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Combinational Drug Therapy Based Mouth Dissolving Tablet of Valsartan and Olmesartan for the Effective Management of Hypertension

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Abstract
This study aimed to develop and optimize orodispersible tablets (ODTs) containing a combination of Olmesartan and Valsartan, to improve the patient compliance and antihypertensive efficacy. The antihypertensive activity of both drugs in different combinations was determined by ACE inhibitory activity, and the result suggested a highly synergistic effect. Fifteen formulations were evaluated using a design of experiments approach, with Croscarmellose sodium, Microcrystalline cellulose and Thymol as independent variables affecting disintegration time, swelling index, and wetting time.
The optimized formulation (F8) showed rapid disintegration (14 seconds) and high drug release (>90%), with acceptable hardness (2.5 kg/cm²), friability (<1%), and thickness (3.5 mm). The tablets exhibited good flow properties, suitable for direct compression, and water absorption ratio ranged from 71.19% to 77.23%, indicating effective hydration and swelling properties. Stability experiments verified that F11 was physically and chemically stable for 90 days at different storage temperatures (25°C/60% RH and 40°C/75% RH).
These findings suggest that the developed ODTs have potential as a novel formulation approach for managing hypertension, offering improved patient compliance, therapeutic outcomes, and convenience.
Keywords: *Olmesartan, Valsartan, Box-Behnken Design, Tablet, Oro-dispersible*

INTRODUCTION

Socioeconomic, environmental, and demographic shifts coupled with unhealthy lifestyle choices—such as smoking, inactivity, consuming large amounts of fat and calories, and drinking alcohol—are considered risk factors for non-communicable diseases, especially cardiovascular conditions. The main cause of the morbidity and mortality issues that exist today is hypertension [1,2].

Hypertension, often known as elevated blood pressure, is a chronic illness characterized by systolic blood pressure readings of 140 mmHg or higher and diastolic readings of 90 mmHg or higher in two different cases. Heart failure, myocardial infarctions, cerebrovascular accidents, and renal failure are among the serious health problems that can result from this syndrome, which greatly increases the risk of heart and kidney damage and frequently causes early death [3]. Hypertension affect a significant population globally. Approximately 1.39 billion people, or 31.1% of all adults globally, experienced the negative effects of chronic illness in 2010. This issue is much more common in lower- and middle-income countries, where around 31.5% of the population, or almost 1.04 billion people, are impacted, compared to 28.5% (349 million) in wealthier countries [4].

Angiotensin Converting Enzyme (ACE) inhibitors are a class of drugs commonly used to treat hypertension. Some of the most commonly used ACE drugs are captopril, ramipril, benazepril, and enalapril. ACE inhibitors work by stopping angiotensin I from becoming angiotensin II and bradykinin from being converted into inactive metabolites [5].

Synthetic drug consumption consistently has positive benefits on the body. This has prompted experts to carry out a great deal of study in an effort to develop a medication that is both safer and more effective. One study examines how two medications work together to treat hypertension.

After being taken orally, the inactive prodrug olmesartan is quickly absorbed and quickly de-esterified in the gastrointestinal system, producing the active metabolite olmesartan [6]. Olmesartan is classified as class II (low solubility and high permeability) by the Biopharmaceuticals Classification System (BCS) because of its low water solubility and low oral bioavailability (around 26%) [7]. Tablets that are taken

orally offer numerous benefits over other dosage forms, including accurate dosing that promotes treatment compliance, good stability, and ease of manufacturing [8].

Valsartan is classified under ARB drugs [9]. Valsartan belongs to a class of drugs called angiotensin-receptor blockers (ARBs), which generally interfere with the Renin-Angiotensin-Aldosterone System (RAAS) by competing with angiotensin II binding at type-1 angiotensin II receptor (AT1). This stops angiotensin II's cellular actions, such as vasoconstriction, cellular proliferation, cytokines, and aldosterone production [10, 11]. The AT2 receptor may be exposed to larger amounts of angiotensin II generated by the negative feedback of the RAAS since valsartan has a 20,000-fold higher affinity for the AT1 receptor than the type-2 angiotensin II receptor (AT2). However, it's unclear exactly what AT2 receptor activity means [11, 12]. Normally, the RAAS helps regulate the body's sodium and water intake. However, excessive RAAS activation can cause hypertension and initiate a chemical reaction in tissues that harms important organs such as the kidneys, heart, brain, and blood vessels. The first metabolite of valsartan has a very low affinity for the AT1 receptor and is essentially inert [13]. Research has indicated that valsartan reduced hypertension and improved patient mortality and morbidity whether used alone or in combination with drugs from other classes [10].

This study looked at how mouth dissolving tablets might enhance the antihypertensive properties of valsartan and olmesartan in vitro. The ACE assay kit was utilized to examine antihypertensive medications [14]. The activity was dissimilituded with that of the common medication, captopril in aqueous solution. It was anticipated that combination oral dissolving tablets of olmesartan and valsartan would have potential as a substitute therapeutic agent in the treatment of hypertension in the future.

