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Research Article

Tablet Formulation Studies on Recrystallized Active Pharmaceutical Ingredients of Valsartan and Olmesartan Medoxomil

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Abstract

Both the Valsartan (VAL) and Olmesartan medoxomil (OLM) are widely prescribed anti-hypertensive agents with angiotensin II type I receptor antagonistic activity. Both VAL and OLM are type of BCS class II drugs and having a low and variable oral bioavailability. Recrystallization of VAL and OLM from different organic solvents improved its aqueous solubility and thereby *in vitro* dissolution properties. In the present investigation, tablets containing Valsartan (VAL), Olmesartan medoxomil (OLM and) recrystallized products were prepared by direct compression method and evaluated for drug content, uniformity of weight, hardness, friability, disintegration time and dissolution properties. All the tablets fulfilled the compendial requirements with regarding to weight variation, friability and disintegration time etc for immediate release tablets. The DP_{15} (drug percent dissolved at 15 min) values for V-1 (tablets of VAL), V-4 (tablets of methanol recrystallized product with crospovidone as disintegrant) and DIOVAN™ 40mg tablet formulations are 45.97, 98.95 and 82.65 respectively and V-4 formulation showed higher dissolution rate when compared to other formulations. The DP_{15} values of O-1(tablets of OLM), O-4 (tablets of acetonitrile recrystallized product with crospovidone as disintegrant and OLMY™ (20mg) tablet formulations are 29.25, 99.93 and 84.82 respectively. O-4 tablet formulations showed higher dissolution rate when compared to other tablet formulations.

Keywords: Valsartan, Olmesartan medoxomil, Recrystallization, Aqueous solubility

INTRODUCTION

Both the Valsartan (VAL) and Olmesartan medoxomil (OLM) are widely prescribed anti-hypertensive agents with angiotensin II type I receptor antagonistic activity. Both VAL and OLM belongs to BCS class II type drugs and are having a low and variable oral bioavailability (VAL-10-35% and OLM -29%) and their absorption is dissolution rate limited[1-4]. Oral bioavailability of drugs from solid dosage forms (tablets, capsules) depends mainly on solubility of drug particles in GI fluids and permeability of dissolved drug molecules across GI membranes[5].

Several techniques were reported to increase dissolution properties of VAL and thus enhancing its oral BA including solid dispersions, cyclodextrin inclusion complexes, formulation of self-microemulsifying drug delivery system (SMEDDS), reduction in particle size (micro- and nanosuspensions), etc[6-9]. Similarly, several approaches were reported to increase dissolution properties of OLM in order to enhance its oral BA including formulation of self-microemulsifying drug delivery system (SMEDDS), reduction in particle size (nanosuspensions), etc[10-12].

Crystal morphology has a great effect on the physicochemical properties of the drug and many drug molecules exist in more than one crystal forms (polymorphism). Modifying and controlling the crystalline nature of a drug *via* recrystallization can improve several pharmaceutical properties of drugs like stability, solubility, rate of dissolution, etc. which in turn may affect the absorption and BA of the drug[13]. Previously authors reported the effect of recrystallization on solubility and *in vitro* dissolution properties of VAL and inferred in significant improvement with recrystallized products (especially methanol solvent recrystallized product) when compared to untreated VAL[14]. Similarly, in an earlier study on the evaluation of the effect of recrystallization on various properties of OLM inferred in significant improvement in aqueous solubility and *in vitro* dissolution properties of recrystallized products (especially acetonitrile solvent recrystallized product) when compared to untreated OLM[15].

The aim of the pharmaceutical technologist is to formulate available medicament into a suitable dosage form depending upon factors such as physicochemical properties of the drug compound, route of administration, age and diseased condition. Amongst the various routes of administration, the oral route is most commonly used and preferred. The dosage forms available for oral administration are liquids like solutions, suspensions and emulsions and the solids like powders, tablets and capsules etc. The physical state of most of the drugs being solid, they are administered in solid dosage forms. Major proportions of the available dosage forms comprise of solids divided into unit and bulk dosage forms. Tablets and capsules generally exemplify unit dosage forms. Hence, in the present investigation, tablets containing VAL, OLM and recrystallized products were prepared by direct compression method and evaluated for drug content, uniformity of weight, hardness, friability, disintegration time and dissolution properties.

