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FORMULATION AND EVALUATION OF DISPERSIBLE TABLETS OF OLMESARTAN MEDOXOMIL

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ABSTRACT

The purpose of this research work was to develop and evaluate dispersible tablets of Olmesartan medoxomil employing different ratios of hydrophilic polymers by direct compression method. The main objective is to avoid first pass effect and to improve bioavailability of Olmesartan medoxomil which is used in the treatment of hypertension. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results suggested no physicochemical incompatibility between the drug and the polymers. Total of 12 formulations consisting of Low substituted Hydroxy propyl cellulose, sodium starch glycolate and crospovidone in the different ratios were prepared. The prepared dispersible tablets were evaluated for in vitro drug release, moisture loss and mechanical properties. The formulations coded as F_6 (Crospovidone) showed maximum release of 98.34% within 14 mins. The formulation F_6 emerging to be ideal formulation for Olmesartan medoxomil. The stability studies were carried out on the most satisfactory formulation F_6 and there was no significant difference in the physicochemical parameters, and in in-vitro drug release profiles.

KEYWORDS: Olmesartan medoxomil; Direct compression method; Dispersible tablets; Crospovidone.

INTRODUCTION

In recent days though novel drug delivery systems have gained more importance in pharmaceutical formulations, conventional dosage forms always have their priority with

worldwide patient acceptance. In the available oral conventional dosage forms, tablets are of great important. Tablets are unit dosage forms in which one usual dose of the drug has been accurately placed. The tablet has a number of advantages. One of the major advantages of tablet over capsules, which have recently proved significant, is that the tablet is an essential tamperproof dosage form. [1, 2]

One important drawback of this dosage form for some patients is difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as "Dispersible Tablets". Dispersible Tablets are also known as quick dissolves, fast melts, fast dissolving, fast disintegrating, rapid-dissolve, or orally dissolving tablets. [3] Their characteristic advantages such as administration, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market. [4]

Despite increasing interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of Superdisintegrants and its consistency of performance are of critical importance to the formulation development of such tablets. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in water and to be swallowed. [5]

Hypertension, or high blood pressure, is a chronic and often a medical condition in which systemic arterial blood pressure is elevated beyond normal. As such, the heart is forced to work harder to overcome the increased systemic pressure in order to deliver blood to tissues, which puts strain on the heart and arteries. Over time, the additional strain leads to cardiovascular dysfunction and is a primary contributing cause of congestive heart failure, myocardial infarction, pulmonary embolism, and kidney failure. Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is,

therefore, independent of the pathways for angiotensin II synthesis. Olmesartan has more than a 12,500-fold greater affinity for the AT1 receptor than for the AT2 receptor. [6, 7]

In the present work Olmesartan medoxomil was formulated as oral dispersible tablets by using superdisintegrants like cross linked carboxymethyl cellulose, sodium starch glycolate, polyvinylpyrollidone etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby release the drug in the saliva.

MATERIALS AND METHODS

Materials: Olmesartan medoxomil was obtained as a gift sample from Quliteck Pharma, Hyderabad. Sodium starch glycolate, Crospovidone, L-HPC, Mannitol, Magnesium stearate and talc were purchased from Drugs India, Hyderabad.

METHODS

Compatibility studies: Compatibility of the drug with the excipients is determined for the physical mixture of the drug and the excipients of the main formulation to Infra red absorption spectral analysis (FTIR). Any changes in chemical composition of the drug after combining it with the excipients were investigated with IR spectral analysis.

Weighed amount of the drug was mixed with 100mg of potassium bromide dried at 40-50^{o}c and mixture was taken and compressed under pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer.

Table 1: Formulation table of Olmesartan Medoxomil

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Olmesartan medoxomil	40	40	40	40	40	40	40	40	40	40	40	40
L-HPC	2.4	4.8	7.2	9.6	-	-	-	-	-	-	-	-
CP	-	-	-	-	2.4	4.8	7.2	9.6	-	-	-	-
SSG	-	-	-	-	-	-	-	-	2.4	4.8	7.2	9.6
Mannitol	99	96.6	94.2	91.8	99	96.6	94.2	91.8	99	96.6	94.2	91.8
Aspartame	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Total tablet weight (mg)	150	150	150	150	150	150	150	150	150	150	150	150

Formulation development: Olmesartan Medoxomil oral disintegrating tablets were prepared by direct compression method. All the ingredients are weighed in required quantity and

transferred into a mortar and triturated for 10minutes until, fine powder is obtained and the materials are sieved through mesh #60. Then the powder is transferred into blender and blended for 10mins for proper distribution of drug. Then the lubricants are added and mixed well. The required quantity of powder is weighed and compressed to obtain tablets.

