FORMULATION OF MOUTH-MELTING TABLETS USING BASIL SEEDS (OCIMUM BASILICUM PILOSUM) MUCILAGE AS SUPER DISINTEGRANT

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ABSTRACT: ***The present investigation was carried out to formulate and evaluate mouth-melting tablets of Olmesartan medoxomil by direct compression method. Olmesartan medoxomil is the novel anti-hypertensive drug having specific angiotensin II type 1 antagonist activity and is used in the management of acute and chronic hypertension. Mouth dissolving tablets of Olmesartan medoxomil drug were prepared by using three different super disintegrants like Ocimum basilicum mucilage powder Croscarmellose sodium, Sodium starch glycolate, and Crosspovidone. The method of tablet preparation is the direct compression method and evaluated for physicochemical evaluation parameters such as hardness, friability, weight variation, drug content uniformity, water absorption ratio, wetting time, in-vitro disintegration time, and in-vitro dissolution studies. In the present study, it was proved that the formulations containing sodium starch glycolate and Ocimum basilicum mucilage powder have shown good in-vitro results compared to other formulations. Formulation F6 has shown excellent results in water absorption ratio. In the above studies, the F6 formulation showed promising results. It was further supported by FTIR analysis which showed that F6 had no interaction with excipients.***

Keywords: Mouth melting tablet, Olmesartan medoxomil, super disintegrants, water absorption ratio, in-vitro drug release.

I. INTRODUCTION

Currently oral delivery is the gold standard in the pharmaceutical industry, where it is regarded as the safest being most convenient, and economical method of drug delivery that has the highest patient compliance[1]. Tablets designed to dissolve on the buccal (cheek) mucous membrane were a precursor to the MDT. Absorption through the cheek allows the drug to bypass the digestive tract for rapid systemic distribution. A fast disintegration time and a small tablet weight both can enhance absorption in the buccal area. The first MDTs disintegrated through effervescence rather than dissolution and were designed to make taking vitamins more pleasant for children[2]. Dissolution became more effective than effervescence through improved manufacturing processes and incorporation of ingredients (such as the addition of mannitol which increases the binding and decreases dissolution time. They are solid dosage forms that dissolve or disintegrate within a minute in the oral cavity without the need for water or chewing and have a pleasant taste[3]. They are popularly known as orally disintegrating tablets (ODT) and also called fast-dissolving, fast-melting or fast-disintegrating. The CDER, FDA defines an ODT to be a solid dosage form containing medicinal substance(s), which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue[4]. The European Pharmacopoeia recognizes the MMTs as Orodispersible tablets or tablets intended to be placed in the mouth that subsequently disperses rapidly before being swallowed. Various terminologies with their acronyms are being used to describe an MMT by various drug delivery researchers and inventor companies[5]. These are: melt in mouth (mouth melt) tablet (MMT); fast-melting tablet (FMT); fast-dissolving/ disintegrating tablet (FDT); orally disintegrating tablet (ODT); mouth dissolve tablet (MDT); rapidly disintegrating tablet (RDT); and Orodispersible tablet (OT)[7].The venture's latest technology, called Frosta™, involves tablet formulations that can melt in a patient's mouth as quickly as 10 seconds – much faster than existing commercial products made by tablet press machines. The fast-melting nature of the tablets resembles the melting of frost, hence the name Frosta™. [7]To fulfill all these needs the concept of melt in the mouth or Orodispersible tablet is developed, a tablet that disintegrates in saliva, without the need of drinking water within 15 to 60 seconds which offers fast absorption & then the onset of action.[8] The main aim is to prepare mouth-melting tablets of Olmesartan Medoxomil by direct compression method using both natural and synthetic super disintegrants. Olmesartan is used to treat high blood pressure (hypertension). Lowering high blood pressure

helps prevent strokes, heart attacks, and kidney problems. Olmesartan belongs to a class of drugs called angiotensin receptor blockers (ARBs). It works by relaxing blood vessels so that blood can flow more easily[9,10].

