FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLET OF ANTIHYPERTENSIVE DRUG

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Abstract:
The objective of present study is to develop the immediate release tablet of an antihypertensive drug, Olmesartan medoxomil. Immediate Release tablets of olmesartan medoxomil drug were prepared by using four different superdisintegrants like cross carmellose sodium, sodium starch glycolate and crospovidone. The method of tablet preparation is direct compression method and evaluated for physicochemical evaluation parameter 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 crospovidone have shown good *in-vitro* results compared to other formulations. However, the formulations containing 8% w/w concentration of any superdisintegrants have shown better optimum results, hence selected as best formulations in this study. Formulation F8 has shown excellent results in water absorption ratio. Hence F8 batch containing 8% cross povidone was found to be an optimized batch.

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INTRODUCTION

For rapid onset of pharmacological effect from drugs, especially in the treatment of acute disorders, we preferred parenteral administration, but this method may not always be convenient for the patient. Therefore, there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using administration routes where a rapidly dissolved drug is immediately absorbed into the systemic circulation. Tablet formulations are generally the first choice for drug administration because of the relative ease of both production and usage. However, for acute disorders, the time to onset of action for a conventional oral tablet is generally not acceptable; this is usually attributable to gastric emptying causing a highly variable lag time between drug administration and onset of intestinal absorption. [1]

Drug delivery via the oral mucosa is a promising route, when one wishes to achieve a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism. [2] Thus, there is a growing interest in developing alternative dosage forms, i.e. Immediate Release tablets, which allow a rapidly dissolving drug to absorb directly into the systemic circulation through the oral mucosa. These kinds of dosage forms are also convenient for children, elderly patients with swallowing difficulties and in the absence of potable liquids. [3] However, in addition to formulation considerations, the suitable properties of the active compound have to be appropriate in order to achieve drug delivery into systemic circulation after intraoral administration. The parent compound has to be soluble, stable and able to easily permeate the mucosal barrier at the administration site. Further, the dosage form has to be rapidly dissolved while retaining a sufficiently long contact time at the administration site. If dissolution of the drug is incomplete, contact time is short and/or permeation too low, part of the dose will not be absorbed through the oralmucosa and will be swallowed, with subsequent effects on bioavailability. [1]

When Immediate Release is keptin oral cavity then saliva quickly penetrates into tablet pores and causes rapid disintegration. [4] The basic approach used in development of Immediate Release tablets is the use of superdisintegrant, which provide instantaneous disintegration of tablets after putting on tongue, thereby releasing the drug in saliva. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. [5] A number of superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycol ate are used for rapid disintegration of tablet. [6] The objective of present study is to develop the MDT of an antihypertensive drug, Olmesartan an angiotensin second inhibitor drug and thereby imparting the significance, ideal characteristics and various aspects related to mouth dissolving tablet formulation as a superior dosage form in treatment of hypertension and to improve the patient compliance. This work is used to develop ODT of drug candidate to improve bioavailability, dissolution time, disintegration time and patient compliance.

Advantages of Tablets

1. They are unit dosage form and they offer the capabilities of all oral dosage forms for the dose precision and the least content variability during dosing.
2. Accuracy and uniformity of drug content optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use (i.e., immediate or extended release).
3. Usually taken orally, but can be administered sublingually, rectally or intravaginally.
4. Their cost is lowest of all oral dosage forms. They are the most compact of all oral dosage forms.
5. They are in general the easier and cheaper to package and ship as compare to other oral dosage forms.
6. Product identification is simple and cheap, requiring no additional processing steps when employing an embossed or monogrammed punch face.
7. They are ease to administer, does not require a specialist.
8. They are better suited to large-scale production than other unit oral forms.
9. They have the better properties of chemical, mechanical and microbiological stability.

Disadvantages of Tablets

1. Some drugs resist compression, due to their amorphous nature or low-density.
2. Drugs having bitter taste, objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating of tablet.
3. Bioavailability problems.
4. Chance of GI irritation caused by locally high concentrations medicament.
5. Difficulty in swallowing tablets in a small proportion of people and so size and shape become important considerations.
6. Slow onset of action as compared to parenteral and solutions.