***In Vitro* Antihypertensive Activity Assay**

Captopril at a specific dose of 0.46 mg/ml was compared to the ACE inhibitory activity of several medication combinations of Olmesartan and Valsartan (2 mg/ml, 3 mg/ml, 4 mg/ml, and 6 mg/ml). Figure 1 displayed their individual rates of inhibition. With the exception of 0.6 mg/ml against captopril, the rate of inhibition shown by dig combinations was noticeably lower at all concentrations.

Group 1:- This contains olmesartan and valsartan in 1 mg + 1mg / kg
Group 2:- This contains olmesartan and valsartan in 1 mg + 2mg / kg
Group 3:- This contains olmesartan and valsartan in 2 mg + 2 mg / kg
Group 4:- This contains olmesartan and valsartan in 2 mg + 4 mg / kg

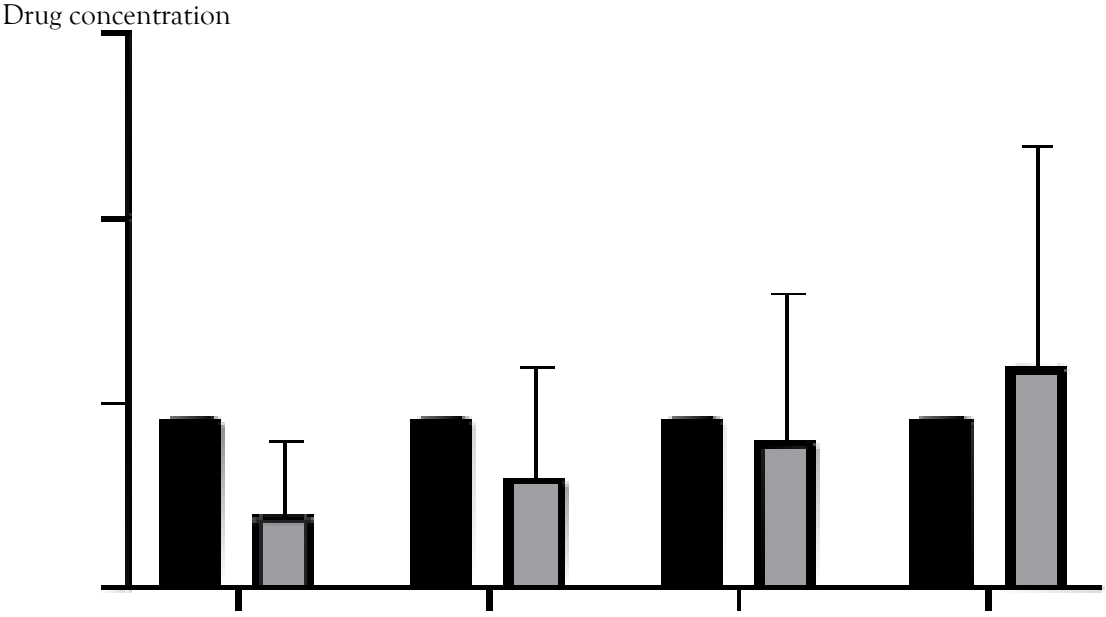

Figure 1: ACE inhibitory activity of various drug concentration in combination of olmesartan and valsartan [2mg/ml (1), 3mg/ml (2), 4mg/ml (3), 6mg/ml (4)] was determined and compared to captopril in specific concentration of 0.46mg/ml.

In this study, 0.6mg/ml showed higher ACE inhibition rate in comparison with other drug concentrations. This result shows that higher dose of these drug combination can enhance the inhibition activity. This activity related to ACE Inhibition has been patented [15]

Method of preparation of orodispersible tablet

Several methods, such as molding, compaction, spray-drying, freeze-drying, and some special ones like melt granulation, phase change, and sublimation, are used to create orodispersible tablets [16].

Cipla Limited in Banglore provided the olmesartan as a gift sample, while LOBA Chemie in Mumbai supplied the sodium starch glycolate and sodium saccharin. Nice Laboratory Reagent in Kochi supplied the menthol and microcrystalline cellulose.

Every chemical is of the finest caliber for analysis.

Design and development of oro-dispersible tablets

Method of preparation of oro-dispersible tablet

Every ingredient was measured using the prescribed formula. The medication, lubricant, disintegrants, and diluents were all run through an 80-mesh sieve. Using a mortar and pestle, the medication was first thoroughly combined with the diluents and disintegrant until the required fineness was reached. After that, magnesium stearate was added and combined. The direct compression approach was used to develop a variety of formulations (F1 to F15). Following micromeritic analyses, the resultant mixes were compressed directly with 8 mm flat punches to produce 200 mg tablets using a single punch rotary machine. A batch of 20 tablets was prepared for each formulation [17-19].