II. MATERIALS AND METHOD

2.1 MATERIALS

Olmesartan Medoxomil was collected as a gift sample from Hetero labs, Jadcherla, polymers, and other excipients were purchased from AR Chemicals, Hyd.

2.2 METHODOLOGY

Compatibility studies:

The drug-polymer compatibility was ascertained by subjecting the drug and homogenates of drug and polymer to Infrared spectrophotometric study.

Fourier Transform Infrared Spectroscopy (FTIR)[11,12]

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a dosage form. The use of the FT-IR technique allows pointing out the implication of the different functional groups of drugs and excipients by analysing the significant changes in the shape and position of the absorbance bands. In this method, individual samples, as well as the mixture of drug and excipients, were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into the disc by applying pressure of 5 tons for 5 mins in a hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm-1 in an FT-IR spectrophotometer. Then the characteristics peaks were obtained of all samples as well as mixtures.

Formulation of mouth-melting tablets by direct compression method[13]:

- Weigh the required amount of drug and other excipients in accordance with the formula.
- Vary the concentrations of certain ingredients to get different formulation powder blends.
- Triturate all those ingredients in a mortar with a pestle to get a uniform powdered blend.
- Compress these powdered blends into tablet dosage forms by a tablet punching machine.

Table-: 1 Composition of the mouth melting tablets

Name of the ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Olmesartan medoxomil	30	30	30	30	30	30	30	30	30
Ocimum basilicum mucilage powder	20	25	30	20	25	30	20	25	30
MCC	80	80	80	80	80	80	80	80	80
Crosscarmellose Sodium	20	25	30	-	-	-	-	-	-
Sodium Starch Glycolate	-	-	-	20	25	30	-	-	-
Cross Povidone	-	-	-	-	-	-	20	25	30
Mannitol	282	265	253	282	265	253	282	265	253
HPMC	40	40	40	40	40	40	40	40	40
Magnesium Stearate	2	3	4	2	3	4	2	3	4
Talc	2	3	4	2	3	4	2	3	4
Sucrose	20	20	20	20	20	20	20	20	20
Color	-	5	5	-	5	5	-	5	5
Methyl paraben	4	4	4	4	4	4	4	4	4
Total weight	500	500	500	500	500	500	500	500	500

Evaluation Of Mouth-Melting Tablets

Determination of powder flow properties[14,15,16]:

Bulk density:

Bulk density was determined by pouring 25 grams of powdered sample in a 100 ml graduated cylinder. The initial volume was recorded. Then the bulk density was recorded by using the formula

Bulk density= weight of the sample in grams/ bulk volume occupied by the sample.

Tapped density:

It was measured by using an electro lab density tester in which a graduated cylinder was mounted on a mechanical tapping device. The initial volume of the powdered sample was recorded and further, it is tapped for certain tapings until no further reduction takes place in the volume. Then it was recorded and tapped density was calculated by the formula

i.e., tapped density= weight of sample in grams/tapped volume.

Compressibility index and Hausner's ratio:

Both compressibility index and Hausner's ratio became popular methods for the determination of the flow properties. They were calculated by using both bulk density and tapped density.

The compressibility index (Carr's index) was calculated by the formula:

Carr's index=tapped density-bulk density/tapped density*100

Hausner's ratio was calculated by the formula:

Hausner's ration=Tapped density / Bulk density.

Determination of Angle of Repose:

The angle of repose is determined by the funnel method. In this method, the funnel is placed at an appropriate height by using a tripod stand having graph paper underneath it. Then the powder blend is poured into the funnel. then measure the height (h) and radius (r) to obtain the angle of repose by using the formula:

$$\mathbf{Tan\ \theta = h/r}$$

Post compression evaluation parameters[17,18]:

Weight variation test:

In general, ten tablets are weighed individually using a single electronic balance pan. The average weight was also calculated. The uniformity of the weight was determined by I.P specifications.

