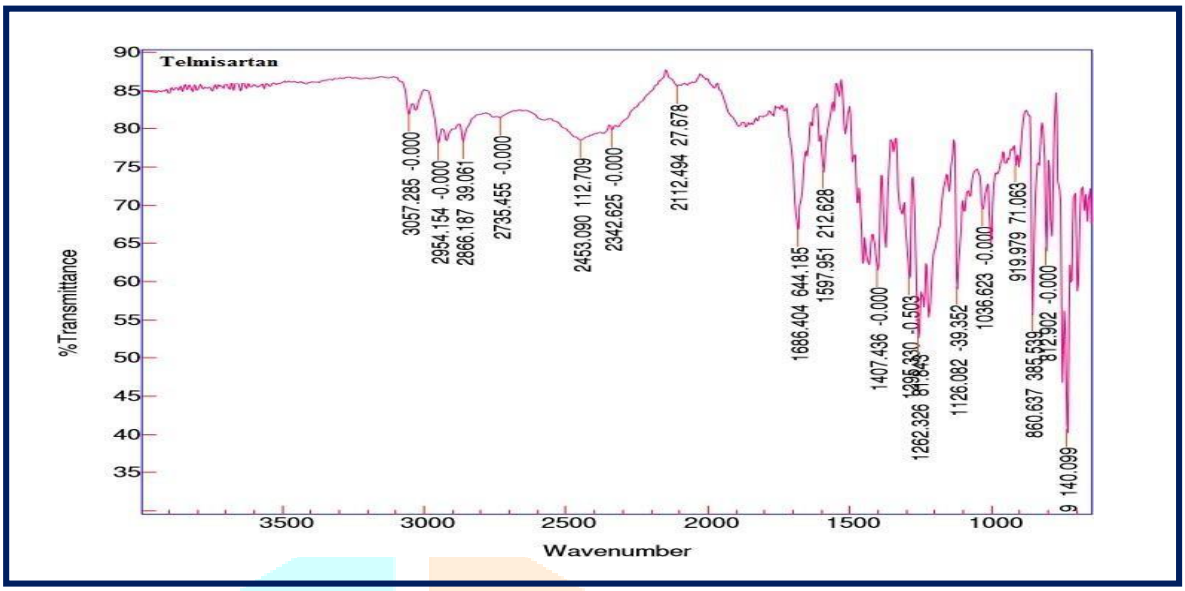


Table No 8: FTIR Value of Pure Telmisartan

Functional group	Theoretical Wave number (cm-1)	Peaks(cm^{-1})	Indication
C-H	2850-3000	2866.137	Alkanes (stretch)
C-N	1080-1360	1295.330	Amines (stretch)
C=C	1620-1680	1686.404	Alkenes (stretch)
O-H	2500-3300	2735.455	Carboxylic acid (stretch)

4.4 PRE COMPRESSION AND POST COMPRESSION PARAMETER:

4.4.1PRE COMPRESSION PARAMETER:

Table No.9: Pre Compression Parameter

BATCH CODE	BULK DENSITY (g/ml)	TAPPED DENSITY (g/ml)	HAUSNER'S RATIO	CARR'S INDEX (%)	ANGLE OF REPOSE θ
C1	0.5384 ±0.191	0.5833 ±0.272	1.0833	7.6923	25.26^0 ± 0.672
C2	0.5599 ±0.281	0.6087±0.293	1.0869	8.000	26.29^0 ± 0.587
C3	0.6087 ± 0.281	0.6363 ±0.321	1.0545	4.3478	26.45^0 ± 0.652
C4	0.5384±0.191	0.6363 ±0.321	1.0400	3.8461	27.04^0 ± 0.498
C5	0.5599±0.221	0.6087±0.293	1.0869	8.000	25.14^0 ±0.622

The tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, hardness, friability, and drug content the result was shown in table.

A.HAUSNER'S RATIO:

In the result of Hausner's ratio of various batches was shown in table no 15. It shows that all batch show excellent flow properties. All Batches were in the range of 1.05±0.03 to 1.09±0.04.

B. CARR'S INDEX:

Carr's index was carried out and result was shown in table no 15 It was found that all batches shown good and excellent flow properties. All batches were in the range of 3.00±0.54 to 8.5±0.35

C.ANGLE OF REPOSE:

The angle of repose of core tablet was carried out and the result was shown in table no 15 It shown that batch C1 and C2 has excellent flow properties and batch C3, C4, C5 shown good flow properties. Angle of repose was found to be in the range of 25.1±0.40 to 28.15±0.25.

4.4.2 POST COMPRESSION PARAMETER OF FCRT:

Table No 10: Post Compression Parameter of FCRT

Batch Code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm3)	Friability(% loss of weight)
C1	352.4±4.3	3.52±0.03	4.3 ± 0.24	0.28
C2	351.1±2.9	3.51± 0.01	4.2 ± 0.24	0.37
C3	350.5±2.4	3.53± 0.04	4.7 ± 0.24	0.25
C4	348.4±2.1	3.50± 0.01	5.5 ± 0.24	0.18
C5	353.9±5.9	3.52±0.03	4.3 ± 0.24	0.48

A. Weight Variation Test- The percentage weight variation of all formulation was shown in table no 10 batches posses weight variation test within pharmacopeial limit and it was found between 348±1 and 354 ±3.

B. Thickness- The thickness of BPRT tablet is shown in table. The thicknesses of BPRT tablets were measured by verniarcaliper. In tha t all of formulation shown uniform thickness. The thickness of all formulation ranged between 3.50±0.02 to 353±0.02 mm. The thickness should be controlled within a ± 5% variation of standard.

C. Hardenss Test- The hardness of batches of BPRT tablet was found to be range between 4.2 ±0.12 to 5.5±0.11 kg/cm3

D. Friability Test- the batches of all formulation of friability test were shown in table all tablet insuring that the tablet were mechanically stable. According to B.P specification, the total loss should not excide than 1 %

E. Dissolution Study of FCRT

Table no 11 : Dissolution study of FCRT

Sr no.	Time (hrs)	C1	C2	C3	C4	C5
1	1	4.9	6.8	3.4	14.1	7.7
2	4	39.4	34.1	39.2	58.3	34.1
3	8	63.2	54.3	58.6	55.7	58.6
4	16	63.7	65.7	73.3	60.6	62.9
5	20	83.5	93.9	93.9	92.1	97

Total Floating Time

TABLE NO. 12 Total Floating Time (hrs)

Formulation Code	Floating Lag Time(sec)	Total Floating Time (hrs)
C1	98	>12
C2	106	>12
C3	105	>12
C4	174	>12
C5	91	>12

V. CONCLUSION

Telmisartan tablet used for the treatment of hypertension. The tablet were successfully formed by using different concentration of polymers for the action of drug to the prolong period of time. FTIR study performed for identification and compatibility study of drug and excipient that found no characteristic changes. The result of DSC was found pure of drug. Powder blend were evaluated for test such as bulk density, tapped density, compressibility index and hausners ratio before being punched as tablet. In in vitro dissolution profile of C1 to C2 were found to have different percentage of drug release. The

percentage of drug release is low for C1 tablet when compared to other formulations. Batch C5 has better percentage drug release that is 97% and also having lower lag time compared to other formulation All the formulation showed very good drug release profile. And hence increase patient compliance and bioavailability.

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