Types and Classes of Tablets [1-3]
Tablets are classified by their route of administration or functions

1. Oral Tablets for Ingestion
a. Compressed tablets or standard compressed tablets
b. Multiple compressed tablets (MCT)
i. Layered Tablets
ii. Compression Coated Tablets
iii. Repeat action tablets
iv. Sustained release or modified release tablets
v. Delayed action or enteric-coated tablets
vi. Film coated tablets
vii. Chewable tablets.

2. Tablets used in Oral Cavity
a. Buccal tablets
b. Sublingual tablets
c. Troches and lozenges
d. Dental cones.

3. Tablets Administered by Other Routes
a. Implantation tablets
b. Vaginal tablets.

4. Tablets Used to Prepare Solutions
a. Effervescent tablets
b. Dispersible tablets
c. Hypodermic tablets
d. Tablet triturates.

Introduction to Immediate Release Dosage Form
Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Disintegrating agents are substances routinely included in tablet formulations and in some hard-shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Superdisintegrant improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants. Traditionally, starch has been the disintegrant of choice in tablet formulation and it is still widely used. For instance, starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants.

Mechanism of Disintegrants
1. High swellability
2. Capillary action and high swellability
3. Chemical reaction.

When introduced to an aqueous environment of use, the tablet rapidly takes up water, leading to swelling of the disintegrant and rapid disintegration of the tablet before the dispersion polymer can form a hydrogel. The disintegrant should be chosen such that it (1) swells rapidly when introduced into the use environment and (2) has a low tendency to form or promote formation of a hydrogel. The rate of swelling of the disintegrant is directly correlated to tablet disintegration times. Tablets containing disintegrants cause more rapid swelling have faster disintegration times at comparable disintegrant levels. The amount of work, W, or swelling energy, due to swelling can be measured using a dynamic mechanical analyzer (DMA). The swelling energy attributable to swelling of the disintegrantin the compact may be calculated from the following equation:

$$W = P\Delta V$$

Where, W is the work or swelling energy of the disintegrant, P is the pressure applied by the probe and ΔV is the volume change of the sample.
To compare disintegrants, the swelling energy per mass of disintegrant is used. Preferably, the disintegrant generates a swelling energy of at least 0.05 J/g within about 10 minutes following addition of water to the liquid reservoir. The most popular disintegrants are corn starch, soluble starch etc. which have been well dried and powdered. Starches have great affinity for water and swell when moistened thus facilitating the rupture of the tablet matrix, its disintegration action in tablets is due to capillary action. Spherical shape of starch increases the porosity of tablet thus promoting capillary action.

Desired Criteria's for Immediate Release tablet:
Immediate Release tablets should:
1. Not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of seconds.
2. Have a pleasing mouth feel.
3. Should be compatible with taste masking.
4. Should be potable without fragility concern.
5. Leave minimal or no residue in the mouth after oral administration.
6. Exhibit low sensitivity to environmental conditions such as humidity and temperature.
7. Allow the manufacture of tablet using conventional processing and packaging equipment at low cost.

Salient Features of Immediate Release Tablet

1. Ease of administration to patients who refuse to swallow a tablet such as, pediatric, geriatric patients and psychiatric patients.
2. Convenience of administration and accurate dosing as compared to liquids.
3. No need of water to swallow the dosage form, which is highly convenient especially for patients who are traveling and do not have immediate access to water.
4. Good mouth feel property of FDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
5. Rapid dissolution and absorption of drug, which may produce quick onset of action.
6. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.

MATERIALS AND METHODS

Olmesartan Medoxomil is received as gift sample from Glenmark pharmaceutical, Turbhe MIDC Mumbai and sodium starch glycolate and crosscarmellose sodium is obtained as gift sample from JCPL Pvt. Ltd. Jalgaon, crossprovidon are obtained from Cherly Laboratories Pvt.
Ltd. 302,Mahape MIDC Mumbai .All other ingredient, reagents and solvents is wear of analytical grade.

Methods Characterization of Drug and Excipients

1. Fourier Transform Infra Red Spectroscopy (FTIR)

FTIR spectra of pure Olmesartan medoxomil and mixture superdisintegrant with other excipient were recorded on Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400-4600 cm-1 at spectral resolution of 4 cm-1 and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

2. Differential Scanning Calorimetry (DSC)

Thermal properties of the pure Olmesartan medoxomil the physical mixture of drug and excipients were analyzed by Shimadzu DSC-60, Shimadzu Limited Japan. The samples were heated in a hermetically sealed aluminumpans. Heat runs for each sample were set from 30 to 350°C at a heating rate of 10°C/ min, using nitrogen as blanket gas.