Thickness test:

Twenty tablets were randomly selected from each formulation and individually measure the thickness by placing them in screw gauge or vernier calipers.

Hardness test:

Hardness is tested by crushing the tablet in a diametric direction by hardness testers such as Pfizer tester, strong cobb tester, etc

Friability

Friability was measured by using Roche friabilator which is rotated for 25 rpm and 25 min.

Then the mouth melting tablets were dusted and weighed for final weight determination.

Wetting volume test:

The tablet was placed in the centre of the petri dish and with the help of the 5ml pipette distilled water was added dropwise on the tablet surface. The volume required for the tablet to disintegrate completely was measured.

Wetting time test: A piece of tissue paper is folded and placed in a petri dish. Add 5ml of distilled water into it. Then place a tablet inside these Petri dishes and time was recorded until complete tablet wetting takes place which is measured in seconds.

Waterabsorptionratio:

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was placed on the tissue paper and allowed to wet completely and reweighed.

Invitrodispersiontimetest:

Drop a tablet in a beaker containing 20ml of phosphate buffer pH 6.8 and time taken for complete disintegration was noted.

Disintegration test:

- Six tablets were taken and kept into each tube of USP disintegration test apparatus with the desired medium.

- To comply with the test, all tablets should disintegrate within a few seconds as per guidelines.

In-vitro Dissolution study:

- The release of formulated tablets was determined by using USP eight-stage dissolution testing apparatus-2 (paddle method).
- The dissolution test was performed by using 500 ml of phosphate buffer solution at 50 rpm.
- A sample of the solution was withdrawn from the dissolution apparatus at specific time intervals and samples were replaced with a fresh dissolution medium. The samples were filtered through Whatman filter paper and the absorbance of these solutions was measured at 257 nm using a double beam UV spectrophotometer.
- The cumulative percentage of drug release was calculated using the standard plot of the drug.

Release kinetics[19]

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing a drug dissolution profile. Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data was selected based on the correlation coefficient(R) value in various models. The models that have shown a high 'R-value were considered as the best fit on the release date.

% drug release = concentration × no.of dilutions × volume of dissolution fluid/1000

Various mathematical models are:

1. Zero-order release model
2. The first order release model
3. Higuchi release model
4. Korsmeyer – Peppas release model

1. Zero Order Release Equation:

The equation for zero-order release is

$$Q_t = Q_o + K_o t$$

Where,

Q_o = Initial amount of drug

Q_t = Cumulative amount of drug release at time "t"

K_o= Zero-order release constant

T= Time in hours

The zero-order kinetics describes the systems in which the drug release rate is independent of its concentration of the dissolved substance. A graph was plotted between the time taken on the x-axis and the cumulative percentage of drug release on the y-axis.

2. First Order Release Equation:

The first order release equation is

$$\text{Log } Q_t = \text{Log } Q_o + K_t /2.303$$

Where,

Q_o = Initial amount of drug

Q_t = Cumulative amount of drug release at time "t"

K= First order release constant

T= Time in hours

Here, the drug release rate depends on its concentration. The first-order kinetics describes the systems in which the drug release rate is concentration-dependent.

3. Higuchi Release Equation

The Higuchi release equation is

$$\mathbf{Q_t = K_H\sqrt{t}}$$

Where,
Q = Cumulative amount of drug release at time "t"
K_H = Higuchi constant
T = Time in hrs

Higuchi described the release of drugs from an insoluble matrix as a square root of a time-dependent process. The Higuchi square root model also gives the drug release from a planar surface of an insoluble heterogeneous matrix by diffusion through the intragranular openings created by the porosity of the formulation. A graph is plotted between the square root of time taken on the x-axis and the cumulative percentage of drug release on the y-axis.

4. Korsmeyer -Peppas Release Equation:

Korsmeyer –Peppas equation is

$$F=M_t / M = K_m t^n$$

Where,
F = fraction of drug released at time 't'
M_t = amount of drug released at time 't'
M = total amount of drug in dosage form
K_m= kinetic constant
n = diffusion or release exponent
t = time in hrs
'n' = Linear regression of log (M_t / M) versus log t

`Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product that assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile.