Optimization of various parameters of oro-dispersible tablet by Full Factorial Design

Response surface methodology was utilized to evaluate the influence of different independent factors on formulation parameters. The Box-Behnken Quadratic Design made it easier to create fourteen different orodispersible tablet formulations. The design of experiment software was used to calculate the replies. The concentration of thymol (X2) as a subliming agent, the concentration of microcrystalline cellulose (X3) as a binder in the wet granulation process, and the concentration of Croscarmellose sodium (X1) as a super disintegrant were selected as the three independent variables, as shown in Table 1. Three dependent variables—disintegration time (Y1), swelling index (Y2), and wetting time (Y3)—were correspondingly identified. Two levels of evaluation were assigned to each of the three independent variables: upper and lower (-1, 0, +1).

Table 1: Test factors for Optimization of process parameters

Factor	**Name**	**-1**	**0**	**+1**
A (X1)	Croscarmellose sodium(mg)	4	6	8
B (X2)	Thymol (mg)	10	15	20
C (X3)	Microcrystalline cellulose (MCC) (mg)	1.5	2.5	3.5
S.No.	Response	Goal		
1	Y1 (disintegration time)	Minimize		
2	Y2 (swelling index)	Maximize		
3	Y3 (wetting time)	Minimize		

Using the Box-Behnken Quadratic Design formula given below, the effect of independent variables on dependent variables at three levels was ascertained. Regression coefficients b1 through b2 and b3 correspond to the variables in this model, whereas Y is the dependent variable and b0 is the arithmetic mean of the fifteen formulations. The interactions between the various parameters are shown in the factors X1, X2, and X3.

$y1=b_0+b_1X_1+ b_2X_2+ b_3X_3+ b_1b_2X_1X_2+ b_1b_3X_1X_3+ b_2b_3X_2X_3+ b_1^2 X_1^2+b_2^2X_2^2+b_3^2X_3^2$

Optimization of various parameters of mouth dissolving tablet by Box-Behnken Quadratic Design

Box-Behnken Quadratic Design was used for the optimization of mouth dissolving tablet prepared by direct compression method. All the fifteen formulations of tablet with their actual value of dependent and independent variables are shown in table 1.

Table 2: Box Behnken design with actual value of all the independent and dependent variables

Croscarmellose sodium (mg)	Microcrystalline cellulose (mg)	Thymol (mg)	Disintegration Time (sec)	Swelling Index (%)	Wetting Time (sec)
60	60	30	31	123	14
6	60	30	31	123	14
6	60	30	31	126	14
6	80	40	26	135	12
6	40	40	35	115	15
6	80	20	31	125	14
6	40	20	35	110	17
8	60	40	25	141	11
4	60	40	38	105	17
8	60	20	28	132	13
4	60	20	40	95	18
8	80	30	23	146	10
4	80	30	34	112	16
8	40	30	32	118	15
4	40	30	45	85	21

$Y_1 = 31.00 - 6.12X_1 - 4.13X_2 - 1.25X_3 + 0.50X_1X_2 - 0.25X_1X_3 - 1.25X_2X_3 + 1.75X_1^2 + 0.75X_2^2 + 0.50X_3^2$
Eq. 1
$Y_2 = 124.00 + 17.50X_1 + 11.25X_2 - 4.25X_3 + 0.25X_1X_2 - 0.25X_1X_3 + 1.25X_2X_3 - 5.87X_1^2 - 2.87X_2^2 + 0.125X_3^2$
Eq. 2
$Y_3 = 14.00 - 2.88X_1 - 2.00X_2 - 0.875X_3 + 0.05X_1X_2 - 0.25X_1X_3 - 0.07X_2X_3 + 0.875X_1^2 + 0.625X_2^2 - 0.125X_3^2$
Eq. 3

Table 3: Regression analysis of independent variables

Response	Type of Model	P Value	R^2	Adjusted R^2	Predicted R^2	Adequate Precision	Standard Deviation	C.V. %
Y_1	Quadratic	0.0004	0.9862	0.9632	0.7896	22.457	1.12	3.46
Y_2	Quadratic	0.0006	0.9837	0.9543	0.7603	19.919	3.54	2.96
Y_3	Quadratic	0.0010	0.9797	0.9432	0.6755	17.801	0.6708	4.55

As mentioned in table 3 the p values of the all three responses were less than 0.05, which means the model is significant. Also, the difference between Predicted R^2 of all the response and Adjusted R^2 was less than 0.2, hence indicating a reasonable agreement in the study.