EXPERIMENTAL

Materials

VAL and OLM (Gift samples from M/s Aurobindo Pharma, Hyderabad, India), Crospovidone (CP) (BASF, USA), Croscarmellose sodium (CCS) (FMC Biopolymer, USA), Sodium starch glycolate (SSG) (JRS Pharma, USA), Microcrystalline cellulose (MCC, PH101) (FMC Biopolymer, USA), Talc (Loba chemie, India), Magnesium stearate (Loba chemie, India) were used. All the solvents were of reagent grade.

Methods

Preparation of VAL and OLM recrystallization products

Two grams of both VAL and OLM were added to 5mL of a specific pure organic solvent (methanol for VAL and acetonitrile for OLM) in seperate 15 mL beakers and heated slowly to 45°C to afford a supersaturated solution. The resulting mixture was then cooled down to room temperature. The resulting recrystallized drug was then collected, dried at 40°C for 15min, and passed through a #80 sieve to obtain a product of uniform particle size. The powdered drug was packed in glass bottles and stored in a desiccator until use[14,15].

Preparation of the tablets by direct compression method

As per the formulae mentioned in the **Table- 1 and 2** required quantities of VAL, OLM, VMET and OACN respectively were mixed with filler i.e, microcrystalline cellulose in a mortar for 10 minutes. Then sodium starch glycolate/croscarmellose sodium/crospovidone, talc and magnesium stearate were added and mixed thoroughly for additional three minutes. The resulting blend was then compressed to tablets on a single punch tablet press (Cadmach India Ltd) to a hardness of 4 kg/cm^2.

Table 1: Formulae for tablets of VAL and recrystallized products

Ingredients(mg/tablet)	V-1	V-2	V-3	V-4
VAL	40	-	-	-
VMET	-	40	-	-
VMET	-	-	40	-
VMET	-	-	-	40
SSG	10	10	-	-
CCS	-	-	10	-
CP	-	-	-	10
MCC	147	147	147	147
Magnesium stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
Total weight of tablet (mg)	**200**	**200**	**200**	**200**

Table 2: Formulae for tablets of OLM and recrystallized products

Ingredients(mg/tablet)	O-1	O-2	O-3	O-4
OLM	20	-	-	-
OACN	-	20	-	-
OACN	-	-	20	-
OACN	-	-	-	20
SSG	10	10	-	-
CCS	-	-	10	-
CP	-	-	-	10
MCC	167	167	167	167
Magnesium stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
Total weight of tablet (mg)	**200**	**200**	**200**	**200**

Evaluation of precompression parameters of formulation powder blends:

Formulation powder blends of VAL, OLM and recrystallized products were evaluated for pre compression parameters like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The results were given in **Table-3** for VAL and **Table- 4** for OLM.

Drug - excipient compatibility studies

Powder blends of VAL, OLM and recrystallized products were subjected to DSC and FTIR studies for the identifying any incompatibility with excipients used in the tablet formulations. The DS thermograms and FTIR spectra were shown in **Figs- 1 -4.**

Evaluation of tablet properties:

The tablets were evaluated for properties like drug content, uniformity of weight, hardness, friability, disintegration time and dissolution properties.

Drug content

Five tablets were weighed and powdered in a mortar. An accurately weighed powder sample equivalent to 40 mg of VAL and 20 mg of OLM was transferred to a 100mL volumetric flask and the VAL and OLM was extracted in to 75mL of methanol. This solution was filtered and collected in to a 100mL volumetric flask and made volume up to 100mL with methanol. The solution was further diluted and the absorbance was measured at 250 nm for VAL and 258 nm for OLM respectively. The estimations were carried out in triplicate. The results were reported in **Table- 5**.