Evaluation tests

Precompression evaluation: [8, 9]

The powder of formulations is subjected precompression evaluation tests like bulk density, tapped density, Hausners ratio, carr's index and angle of repose to determine the flow properties and compressibility nature.

Post compression evaluation

Hardness: The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in Kg / cm^2.

Friability (F): The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four mins. The tablets were weighed again (W_{final}). The percentage friability was then calculated.

Weight Variation: Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets weighing more than 325mg is ± 5%.

Thickness: The thickness of the tablets was measured by screw gauge. It is expressed in mm.

Disintegration Time: The Invitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Content uniformity test: [10]

Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of formulation was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The drug

content was determined by measuring the absorbance at 256 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated.

Invitro dissolution studies: The Invitro dissolution study was carried out in USP dissolution test apparatus type 2 (paddle) with 900ml of 0.1N HCl as the dissolution media. The dissolution media is maintained at a temperature of 37 ± 0.5° C. The paddles are run at 100 RPM and the tablets are placed in the dissolution basket. The samples are withdrawn for every 5mins and replaced with the same amount of dissolution media. Samples withdrawn were filtered through watmann filter paper and assayed spectrophotometrically at 256nm and the percentage drug release was calculated. [11]

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. The time required for water to reach upper surface of the tablet is noted as a wetting time. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured. The method was slightly modified by maintaining water at 37^{o}C. A tablet was placed on the tissue paper and small amount of amaranth powder was placed on upper surface of tablet. The time required for development of a red color on the upper surface of the tablet was recorded as wetting time. [12]

$$R = 100 \times \left(\frac{W_b - W_a}{W_a} \right)$$

Where, W_a is weight of tablet before water absorption; W_b is weight of tablet after water absorption; R is water absorption ratio.

Stability Studies

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40°C / 75% RH for 3months and evaluated for their physical appearance, drug content and drug excipient compatibility at specified intervals of time.