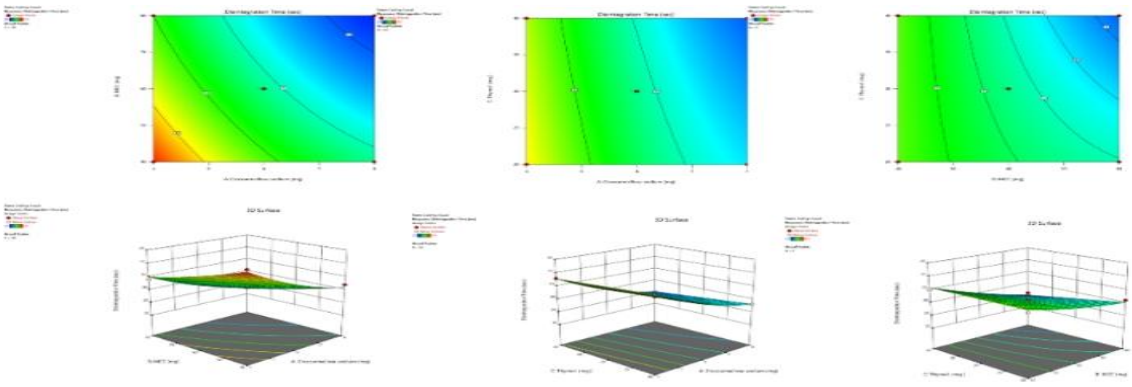

Figure 2: Contour plots and 3D surface plots of the effects of independent variables on disintegration time

The contour plots as well as the 3D surface plot shown in Figure 2, illustrate that with the increase of the concentration of Croscarmellose sodium, Microcrystalline cellulose and thymol Disintegration time decreases.

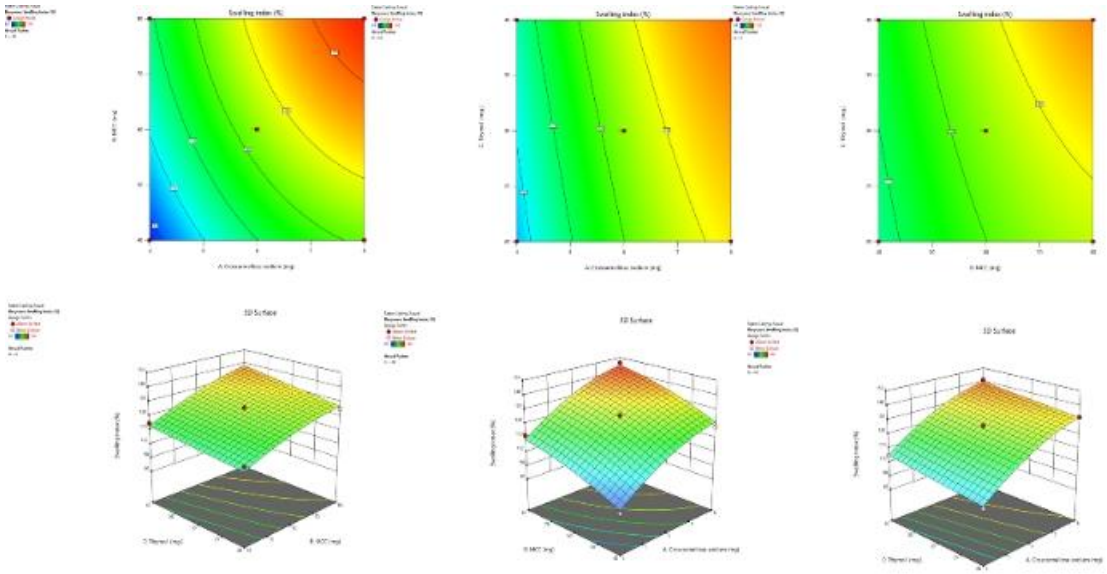

Figure 3: Contour plots and 3D surface plots of the effects of independent variables on swelling index

The contour plots as well as the 3D surface plot shown in Figure 3, illustrate that with the increase of the concentration of Croscarmellose sodium, Microcrystalline cellulose and thymol swelling index increases.