The prepared Olmesartan tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c, and refrigerator 2-8°c for 90 days[20].

III. RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected polymers and other excipients was evaluated using the FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymer, and other chemicals.

FTIR SPECTRUM OF PURE DRUG (OLMESARTAN MEDOXOMIL)

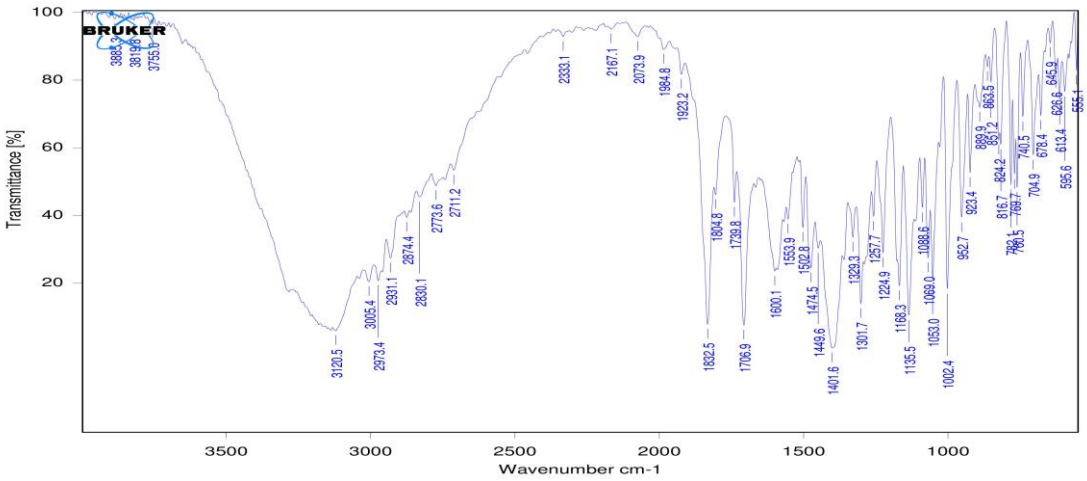

Fig.1. FT-IR Sample for Optimized Formulation

INFERENCE: The spectra obtained from the physical mixture show that all the principal peaks are at or around the requisite wave number of pure drugs. Thus it may be inferred that there was no chemical interaction between drug and polymer and the purity and integrity of the drug were maintained in the physical mixtures. From the

figure, it was observed that there were no changes in these main peaks in the IR spectra of a mixture of drugs and polymers, which show there were no physical interactions because of some bond formation between drugs and polymers. This further confirms the integrity of pure drugs and compatibility with excipients.

Evaluation Of The Prepared Tablets For Physical Parameters:

Evaluation studies

Precompression parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulations and found in the range of 0.42-0.51.

Tapped density: The tapped density for the formulated blend was carried out for all formulations and found in the range of 0.53-0.64.

The angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 26^0 to 39^0

Compressibility index: Compressibility index was carried out, it found between 12.96 % to 26.1% indicating the powder blend has the required flow property for compression.

Discussion: all formulations show good compressible properties

Post compression parameters

Weight variation

All the formulated (F1 to F9) tablets passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight.

Thickness

Tablet's mean thickness was uniform in F1 to F9 formulations and was found to be in the range of 0.549mm to 0.607mm.

Hardness

The measured hardness of tablets of each batch ranged from 2.5 to 2.616 kg/cm^2. This ensures good handling characteristics of all formulations.

Content Uniformity

The percentage of drug content for F1 to F9 was found to be between 88.55% and 97.89% of Olmesartan, it complies with official specifications.