RESULTS AND DISCUSSION

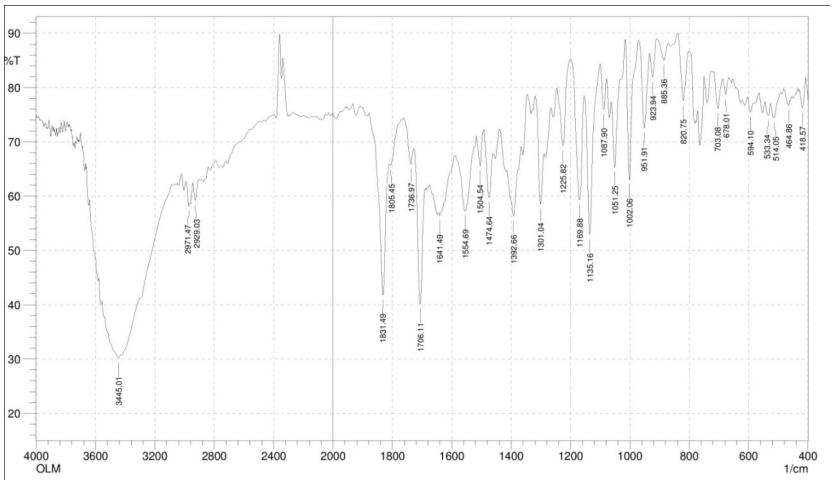

Figure 1: FT-IR of pure drug

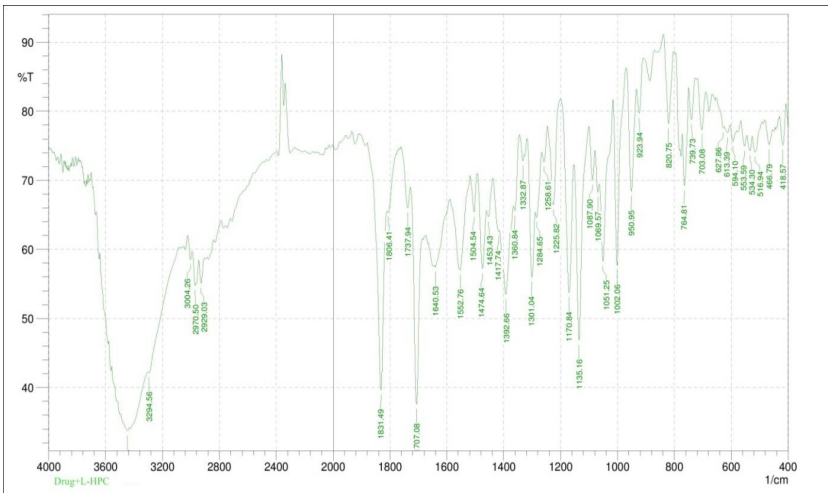

Figure 2: FT-IR of Drug with L-HPC

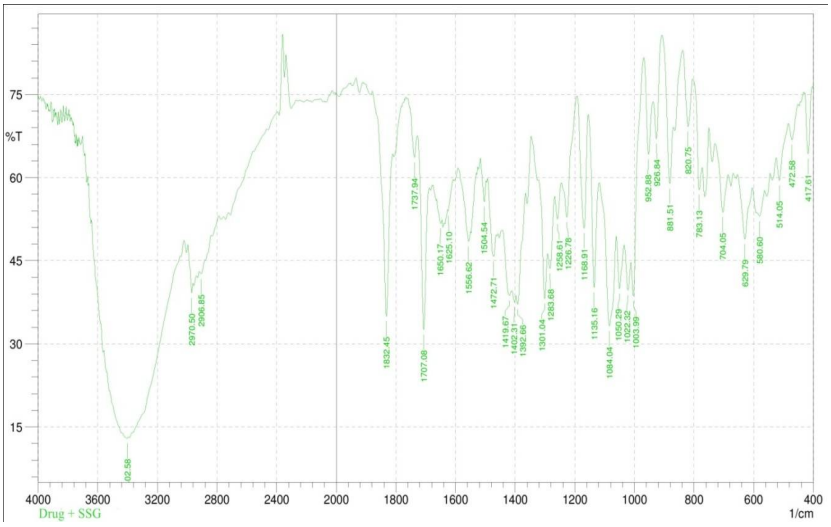

Figure 3: FT-IR Drug with sodium starch glycolate

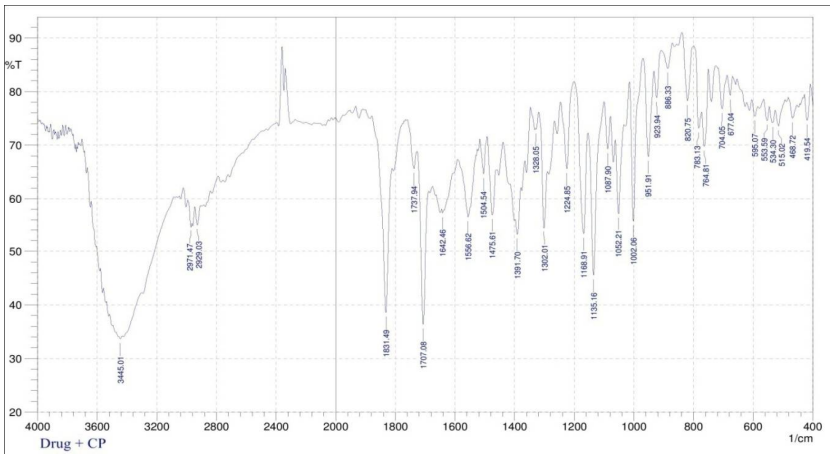

Figure 4: FT-IR of Drug with crospovidone

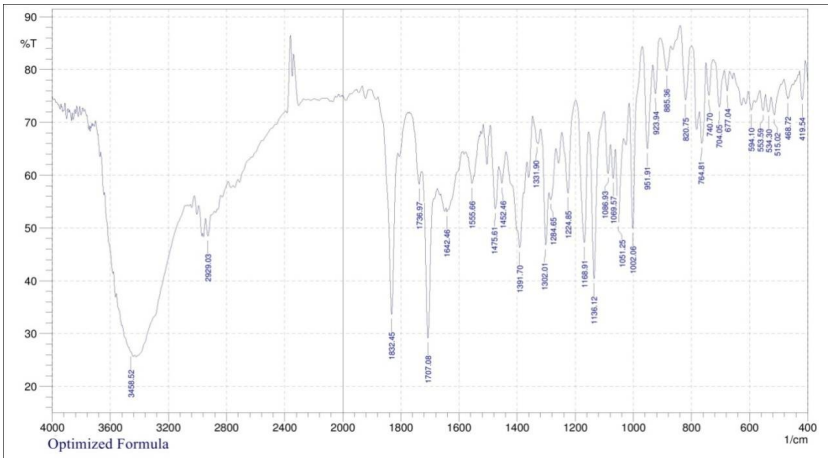

Figure 5: FT-IR of optimized formula

Compatibility Studies by FTIR Study

The FT- IR Spectrum of pure Olmesartan medoxomil drug was compared with that of physical mixture of Olmesartan medoxomil and other ingredients, Olmesartan medoxomil and L-HPC, Olmesartan medoxomil and Mannitol etc. (Fig:1-5). There was no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the polymers used in the tablets.

Pre Compression Studies: The precompression parameters were determined for the powder blend and the results are presented in the table 2. The bulk density values ranged from 0.48-0.55 gm/cc, tapped density was in between 0.55-0.66 gm/cc, carrs index values between 10.90-26.21, hausner's ratio was in the ratio of 1.12-1.25 and angle of repose ranged from 31°8'-35°5' from all these results it is concluded that powder has good compressibility and good flow properties.

Table 2: Pre-compression parameters of Olmesartan medoxomil

Formulation code	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index	Hausner ratio	Angle of repose(Ɵ)
F1	0.52	0.65	20.02	1.25	34°2'
F2	0.55	0.64	26.21	1.16	35°5'
F3	0.49	0.57	14.04	1.163	33°2'
F4	0.48	0.55	12.72	1.14	32°4'
F5	0.50	0.58	13.79	1.16	33°0'
F6	0.53	0.61	13.11	1.15	32°1'
F7	0.49	0.55	10.90	1.12	33°5'
F8	0.53	0.61	13.11	1.15	32°1'
F9	0.53	0.66	19.69	1.24	31°8'
F10	0.51	0.65	21.53	1.27	35°4'
F11	0.54	0.61	11.47	1.12	32°5'
F12	0.52	0.65	20.00	1.25	33°1'