Direct Compression Method

Olmesartan medoxomil immediate release tablet were prepared by the direct compression method using different excipients. The excipients used were Micro crystalline cellulose, Mannitol, Croscarmellose Sodium, Sodium starch glycolate and Lactose. Compositions of various formulations are shown in Table 2. All the ingredients of the immediate release tablets of Olmesartan medoxomil were weighed and mixed in mortar with the help of pestle. Then the blended material was slightly compressed on the 8 mm flat–biconvex punch using a Rimek MINI PRESS-I MT tablet machine. The total weight of the formulation was maintained 200 mg. The hardness was adjusted to 2-4 kg/cm2.

Evaluation of Powder Blend

1. Angle of Repose

Angle of repose (θ) was determined using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blends were allowed to flow through the funnel freely onto the surface. The diameter of the blend cone was measured and angle of repose was calculated using the following equation:

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

Where, h and r are the height and radius of the cone.

2. Bulk Density and Tapped Density

Bulk density of the drug was determined by pouring gently 2 gm of drug sample through a glass funnel into a 10 ml clean dry graduated measuring cylinder. The volumes occupied by the sample were recorded.
LBD=weight of the powder / volume of the packing
TBD= weight of the powder / tapped volume of the packing

3. Compressibility index

The compressibility index (Carrs index) of the all formulations were determined by using the below mentioned equation:

$$\textbf{Carrs Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

4. Hausners ratio

Hausners ratio is an indirect index of ease of powder flow. It is calculated by the following formula,

$$\textbf{Hausners Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower Hausner's ratio (<1.25) indicates better
Flow properties than higher ones (>1.25)

Table 1: Hausner's Ratio as an Indicator of Powder Flow Properties

S. No.	Hausner's Ratio	Type of Flow
1	<1.18	Excellent
2	1.19-1.25	Good
3	1.3-1.49	Passable
4	>1.5	Very poor

Evaluation of Tablets

1. Appearance

The Tablets were observed visually and did not show any defect such as Capping, Chipping and Lamination.

2. Thickness and Diameter

The thickness and diameter of the tablet was carried out using vernier caliper. Five tablets were used for the above test from each batch and results were expressed in millimeter.

3. Hardness Test

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. Monsantor hardness tester measured the hardness studies and results were expressed in kg/cm2.

4. Weight variation Test

Twenty tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was determined according to I.P. specification. As per I.P. not more than 5% and none deviate more than twice that percentage.

5. Friability Test

It was done in biological museum friability test apparatus where the tablets were subjected to combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre-weighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that loss less than 0.5 to 1.0% oftheir weight are generally considered acceptable.

$$\textbf{\%Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

6. Uniformity of Drug Content

Ten tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 20 mg of Olmesartan medoxomil was taken. The amount of drug present in a 20 mg equivalent amount of powder was determined by, dissolving the powder mixture in 100 ml of
methanol and suitably diluted with methanol and UV absorbance was measured at 248 nm. Drug concentration was determined from standard graph.

7. Wetting Time

Five circular tissue paper of 10 cm diameter were placed in a Petri dish. 10 ml of simulated saliva pH (pH 6.8phosphate buffer) was poured into the tissue paper placed in the Petri dish. Few drops of eosin solution were added to the Petri dish. A tablet was placed carefully on the
surface of the tissue paper. The time required for the solution to reach upper surface of the tablet was noted as the wetting time.

8. In-vitro Drug Release Study

The drug release rate from immediate release tablets was studied using the USP type II dissolution test apparatus. The dissolution test was performed using 900 ml of phosphate
buffer (pH 6.8) as the dissolution medium at 50 rpm and 37±0.5°C. 5 ml of aliquots were periodically withdrawn and the sample volume was replaced

with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 257 nm.

9. Water Absorption Ratio

A piece of tissue paper folded twice was kept in a petridish (internal diameter 5.5 cm) containing 6 ml of purified water. The pre-weighed tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation-

R = 100 (Wa-Wb)/Wb

Where, Wb and Wa are the weight before and after water absorption, respectively.