Table-: 2 Evaluation Parameters for Optimized formulation

Formulation code	wt. vart (mg)	Hardness (kg/cm2)	Thickness (mm)	friability
F1	499.3±1.263	2.506±0.0739	0.594±0.011	0.14±0.2
F2	500±0.787	2.546±0.0776	0.6±0.008	0.25±0.3
F3	500.3 ±1.401	2.586±0.156	0.604±0.011	0.33±0.4
F4	499.9±0.691	2.5±0.0643	0.596±0.011	0.11±0.5
F5	500±0.83	2.57±0.123	0.6±0.008	0.29±0.3
F6	500.2±1.584	2.596±0.124	0.607±0.011	0.34±0.6
F7	499.5±1.737	2.5±0.0694	0.594±0.011	0.12±0.3
F8	500±0.909	2.576±0.159	0.6±0.008	0.21±0.7
F9	500.1±1.341	2.616±0.194	0.606±0.011	0.35±0.9

Table-:3 Evaluation Parameters for Optimized formulation

Formulation code	Dispersion test (sec)	Wetting volume(ml)	wetting time (sec)	water absorption ratio (%)	content uniformity
F1	54.28±0.21	4.16±0.04	58.76±1.24	66.9± 3.96	0.594±0.011
F2	51.26±0.46	4.2±0.08	67.84±0.47	69.6±4.15	0.6±0.008
F3	47.28±0.72	4.4±0.04	78.13±0.26	71.2±4.32	0.604±0.011
F4	57.18±0.81	4.32±0.07	59.18±1.27	67.8±3.81	0.596±0.011

F5	53.26±0.62	4.49±0.06	68.34±1.63	69.4±4.06	0.6±0.008
F6	51.14±0.71	4.83±0.04	77.13±0.74	70.8±4.28	0.607±0.011
F7	58.03±0.82	4.27±0.03	54.23±0.34	68.2±3.49	0.594±0.011
F8	54.61±0.43	4.46±0.07	61.16±1.23	70.6±4.26	0.6±0.008
F9	51.46±0.21	4.74±0.06	79.23±1.46	72.1±4.53	0.606±0.011

Discussion: All Formulations tested for Physical parameters like Hardness, thickness, Weight Variation, Friability, and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of the formulation was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

In-vitro Dissolution studies

Table-:4 In-vitro dissolution Profiles for tablets

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	18.64	17.54	18.85	19.26	16.76	20.55	18.59	21.48	23.64
10	40.93	35.72	27.91	39.72	24.7	39.74	34.68	48.78	49.62
15	63.7	48.82	52.25	56.41	46.85	52.45	48.92	60.42	52.62
20	89.62	79.72	73.94	73.15	69.23	68.2	78.9	73.19	72.86
25	92.21	85.92	88.92	89.98	77.23	87.9	91.92	85.65	85.73
30	95.52	92.83	95.13	94.21	90.65	98.16	97.34	96.9	94.56