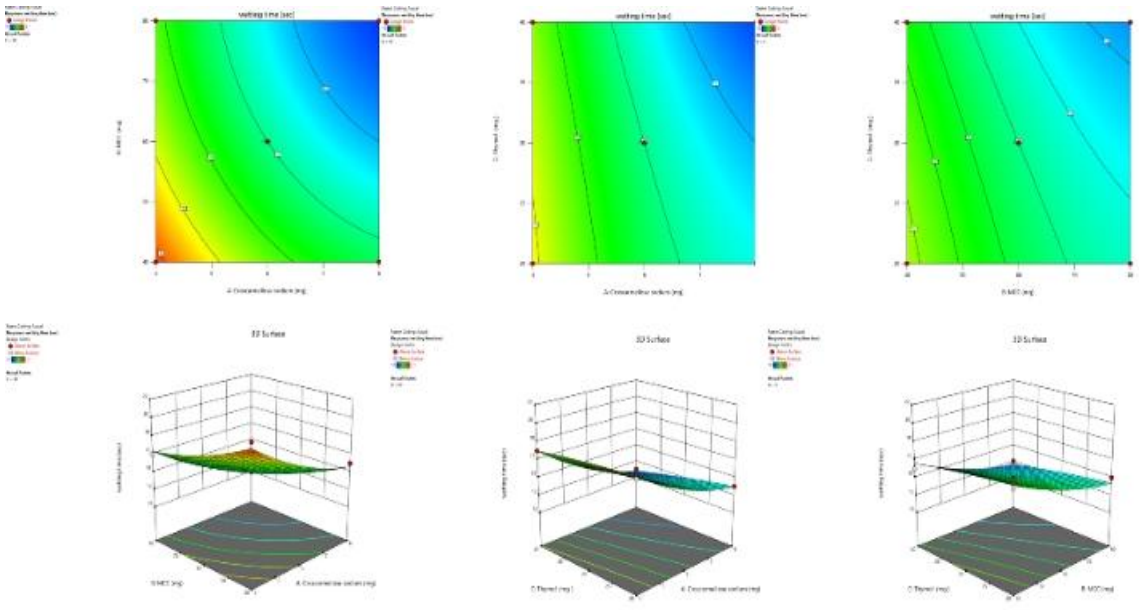

Figure 4: Contour plots and 3D surface plots of the effects of independent variables on wetting time

The contour plots as well as the 3D surface plot shown in Figure 4, illustrate that with the increase of the concentration of Croscarmellose sodium, Microcrystalline cellulose and thymol wetting time decreases.

Evaluation of oro-dispersible tablets

Pre-compression Parameters

Bulk density (20,21), Tapped density (22), Powder Flowability (23), Angle of Repose (24), compressibility factor (25), Housner's Ratio (26) was determined.

Post-compression Parameters

Thickness

Oro-dispersible tablets' thickness was measured with a vernier calliper (Insize 200mm Digital Vernier Caliper, 1112-200, India) [27].

Tablet Hardness

Tensile strength, expressed in Kg/cm^2, is a measure of a tablet's strength. This figure indicates how much power is required to compress a tablet and cause it to break. A Monsanto tablet hardness tester was used to take the measurement [28].

Weight Variation Test

A sample of twenty tablets was chosen at random to evaluate the weight differences of the tablets. A single pan balance was used to weigh each tablet separately as well as all at once. After that, the tablets' average weight and standard deviation were determined [29].

The IP and USP limit for weight variation of tablets is mentioned in **table 3.**

Table 4 : Standard values of weight variation

Sr. No.	IP/BP	USP	Limit
1.	80 mg or less	130mg or less	± 10%
2.	More than 80mg or Less than 250mg	130mg to 324mg	± 7.5%
3.	250mg or more	More than 324mg	± 5%

The percentage deviation weight variation was calculated by using given formula:

Percentage deviation = (W_{avg}) – $(W_{initial})$ / (W_{avg}) x 100

Where, W_{avg} = Average weight of tablet, $W_{initial}$ = Individual weight of tablet.

Friability

This evaluation was conducted using the Roche friabilator. Twenty pre-weighed tablets were put inside the apparatus, which was then run at a speed of 25 rpm for 100 revolutions, or four minutes. The tablets were reweighed and dust-free after the procedure. The given formula was used to determine the percentage of friability.

Percentage friability = Initial weight- Final weight/ Initial weight x 100

Wetting Time

A 5.5 cm diameter petri dish containing 6 cm of filtered water was filled with a piece of tissue paper that had been folded twice. A tiny bit of powdered amaranth was put on the top of a pill and placed on the tissue paper. The duration required for the tablet's surface to turn red was noted as the wetting time [30,31].

Water absorption ratio

The same method used for wetting time without the amaranth was used to determine it. Weighing the tablet both before and after soaking [31,32]. The water absorption ratio, R, was determined as per the equation:

$R= Wa-Wb/Wb \times 100$

Where,

Wb= Weight of tablet before wetting

Wa = Weight of tablet after wetting

In vitro dispersion time

Disintegration time is the amount of time, expressed in seconds, that a tablet takes to decompose when exposed to saliva or water. An orodispersible tablet was put in a 50 ml beaker with phosphate buffer at

pH 6.8 to measure the tablet's in-vitro disintegration time. Three tablets were selected at random from each formulation, and the amount of time it took for each to dissolve was noted [33,34].

Dissolution Studies

A basket-type dissolution device was used to evaluate the prepared tablets' dissolution profile. The dissolution media consisted of 500 milli-liters of 0.1 N HCl, and the temperature was maintained at 37±0.5 °C. For thirty minutes, the basket was rotated at 75 rpm. Ten milli-liters of the sample were taken and replaced with new medium every five minutes. Valsartan's absorbance was measured at 248.21 nm, while olmesartan's was recorded at 257 nm [35,36].

I*n vitro* drug release

The process by which a drug is released from its formulation to travel through absorption, distribution, metabolism, and excretion (ADME) and eventually become available for therapeutic actions is referred to as drug release. It is acknowledged that this procedure is essential to the creation of new drugs. In certain situations, it can be used as a stand-in for assessing bioequivalence. Using a general equation that quantitatively depicts the dissolving curve in connection to several parameters related to pharmaceutical dosage forms improves the quantitative interpretation of dissolution test data. In some situations, such as zero-order kinetics, this equation can be obtained by theoretically analyzing the process [37,38].