Table 2: Composition of Olmesartan Medoxomil Immediate Release Tablet

Ingredients (Quantity in mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Olmesartan	20	20	20	20	20	20	20	20	20
SSG	4	6	8						
CCS				4	6	8			
Cross Povidone							4	6	8
Microcrystalline Cellulose	50	50	50	50	50	50	50	50	50
Lactose Monohydrate	104	102	100	104	102	100	104	102	100
Mannitol	10	10	10	10	10	10	10	10	10
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	10	10	10	10	10	10	10	10	10
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Table 3: Evaluation of Mixed Blend of Drug and Excipients

Formulation Code	**Bulk Density (gm/cm^3)**	**Tapped Density (gm/cm^3)**	**Carr's Index (%)**	**Angle of Repose (θ)**
F-1	0.892±0.004	1.115±0.03	20±0.4	28.7±1.1
F-2	0.890±0.04	1.105±0.03	19±0.5	31.87±0.8
F-3	0.884±0.013	1.089±0.01	18.8±0.3	31.87±1.1
F-4	0.878±0.023	1.078±0.02	18.63±0.5	28.78±0.8
F-5	0.922±0.03	1.054±0.03	18.5±0.6	28.5±0.3
F-6	0.95±0.026	1.129±0.03	18±0.3	30.82 ±0.4
F-7	0.885±0.033	1.064±0.03	18.6±0.2	28.5±0.7
F-8	0.890±0.042	1.085±0.02	18.2±0.1	28.9±0.3
F-9	0.892±0.05	1.087±0.04	18.4±0.2	28.9±0.4

*All the values are expressed as mean± SE, n=3

Table 4: Various Physicochemical Characterization of Olmesartan Medoxomil Immediate Release Tablet

Formulation Code	**Hardness (kg/cm2)***	**Thickness (mm)***	**Diameter (mm)***	**Friability (%)***	**Disintegration time(sec)***	**Weight Variation (%)***
F-1	3.6±0.3	2.48±0.03	8.04±0.02	0.89±0.02	34±2	1.34±0.5
F-2	3.8±0.3	2.40±0.01	8.08±0.02	0.88±0.01	30±1	3.54±0.6
F-3	3.6±0.2	2.38±0.02	8.07±0.03	0.81±0.03	28±1	3.65±0.3
F-4	3.8±0.33	2.28±0.04	8.13±0.03	0.68±0.04	30±2	2.34±0.8
F-5	3.4±0.23	2.36±0.02	8.10±0.01	0.79±0.03	32±3	2.68±0.7
F-6	3.8±0.3	2.38±0.02	8.13±0.03	0.85±0.03	40±2	2.96±0.4
F-7	3.4±0.3	2.35±0.03	8.20±0.02	0.88±0.03	40±2	3.6±0.5
F-8	3.8±0.2	2.48±0.02	8.20±0.02	0.78±0.05	38±3	3.3±0.4
F-9	3.8±0.1	2.31±0.02	8.10±0.02	0.54±0.02	27±0.3	3.2±0.6

*All the values are expressed as mean± SE, n=3

Table 5: Various Physicochemical Characterization of Olmesartan Medoxomil Immediate Release Tablet.

Formulation Code	**Wetting Time (Sec)***	**Water Absorption Ratio (hrs)***	**Assay (%)**
F-1	38±2	60±1.133	95.08±1.34
F-2	36±2	70.66±0.9	105±2.32
F-3	35±1	86.66±2.6	101±2.2
F-4	38±1	57.89±3.3	99.16±1.5

F-5	38±2	58±3.3	97.50±2.4
F-6	32±1	60.18±2.3	103.33±1.7
F-7	39±1	72±0.7	105.83±2.6
F-8	38±1	80±1.3	105.83±2.4
F-9	29±1	88.22±2.2	102.25±1.8

*All the values are expressed as mean± SE, n=3

Table 6: Cumulative % Release of Olmesartan Medoxomil from Immediate Release Tablets