Uniformity of weight of tablets

The individual and total weight of twenty tablets from each batch was determined. Percentage deviation of the individual weights from the average weights was calculated. The results were given in **Table-5**.

Hardness

The hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, India). The results were given in **Table- 5**. The results reported were average of 10 tablets for each formulation.

Friability

The percentage loss in weight of a sample of 10 tablets in each formulation was determined in Roche friabilator (M/s Remi India) for 4 minutes (100 revolutions). The results were given in **Table- 5.**

Disintegration time

The disintegration time was determined for 6 tablets with a USP/IP disintegration apparatus (M/s Campbell Electronics, India). The results were given in **Table- 5.**

***In vitro* Dissolution studies**

In vitro dissolution studies of formulations were carried out in 1000 mL of phosphate buffer of pH 6.8 for VAL as per USP and 900 mL for OLM using USP XXI Type II Dissolution Rate Test Apparatus (Model DS 8000, M/S Lab India). A speed of 50 rpm and a temperature of 37°±1°C were used in each test. Five mL aliquots were withdrawn at predetermined time intervals, filtered using a 0.45 µ nylon disc filter and replaced with 5 mL of fresh dissolution medium. The filtered samples were suitably diluted if necessary and analyzed for VAL and OLM concentrations by measuring absorbance at 250 nm and 258 nm respectively. The dissolution experiments were conducted in triplicate. Percent VAL and OLM dissolved at different time intervals and various dissolution parameters were given in **Tables- 5.6 & 5.7** and dissolution profiles were shown in **Figs- 5.17 & 5.18.**

Stability studies

Optimized formulation was subjected to stability studies by placing in a stability chamber (Remi, India) for three months. Temperature and relative humidity was maintained at 40 ± 2° C and 75 ± 5 % relative humidity. The tablets were evaluated for drug content, hardness, friability, disintegration time and percent dissolved at 15 minutes.

RESULTS AND DISCUSSION

Evaluation of precompression parameters of formulation powder blends

Formulation powder blends of VAL, OLM and recrystallized products were evaluated for pre compression parameters like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The flow and compressibility properties of powder blends with recrystallized products of VAL and OLM were improved, when compared to VAL and OLM.

Drug-excipient compatibility studies

The DSC thermograms of VAL and OLM and recrystallized products were shown in **Figs- 1 2**. The melting endotherm of VAL was observed at 103^{O} C, corresponds to its melting point and similarly with recrystallized product formulation blends, a broad endothermic appeal was observed in range of 50-150^{O} C as observed with the recrystallized products of VAL. These results indicate that there is no drug-excipient interaction with the blends of VAL and its recrystallized product of VMET. The melting endotherm of OLM was observed at 187^{O} C, corresponds to its melting point and similarly with recrystallized product formulation blends a similar endothermic peak was observed and is an indication of no drug-excipient interaction with the blends of OLM and its recrystallized product of OACN.