Stability studies

Studies on the stability of the optimized formulation F11 were performed. For ninety days, the formulation was kept in an airtight container at three different temperatures: 4 ± 1°C, 25 ± 2°C with 60% relative humidity ± 5%, and 40 ± 2°C with 75% relative humidity ± 5%. The initial drug content was regarded as 100%, and the residual drug content in the samples was examined [39,40].

CHARACTERIZATION OF ORODISPERSIBLE TABLET

Pre-compression parameters

Bulk density:

The results of bulk density are lies in the range 0.378-0.559 g/cc mentioned in **table no. 5.**

Tapped density:

The results of Tapped density are lies in the range 0.45-0.618 g/cc and mentioned in **table no. 5.**

Table 5: Results of bulk density and tapped density

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)
F1	0.378	0.45
F2	0.409	0.456
F3	0.478	0.557
F4	0.502	0.521
F5	0.376	0.445
F6	0.531	0.585
F7	0.542	0.598
F8	0.565	0.534
F9	0.388	0.482
F10	0.472	0.582
F11	0.499	0.523
F12	0.466	0.432
F13	0.453	0.547
F14	0.559	0.618
F15	0.486	0.439

Flow Property of powders

Angle of repose:

The results of angle of repose of fifteen formulations ranges from 31.29° to 33.51°, which indicates good flow characteristics. All the results are mentioned in **table no. 6.**

Carr's Index:
The value of Carr's index is in between 15.2-16.42 to indicate good flow and compressibility of powder blend. The results of fifteen formulations are mentioned in **table no. 6.**
Hausner's ratio:
The value of Hausner's ratio ranges from 1.05 to 1.24 which indicates that the pre-compressed blend, has good flow property. The results of fifteen formulations are mentioned in **table no.6.**

Table 6: Flow properties of powder

Formulation code	Angle of repose	Carr's Index	Hausner's Ratio
F1	33.51°	15.2	1.11
F2	31.62°	12.60	1.15
F3	32.79°	13.25	1.09
F4	31.56°	11.25	1.12
F5	33.71°	16.42	1.15
F6	32.54°	11.9	1.12
F7	33.23°	11.40	1.15
F8	31.76°	11.23	1.09
F9	33.37°	12.03	1.11
F10	31.48°	13.45	1.05
F11	32.50°	10.32	1.14
F12	33.03°	11.41	1.10
F13	32.17°	13.23	1.23
F14	31.29°	12.37	1.24
F15	30.75°	12.04	1.15

Post compression parameters
Thickness: The values tablet thickness was ranged from 3.29 to 3.69 mm, which is acceptable for easy disintegration. All the results are mentioned in **table no. 7.**
Hardness: The hardness of tablets was ranged between 2.31 to 2.69 kg/cm^3 which indicated good mechanical strength. All the results are mentioned in **table no. 7.**
% **Friability:** The friability of eight formulations was between 0.48 to 0.68 % which is within the limits and indicates a good resistance of tablets to mechanical stress **table no. 7.**

Table 7: Results of Hardness, Thickness and % friability

Formulation code	Hardness (kg/cm^3)	Thickness (mm) ± SD	% Friability
F1	2.51± 0.121	3.36± 0.022	0.72± .035
F2	2.68± 0.125	3.49± 0.023	0.54± 0.026
F3	2.61± 0.126	3.34± 0.061	0.55± 0.023
F4	2.52± 0.134	3.35± 0.079	0.56± 0.028
F5	2.31± 0.171	3.28± 0.013	0.48± 0.036
F6	2.63± 0.182	3.62± 0.025	0.63± 0.043
F7	2.62± 0.153	3.42± 0.035	0.62±0.043
F8	2.65± 0.181	3.61± 0.026	0.49± .0312
F9	2.62± 0.135	3.58± 0.025	0.59± 0.049
F10	2.69± 0.151	3.17± 0.093	0.51± 0.016
F11	2.56± 0.156	3.68± 0.079	0.68± 0.035
F12	2.46± 0.192	3.39± 0.047	0.53± 0.025
F13	2.58± 0.169	3.29± 0.054	0.62± 0.052
F14	2.54± 0.162	3.69± 0.089	0.65±0.051
F15	2.34± 0.142	3.27± 0.019	0.53±0.042

% **Weight variation:** Randomly, 20 tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±7.5%. The results of fourteen formulations are mentioned in **table no.8.**

Wetting time: Wetting time is a function of internal structure of a tablet and hydrophilicity of the excipients. The wetting times of all the formulations were within 1 min as mentioned in **table no.8.**

% **water absorption ratio:** The results of fifteen formulations is in between 71.19- 77.23 % are mentioned in **table no. 8.**