Post Compression Studies: The hardness of the tablets was found to be 3.5 to 4.1 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 2.3 to 2.5mm. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeia limits i.e. ±7.5%.

The most important parameter that needs to be optimized in the development of oral disintegrating tablets is the disintegration time of tablets. In the present study disintegration time of all batches were found in the range of 89 to 131 sec fulfilling the official Requirements for disintegrating tablets. It depicts the disintegration behavior of the tablets in 1.2 pH buffer (0.1N HCl).

Formulation F6 was selected as optimized batch containing CP as superdisintegrant. It was shown disintegration time of 89 seconds. It was observed that less disintegration time was observed when cross povidone was used as superdisintegrant, may be due to swelling at faster rate upon contact with water and elimination of lump formation after disintegration when compared with sodium starch glycolate and crosscarmellose sodium. F6 was found to be the best as this formulation shown less disintegration time and possessing good tabletting properties.

Wetting time was used as a parameter to correlate with disintegration time in oral cavity. This is an important criterion for understanding the capacity of disintegrants to swell in the presence of little amount of water. Since the dissolution process of a tablet depends upon the wetting followed by disintegration of the tablet.

It could be assumed that wetting was the only cause of disintegration. This indicates that that aqueous medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bonds and breaks the tablet into fine particles. The wetting time of the formulated tablets were found in the range of 183 to 225 sec.