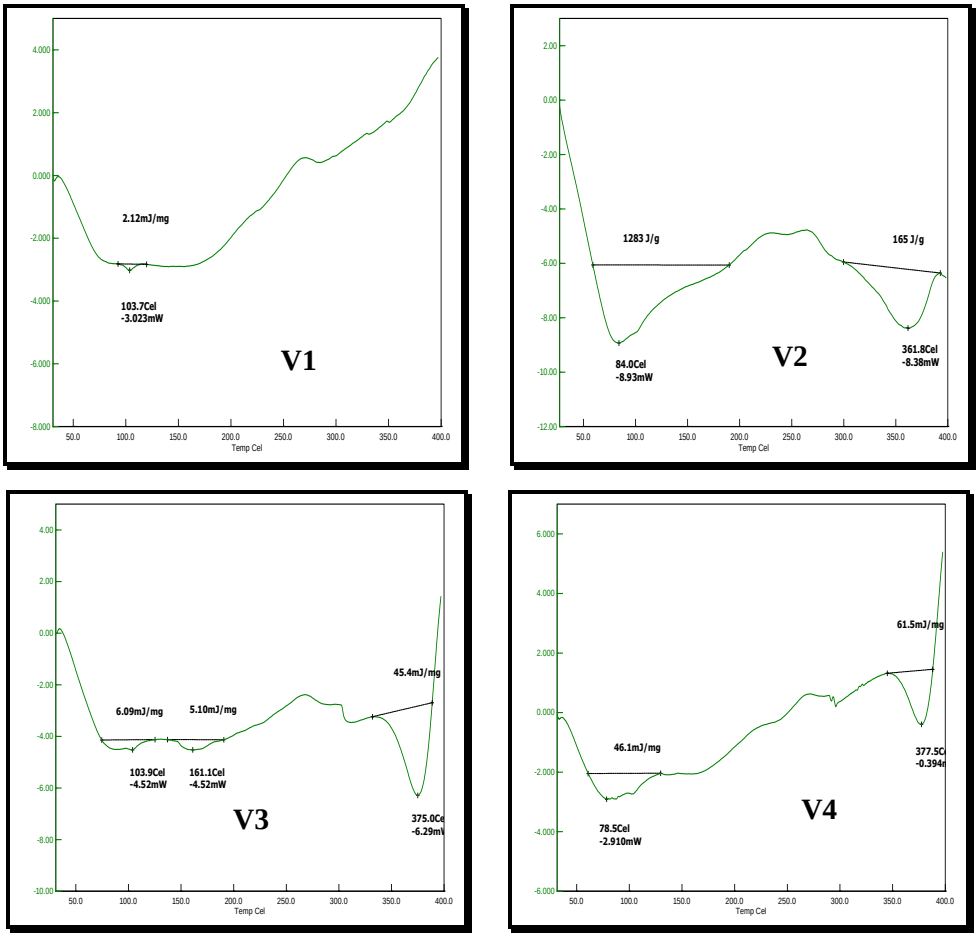

Figure 1: DSC thermograms for VAL tablet formulations powder blends

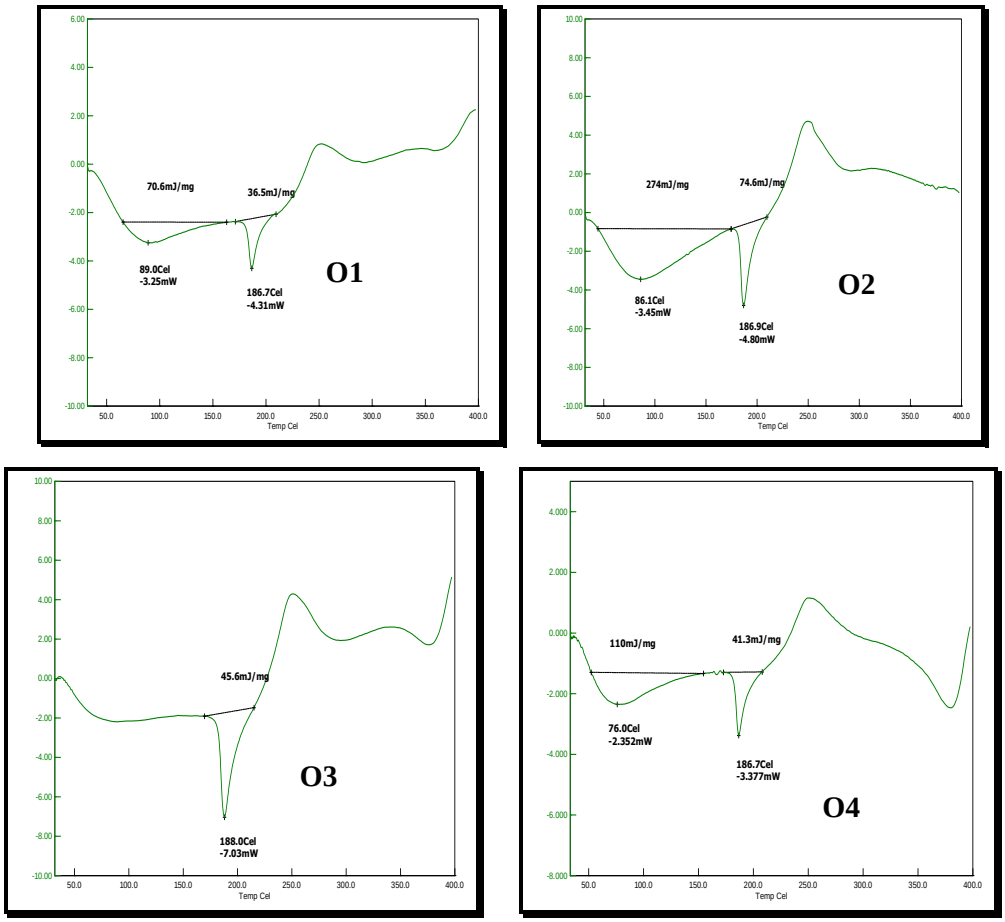

Figure 2: DSC thermograms for OLM tablet formulations powder blends

The FTIR spectras were also confirmed the results of DSC studies indicating no excipient interaction with VAL, OLM and recrystallized products. VAL has two characteristic carbonyl absorption bands at 1725 and 1598 cm^{-1} that correspond to carboxyl and amide carbonyl stretching respectively. The peak at 3393cm^{-1} indicates the presence of an N-H functional group. The band at 2961cm^{-1} indicates the presence of C-H group stretching vibration. The spectrum reveals the characteristic peaks in the typical range at 1205-1052 cm^{-1} confirms the presence of characterisitc tetrazole ring in the VAL. The characteristic peaks of OLM at 3290.86 cm^{-1} (N-H stretching), 1831.90 cm^{-1}(C-O stretching in dioxone ring), and 1707.29 cm^{-1} (C-O stretching) were observed. All the significant bands of VAL and OLM were retained in the formulation blends indicating no excipient interaction with VAL, OLM and recrystallized products. The spectras were shown in **Figs- 3 & 4.**