Table 8: Weight variation, wetting time and water absorption of tablets

Formulation code	Weight Variation (Avg Wt (mg) ± SD	Wetting time (Sec) ± SD	%Water absorption ratio ± SD	Disintegration time (Sec) ± SD
F1	198± 0.16	8± 0.35	74.7± .035	31± 0.391
F2	199± 0.25	6± 0.27	72.3± .072	28± 0.326
F3	200± 0.37	6± 0.52	75.1± 0.35	16± 0.284
F4	201± 0.16	5± 0.35	71.19± 0.09	25± 0.521
F5	199± 0.25	9± 0.35	77.23± 0.41	17± 0.254
F5	201± 0.36	9± 0.47	76.31± 0.52	26± 0.236
F7	198± 0.09	7± 0.38	75.35±0.26	31± 0.165
F8	199± 0.06	6±0.65	72.26± 0.48	14±0.312
F9	201± 0.42	8± 0.62	71.83± 0.36	29± 0.441
F10	199± 0.94	7± 0.53	74.29± 0.42	17± 0.122
F11	202± 0.68	6± 0.34	71.58± 0.18	22± 0.325
F12	197± 0.84	8± 0.26	74.38± 0.52	22± 0.256
F13	199± 0.72	5± 0.79	74.49± 0.65	33± 0.165
F14	201± 0.40	7± 0.53	76.12± 0.85	21± 0.261
F15	200± 0.20	6±0.65	71.58± 0.18	15±0.371

Disintegration time: the disintegration time of fifteen formulations ranges from 14 sec to 33 sec, which is within the limit. The result of fourteen formulations is mentioned in **table no. 8.**

In-vitro drug release: The results of percentage cumulative drug release are (F1-F15) is summarized in **Table no. 9 and Table no. 10.**

Table 9: In-vitro drug release profile of orodispersible formulations

→Time (Seconds) / ↓Formulation code	0	5	15	30	60
F1	0	7.93±0.82	28.85±0.43	73.01±0.18	82.92±0.17
F2	0	8.75±0.86	30.24±0.03	75.67±0.36	84.98±0.74
F3	0	13.26±0.86	43.03±0.92	91.84±0.19	97.91±0.59
F4	0	15.56±0.95	45.35±0.37	93.97±0.92	98.28±0.57
F5	0	9.51±0.25	41.03±0.28	88.98±0.26	95.95±0.18
F6	0	13.78±0.29	48.98±0.06	92.90±0.64	93.78±0.05
F7	0	11.71±0.21	37.59±0.91	81.78±0.37	91.08±0.28
F8	0	**17.24±0.12**	**45.45±0.63**	**93.31±0.81**	**97.63±0.41**
F9	0	14.98±0.98	44.06±0.73	92.35±0.19	97.25±0.95
F10	0	16.21±0.37	40.43±0.29	85.12±0.49	94.08±0.71
F11	0	11.56±0.68	32.56±0.53	75.96±0.86	85.97±0.35
F12	0	10.45±0.64	31.46±0.15	78.67±0.7	87.96±0.56
F13	0	9.99±0.55	33.26±0.64	78.06±0.83	86.97±0.91
F14	0	11.41±0.69	41.19±0.55	89.74±0.52	96.72±0.86
F15	0	8.25±0.25	30.46±0.55	77.87±0.5	88.76±0.48