Time (hr)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
2	11.22	6.59	17.29	42.63	23.58	21.83	35.93	55.07	40.12
5	25.02	13.07	27.90	64.25	38.51	30.68	51.07	61.78	61.54
10	32.74	20.80	42.73	71.46	49.42	44.07	64.25	71.25	68.35
15	40.05	27.28	53.64	73.62	54.06	49.83	79.59	88.97	71.89
20	43.24	32.84	70.02	75.27	56.73	50.97	82.58	90.72	73.63
30	49.94	37.79	78.46	75.68	57.15	56.12	86.49	89.69	76.21
40	53.64	39.85	82.48	80.42	59.78	57.56	88.55	91.23	81.36
50	55.40	42.42	85.77	85.98	68.89	67.55	89.02	97.41	84.64
60	64.56	62.91	92.88	91.64	76.81	89.80	91.75	99.78	90.84

(mean ±S.D., n= 3)

RESULTS AND DISCUSSION

The values of angle of repose were found within the range 280.50 – 310.87 degrees indicating good flow properties. The values of compressibility index were found within the range 18 – 20 %. This indicates passable flow. Weight variation passes the limits as % deviations were within 10 %. The overall precompression study revealed good flow and compression properties of the powder blend. The weight variation was found within 10 % as specified for tablet weight 200 mg. Hence the tablet batches have passed the tests for weight variation as per IP limits. Friability was found below 1 %. Hence tablet batches pass the friability test. Hardness was found within the range 3.4 - 3.8 identical to marketed tablets. In all formulations F1 – F9, it was observed that an increase in concentration of a superdisintegrant tends to higher water absorption ratio and least wetting time. Disintegration time was inversely proportional to the concentration of superdisintegrants in cases of croscarmelose sodium and crospovidone but in case of sodium starch glycolate, as the concentration of superdisintegrant increases the disintegration time was also increased. Formulation F8 has shown good results in disintegration time, wetting time and water absorption ratio and drug release of 99.78 % in 60 minutes. Formulation F4 has shown better results in disintegration time, least wetting time and higher water absorption ratio and drug release of 98 % within 3 minutes. Formulation F9 has shown excellent results in water absorption ratio. The disintegration time and wetting time was found to be least for F9 formulation and the drug release of 98.38 % in 3 minutes. Hence F8 batch containing 8% cross povidone was found to be an optimized batch.