Table 3: Post compression parameters of olmesartan medoxomil

Formulation	Hardness (Kg / cm^2)	Friability (%)	Thickness (mm)	Disintegration time (sec)	Weight variation(mg)	Wetting time(sec)
F1	3.5	0.41	2.5	112	152	215
F2	3.8	0.46	2.4	115	150	198
F3	3.6	0.48	2.4	121	151	184
F4	4.1	0.42	2.3	124	152	201
F5	3.8	0.49	2.5	96	153	215
F6	3.5	0.45	2.5	89	149	214
F7	3.5	0.44	2.4	127	147	219
F8	3.6	0.47	2.5	114	151	225
F9	3.8	0.49	2.3	131	148	183
F10	3.9	0.48	2.5	98	148	214
F11	3.5	0.41	2.4	122	149	215
F12	3.2	0.42	2.5	124	146	214

In-Vitro Dissolution Studies: Dissolution studies for the prepared tablets were performed and results are given in table 4. From the results it was found that the drug is completely released from the formulations within 16mins. Of all the formulations formulation F6 has show maximum of 98.34% at the end of 14mins. Thus it was considered as optimized formulation, and the superdisintegrant used in that formulation is Crospovidone.

Table 4: Dissolution Table of Formulations in 0.1N HCl

	2min	4min	6min	8min	10min	12min	14min	16min
F1	25.03	33.97	42.91	55.43	64.37	73.31	85.82	96.55
F2	28.6	37.54	41.12	59	64.37	80.46	87.61	92.98
F3	28.6	39.33	46.49	55.43	60.79	75.09	85.82	98.34
F4	32.18	39.33	46.49	51.85	59	64.37	75.09	85.82
F5	42.91	50.06	62.58	75.09	87.61	96.55	96.55	98.34
F6	46.49	51.85	62.58	76.88	85.82	94.76	98.34	98.34
F7	21.45	28.6	33.97	42.91	48.27	57.21	64.37	71.52
F8	25.03	26.82	32.18	46.49	62.58	71.52	76.88	85.82
F9	28.6	32.18	42.91	51.85	60.79	67.94	82.28	92.9
F10	33.97	42.91	48.27	60.79	69.73	78.67	85.82	94.76
F11	41.12	44.7	50.06	67.94	75.09	85.82	94.76	98.34
F12	19.66	25.03	30.39	41.11	51.85	64.37	73.31	85.82

Stability studies: The stability of this optimized formulation was known by performing stability studies for three months at accelerated conditions of 40^0C + 75 % RH on optimized formulation. The formulation was found to be stable, with no change in the hardness, disintegration time and drug content and in- *vitro* drug release pattern.

Table 5: Stability Data of Formulation 6 at 40 ± 2^0C / 75 ± 5% RH.

Time in days	Physical changes	Percentage of drug content* ±SD	Moisture content	Percentage of drug release
1st day (initial)	Round flat shaped tablets, using 7mm punch	99.51±0.48	0.82	99.5%
30th day (1 month)	No changes	99.35±0.11	0.78	99.3%
60th day (2 month)	No changes	98.12±0.13	0.80	98.6%
90th day (3 month)	No changes	97.81±0.28	0.78	98.2%

* SD- Standard deviation

CONCLUSIONS

In the present work, oral dispersible tablets of Olmesartan medoxomil were prepared by direct compression method. Based on the above study following conclusions can be drawn: IR-spectroscopic studies indicated that there are no drug–excipients interactions and the drug functional group ranges within the limit. Tablets prepared by direct compression method were found to be good without any chipping, capping and sticking. The hardness of the prepared tablets was found to be in the range of 3.5 to 4.1kg/ cm^2. The friability values were found to be in the range of 0.41 to 0.49%. Disintegration time was found to be in the range of 89sec to 131sec.Formulation 6th showed good results than rest of the 12 formulations in pre and post compression studies. The values of standard deviation for average weight, drug content of the prepared tablets indicate weight and drug content uniformity within the batches. Formulations 6th displayed faster drug release when compared to remaining 12 formulations considered in 0.1N HCl. Short-term stability studies of promising formulations indicated that there are no significant changes in drug content.

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