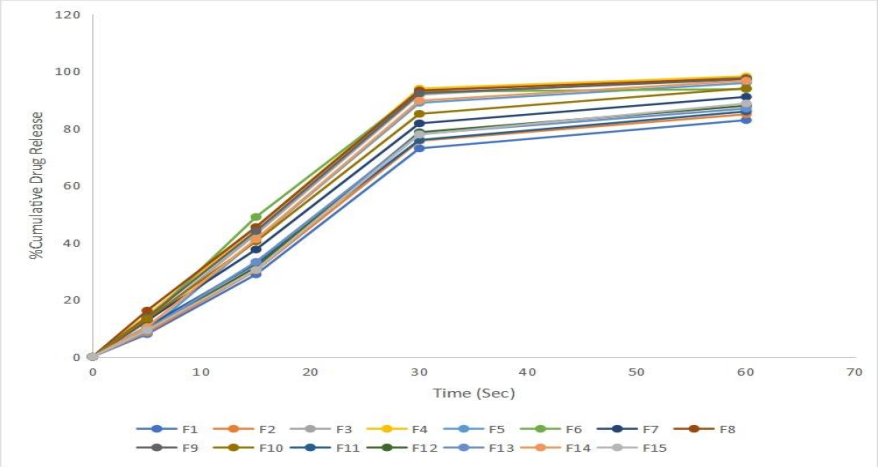

Figure 5: In-vitro drug release profile of orodispersible formulations

Table 10: In-vitro drug release profile of orodispersible formulations

→ Time (Seconds) / ↓ Formulation code	0	5	15	30	60
F1	0	7.93±0.82	29.82±0.44	69.01±0.24	78.62±0.27
F2	0	8.75±0.86	33.24±0.23	76.67±0.42	85.18±0.35
F3	0	13.26±0.86	38.25±0.52	88.94±0.29	96.91±0.29
F4	0	15.56±0.95	42.35±0.26	90.97±0.83	93.18±0.67
F5	0	9.51±0.25	42.13±0.38	86.56±0.46	94.52±0.18
F6	0	13.78±0.29	48.98±0.26	85.90±0.24	94.78±0.05
F7	0	11.71±0.21	39.59±0.91	83.75±0.32	92.68±0.36
F8	0	**17.24±0.12**	**46.45±0.33**	**94.71±0.63**	**98.46±0.41**
F9	0	14.98±0.98	44.36±0.63	93.65±0.19	97.65±0.78
F10	0	19.21±0.37	42.35±0.26	87.12±0.59	91.08±0.91
F11	0	11.56±0.68	33.56±0.63	76.96±0.83	86.97±0.69
F12	0	10.45±0.64	28.46±0.69	72.67±0.79	80.96±0.66
F13	0	9.99±0.55	28.26±0.64	65.35±0.69	79.97±0.97
F14	0	11.41±0.69	43.19±0.52	82.74±0.95	89.72±0.36
F15	0	11.25±0.25	29.46±0.65	65.87±0.29	76.76±0.49

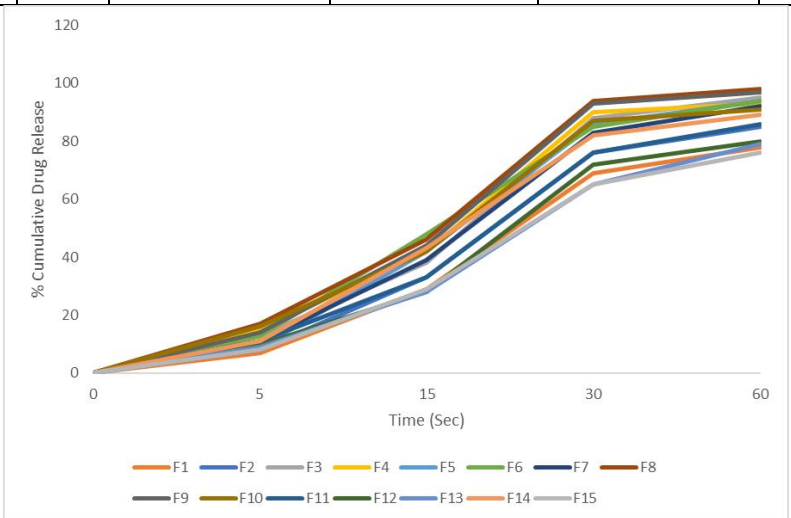

Figure 6: In-vitro drug release profile of orodispersible formulations

Stability study

Over a three-month period, the stability research was conducted at 25°C with 60% relative humidity and 40°C with 75% relative humidity. For these stability evaluations, F8 was selected, and the results showed no appreciable variations in color, appearance, or friability percentage. The drug release rate profile and the percentage drug content for both medications in the orodispersible tablets kept at 25°C/60% RH and 45°C/75% RH also did not significantly change. Additionally, the findings showed that by the end of the study, very little drug degradation had taken place. Consequently, the results of the stability research indicate that the formulation is stable and that it can remain stable under the right storage and packaging conditions.

CONCLUSION

This study was designed to develop and optimize orodispersible tablets (ODTs) comprising a combination of **Olmesartan** and **Valsartan**, targeting enhanced **antihypertensive activity**. Considering the global prevalence and severity of **hypertension**, especially in low and middle income countries, this work explores a novel formulation approach to improve patient compliance and drug efficacy. The combination of Olmesartan and Valsartan demonstrated ACE inhibitory activity, with the **6 mg/mL concentration** showing higher inhibition than lower concentrations. While still lower than **standard captopril (0.46 mg/mL)**, this suggests a dose-dependent improvement in antihypertensive potential. Fifteen formulations (F1–F15) were evaluated with three independent variables (Croscarmellose sodium, Microcrystalline cellulose, and Thymol) affecting disintegration time, swelling index, and wetting time. The model showed high **predictive accuracy** ($R^2 > 0.94$ for all responses), with **formulation F8** and **F4** showing optimal performance in terms of rapid disintegration and high drug release. Pre-compression parameters (angle of repose, Carr's index, and Hausner ratio) indicated good to excellent flow properties, suitable for direct compression. Post-compression evaluation showed tablets with acceptable hardness (2.31–2.69 kg/cm²), friability (<1%), and thickness (3.29–3.69 mm). **Wetting time** and **disintegration time** were rapid (as low as **14 seconds)** which is ideal for ODTs. **Water absorption ratio** ranged from **71.19% to 77.23%**, indicating effective hydration and swelling properties. The optimized formulation (F8) maintained **drug content stability over 90 days** under various storage conditions, confirming its physical and chemical stability.

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