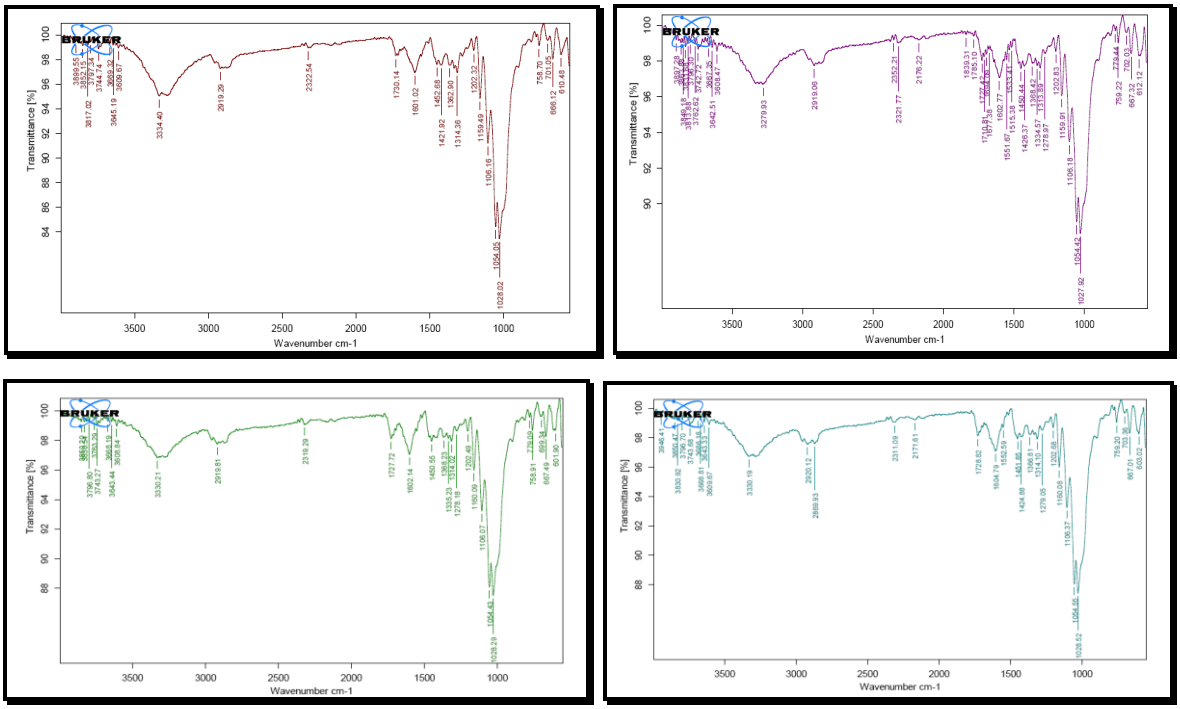

Figure 3: FTIR spectra of VAL and its formulation blends

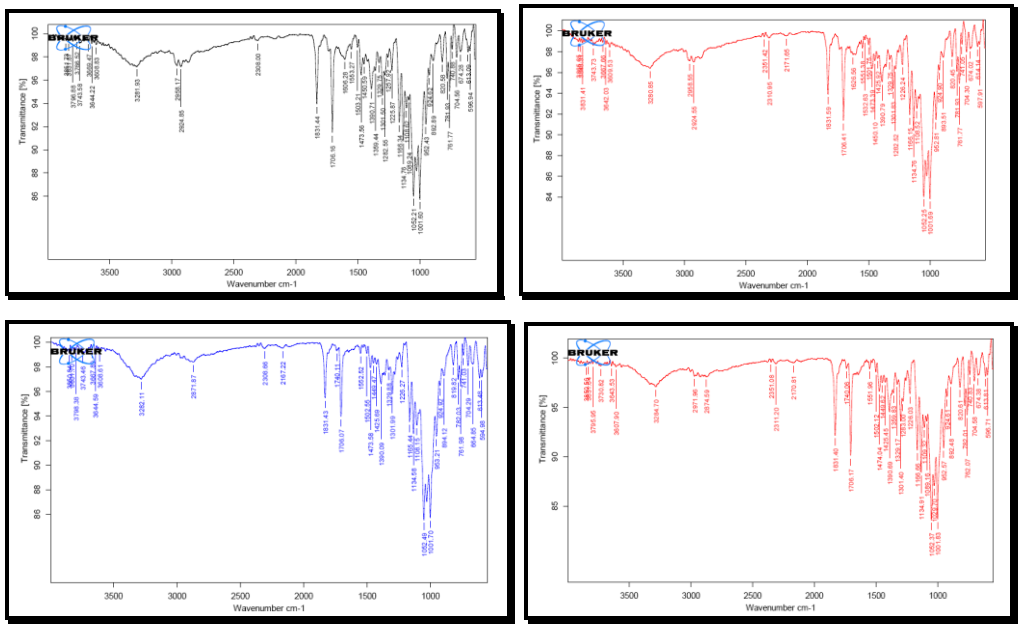

Figure 4: FTIR spectra of OLM and its formulation blends

Tablet formulations containing VAL, VMET (dose of 40 mg) and OLM, OACN (dose of 20 mg) were prepared by direct compression method as per the formulae given in **Tables-1 & 2.** The tablets were evaluated for drug content, uniformity of weight, hardness, friability and disintegration time and dissolution rate studies. The results are summarized in **Tables- 5.5 -5.10** and shown in **Figs- 5.17 and 5.18.**

Table 3: Tablet properties of VAL and formulations mean ± SD (n=3)

Formulation	Drug content (mg/tab)	Mean weight (mg) (Percent deviation)	Hardness (Kg/cm^2)	Friability (% wt loss)	Disintegration time (min)
V-1	40.20 ± 1.3	200.85 (-0.09 to +1.27)	5 ± 0.00	0.34 ± 0.05	5 ± 0.25
V-2	39.98 ± 0.97	201.45 (-0.25 to +2.10)	4.5 ± 0.00	0.47 ± 0.07	4.25 ± 0.20
V-3	39.82 ± 0.85	201.85 (-0.07 to +2.39)	5 ± 0.00	0.59 ± 0.04	3.5 ± 0.15
V-4	39.51 ± 1.1	200.65 (-0.19 to +3.31)	4.5 ± 0.00	0.44 ± 0.06	3.10 ± 0.25