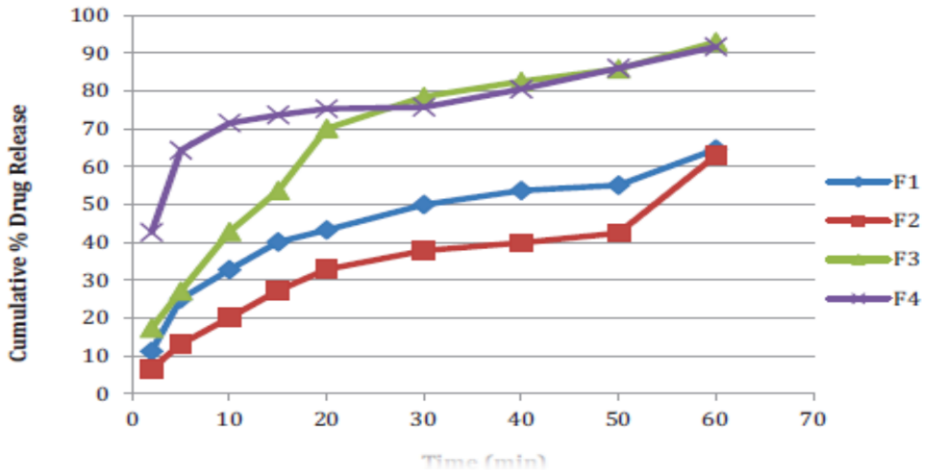

Figure 1: Dissolution profile of batch F1-F4

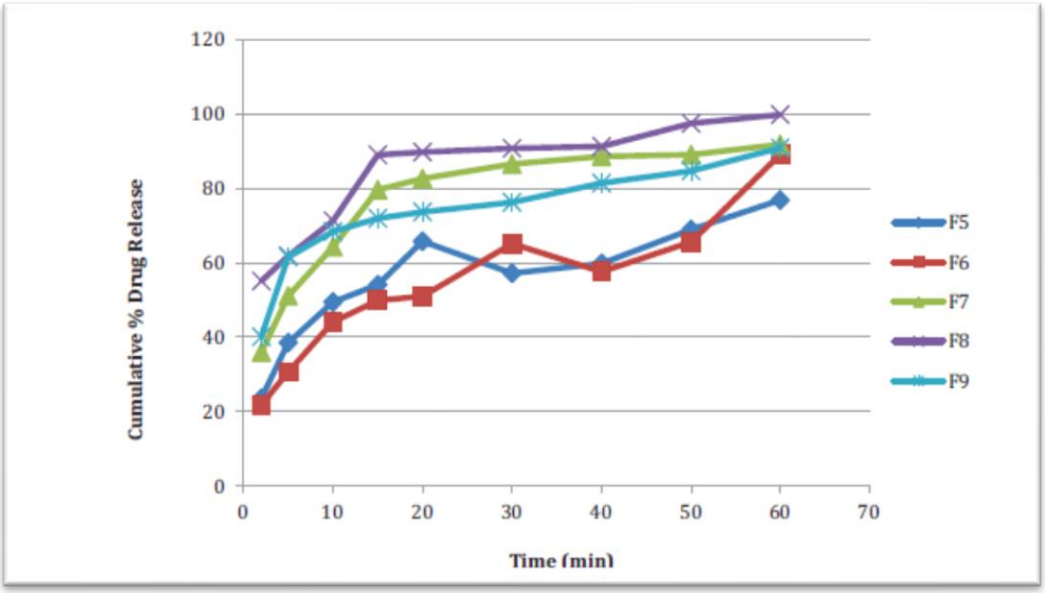

Figure 2: Dissolution profile of batch F5-F9

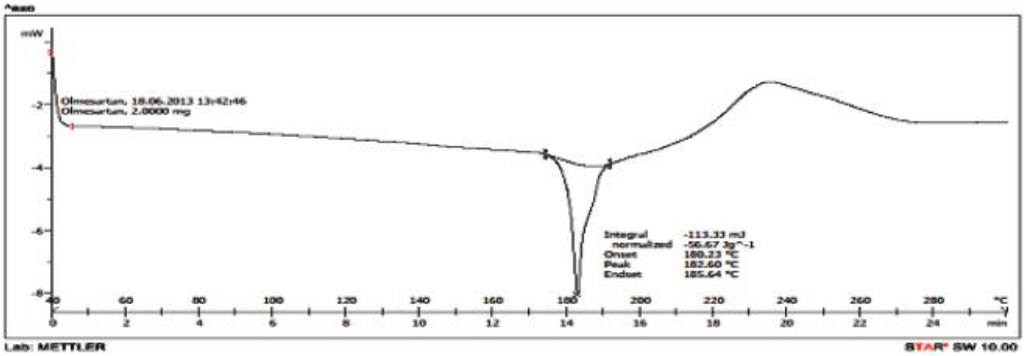

Figure 3: DSC of olmesartan medoxomil

Physicochemical Evaluation

Immediate release tablets of Olmesartan medoxomil were prepared by using crosscarmellose sodium, Sodium starch glycolate, Crospovidone and algenic acid. Mannitol used as bulk forming agent, magnesium stearate and talc were used as lubricant and glidant, respectively. Findings of the physicochemical characterization are shown in Table 4. Average weight of Olmesartan medoxomil tablets in all the formulations varied between 198.20 mg to 199 mg. Variation was determined less than 7.5% which is found to be within limits as prescribed in USP. Thickness of tablets of all the formulations was observed in between 2.35 mm to 2.45 mm which is found to be satisfactory. The hardness for different formulations was found to be between 3.4 to 3.8 kg/cm2 indicating satisfactory mechanical strength. The friability was below 1% for all formulations, which is an indication of good mechanical resistance of the tablets. Drug content varied in between 98.85% to 99.91% for different formulations, indicating good content uniformity.

CONCLUSION

In present study, the Immediate release tablet of Olmesartan medoxomil, with an antihypertensive drug was formulated with an objective to improve patient compliance and achieve rapid onset of action. Three different superdisintegrants croscarmellose sodium, sodium starch glycolate and Cross-providone were used in Formulation. Formulation F8 containing 8% crossprovidone has shown the best result for disintegration time 27 seconds.The disintegration time is less than the marketed immediate release tablet. In-vitro dissolution study showed 98.38%. Drug released at the end of 3 minutes. The overall result of F8 formulation was excellent. Hence formulation F8 was concluded as an optimized formulation. Thus, immediate release tablet of Olmesartan can be synthesized and can have good patient compliance.

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