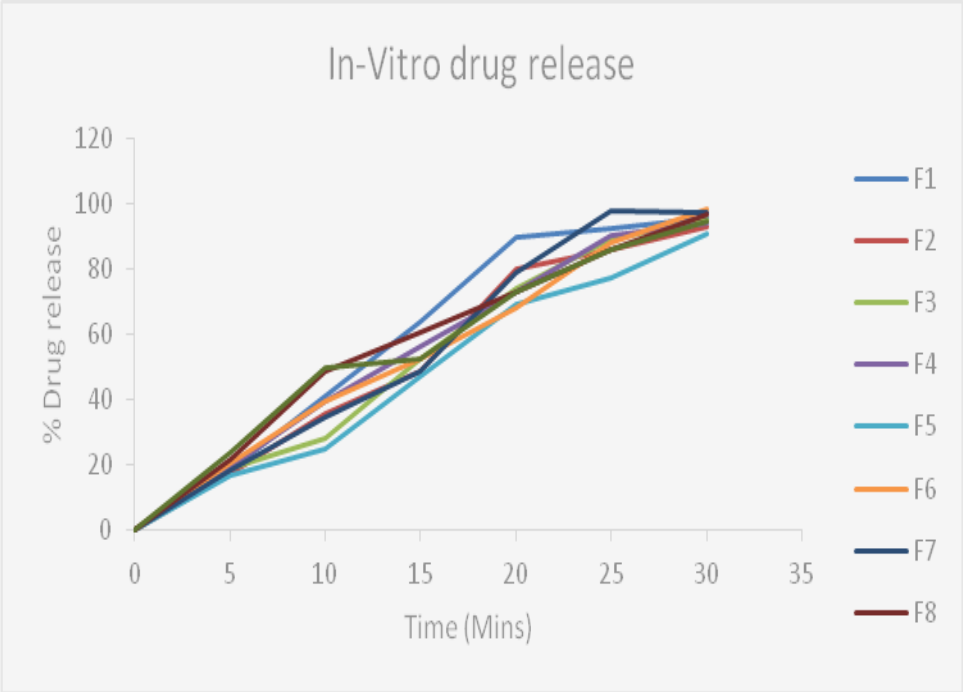

Fig.2. In-vitro dissolution Profiles for tablets

Conclusion: Among all formulations, F6 shows better drug release when compared with all other formulations. So formulation F6 was selected as the optimized formula.

Discussion

In vitro dissolution studies were performed on the above promising formulation, namely, formulation 4.

Drug Release Kinetics

Zero-order kinetics

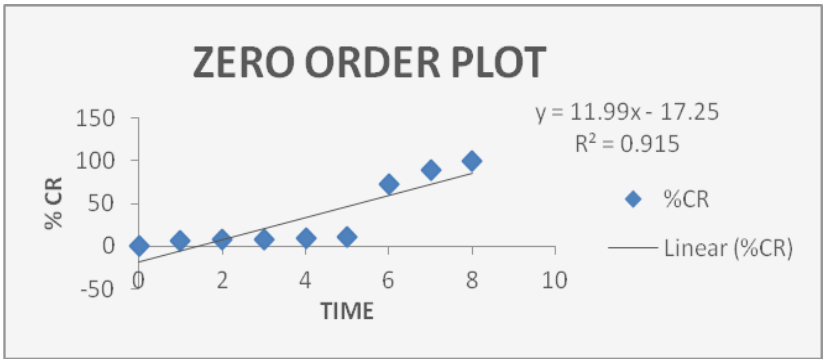

Fig.3. Zero Order Plot For best preparation

First-order kinetics

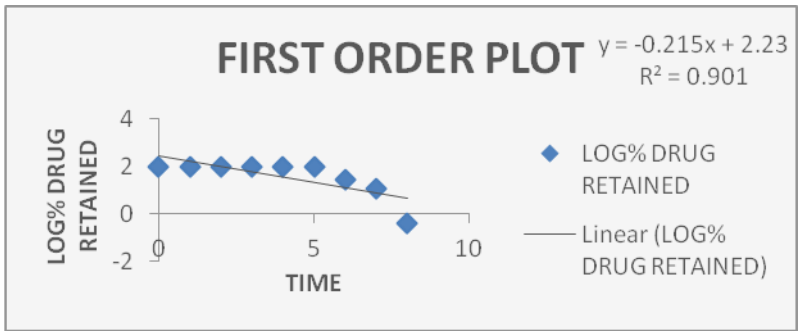

Fig.4. First Order Plot for best preparation

Higuchi Model:

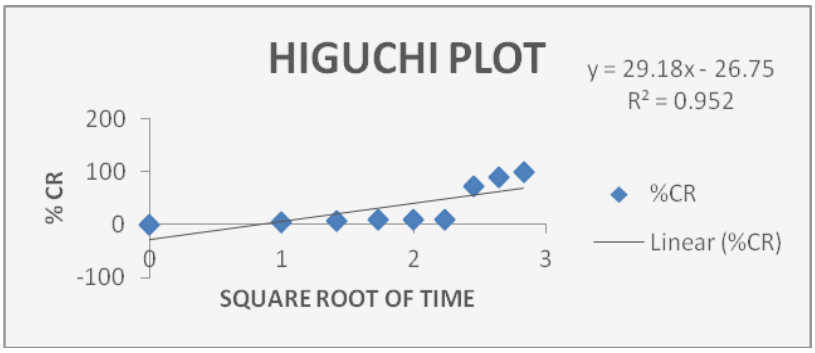

Fig.5. Higuchi Plot for best preparation

Korsmeyer Peppas equations:

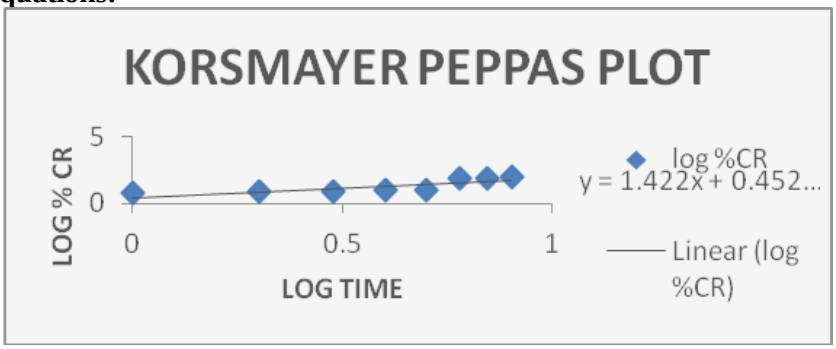

Fig.6. KorsMayer Peppas Plot For best preparation

Release Kinetics

To know the drug release kinetics from these formulations, the dissolution data were subjected to different kinetic models such as Zero-order and Higuchi's square root kinetics model. The line of equations and regression coefficient of kinetic study for all the formulations are shown in the table. The regression coefficient was considered as the main parameter to interpret release kinetics. From the above results obtained the drug release

mechanism was found to be dissolution control.

Stability studies

Table-:5 Stability Studies of Optimized Formulation F6

S.NO	Time in days	Physical changes	Mean % drug content ± SD		
			Mouth melting tablet		
			250C/60%	300C/75%	400C/75%
1.	01	No Change	98.16 ±0.11	98.16±0.11	98.16 ±0.11
2.	30	No Change	97.32± 0.29	97.35± 0.25	97.55± 0.25
3.	60	No Change	96.58± 0.31	96.61 ±0.24	96.63±0.30
4.	90	No Change	95.59 ±0.32	95.60±0.23	95.62 ±0.32

Discussion

There was no significant change in physical and chemical properties of the tablets of formulation F6 after 3 Months, parameters like % drug release and assay values at various conditions (at 40^0C/ 75% RH) as per ICH guidelines quantified at various time intervals were shown in Table and dissolution profile.

IV. SUMMARY AND CONCLUSION

Mouth melting tablets have the potential to be more effective than traditional solid dosage forms. This drug delivery technique is one of the most innovative of all revolutionary drug delivery systems. In comparison to traditional oral dosage forms, they may have higher patient acceptance and compliance, as well as superior biopharmaceutical characteristics, efficacy, the quick beginning of the action, and safety. MMT's best feature is its ability to disintegrate quickly So to formulate mouth-melting tablets using basil seeds (Ocimum basilicum pilosum) mucilage as super disintegrant. Pre-formulation studies it was decided to prepare mouth dissolving tablets prepared by direct compression method. In the formulation of sodium starch glycolate, and sodium starch fumarate was used as super disintegrants. Before compression, the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hauser's ratio. The compressed tablets were also evaluated for weight variation, hardness, friability, drug content, disintegration time, wetting time, in vitro drug release, and stability studies. In the above studies, the F6 formulation showed promising results. It was further supported by FTIR analysis which showed that F6 had no interaction with excipients. The stability studies were carried out for the optimized batch F6 for 90days and it showed acceptable results. So F6 formulation was considered as the optimized formulation.

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