Table 4: Tablet properties of OLM and formulations mean ± SD (n=3)

Formulation	Drug content (mg/tab)	Mean weight(mg) (Percent deviation)	Hardness (Kg/cm^2)	Friability (% wt loss)	Disintegration time (min)
O-1	20.09 ± 0.55	202.20 (-0.41 to +2.56)	4.5 ± 0.00	0.42 ± 0.04	4.25 ± 0.10
O-2	19.95 ± 0.69	202 (-0.15 to +2.96)	4.5 ± 0.00	0.49 ± 0.06	4 ± 0.12
O-3	20.28 ± 0.47	203.70 (-0.14 to +3.15)	4.5 ± 0.00	0.59 ± 0.05	4.10 ± 0.15
O-4	20.13 ± 0.63	202.35 (-0.81 to +3.27)	5 ± 0.00	0.63 ± 0.04	3.52 ± 0.12

Drug content

The drug content of tablets was within the range of 100 ± 5% of labeled claim and the results were satisfactory **(Tables 3 &4).**

Uniformity of weight

The results were summarized in **Tables 3 &4** showed that a good degree of uniformity of weight was achieved for all the batches of tablet formulations prepared. The percent deviation did not exceed 7.5%, indicating excellent uniformity of weight in all the batches of tablet formulations prepared.

Mechanical properties

All the batches of tablet formulations prepared exhibited good mechanical properties with regard to both hardness and friability. The values are given in **Tables 3 & 4**. No significant difference in hardness values within the batches of tablet formulations prepared was observed. The friability values of all the batches of tablet formulations prepared are less than 1%.

Disintegration time

All the tablet formulations (V-1 to V-4 and O-1 to O-4) prepared by direct compression method fulfilled the compendial requirement of disintegration time for compressed tablets where the times are less than 15 minutes **(Tables 3 & 4).**

***In vitro* Dissolution studies**

All the tablet formulations were subjected to *in vitro* dissolution rate studies using phosphate buffer of pH 6.8 as dissolution medium, in order to assess various dissolution characteristics like $t_{50\%}$, DP_{15}, DE_{15}% and dissolution rate constant values. The corresponding values are given in **Tables 5 & 6**. and the dissolution profiles are shown in **Figs 5 &6.**

Table 5: Dissolution parameters of VAL tablet formulations (n=3)

Formulation	$t_{50\%}$(min)	DP_{15} Mean ± SD	DE_{15} (%) Mean ± SD	K(min^{-1}) Mean ± SD
V-1	18	45.97 ± 0.76	27.31 ± 0.25	0.033 ± 0.005
V-2	10	66.40 ± 1.03	40.28 ± 0.57	0.094 ± 0.009
V-3	8	71.26 ± 0.70	44.94 ± 0.06	0.090 ± 0.003
V-4	4	98.95 ± 0.45	60.19 ± 0.25	0.276 ± 0.018
DIOVAN™ 40	6	82.65 ± 0.72	51.42 ± 0.26	0.227 ± 0.036

Table 6: Dissolution parameters of OLM tablet formulations (n=3)

Formulation	$t_{50\%}$(min)	DP_{15} Mean ± SD	DE_{15} (%) Mean ± SD	K(min^{-1}) Mean ± SD
O-1	34	29.25 ± 0.86	13.83 ± 0.32	0.013 ± 0.000
O-2	11	59.95 ± 0.71	33.70 ± 0.20	0.144 ± 0.020
O-3	10	68.97 ± 0.70	39.29 ± 0.42	0.155 ± 0.082
O-4	6	99.93 ± 1.03	57.15 ± 0.13	0.268 ± 0.114
OLMY™ 20	6	84.82 ± 1.40	48.62 ± 0.56	0.124 ± 0.004

The $t_{50\%}$ values of V-1, V-2, V-3, V-4 and DIOVAN™ (40mg) tablet formulations are 18, 10, 8, 4 and 6 min respectively. The $t_{50\%}$ values of O-1, O-2, O-3, O-4 and OLMY™ (20 mg) tablet formulations are 34, 11, 10, 6 and 6 min respectively. Overall, the $t_{50\%}$ values of VAL formulations prepared by direct compression method were in the order V-4 < DIOVAN™ < V-3 < V-2 < V-1 and the $t_{50\%}$ values of OLM formulations prepared by direct compression method were in the order O-4 < OLMY™ < O-3 < O-2 < O-1.

The DP_{15} values of V-1, V-2, V-3, V-4 and DIOVAN™ 40mg tablet formulations are 45.97, 66.40, 71.26, 98.95 and 82.65 respectively and V-4 formulation showed higher dissolution rate when compared to V-1, V-2,V-3 formulations and DIOVAN™ (40mg) tablets. The DP_{15} values of O-1, O-2, O-3, O-4 and OLMY™ (20mg) tablet formulations are 29.25, 59.95, 68.97, 99.93 and 84.82 respectively. O-4 tablet formulations showed higher dissolution rate when compared to OLMY™ 20mg, O-1, O-1 and O-3 tablet formulations.

The DE_{15} % values of V-4 formulations are higher when compared to V-1, V-2, V-3 and DIOVAN tablet formulations. A 2.20, 1.49, 1.33 and 1.17 fold increase in DE_{15} % values of V-4 when compared to V-1, V-2, V-3 and DIOVAN™ (40mg) tablet formulations. The DE_{15} % values of O-4 formulations are higher when compared to O-1, O-2, O-3 and OLMY™ 20mg tablet formulations. A 4.13, 1.69, 1.45 and 1.17 fold increase in DE_{15} % values of O-4 when compared to O-1, O-2, O-3 and OLMY (20mg) tablet formulations. Formulations prepared with crospovidone as superdisintegrant showed higher dissolution rates for both VAL (V-4) and OLM (O-4) among other disintegrants ued in the studies. Overall, tablet formulations of recrystallized VAL and OLM products with crosspovidone as super disintegrant showed, superior dissolution properties when compared to drugs alone and marketed products.

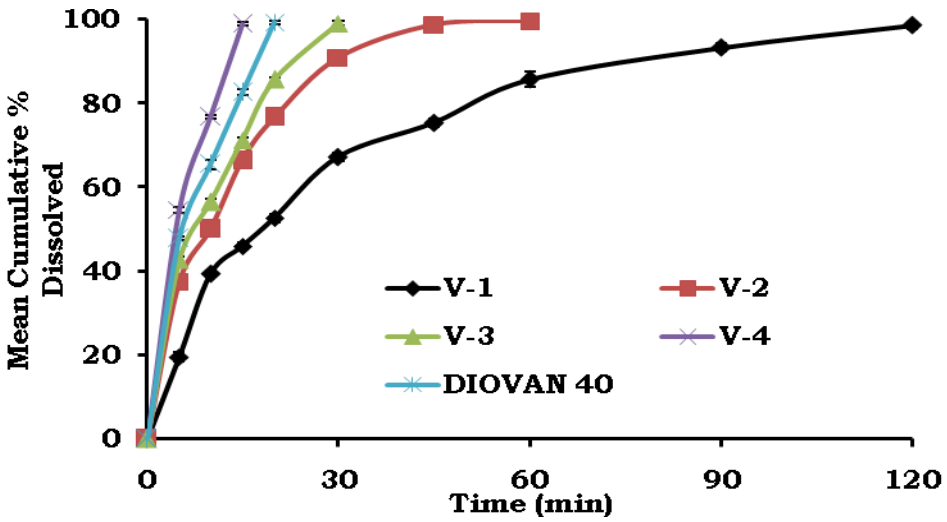

Figure 5: Compartive *in vitro* dissolution profiles of VAL tablet formulations

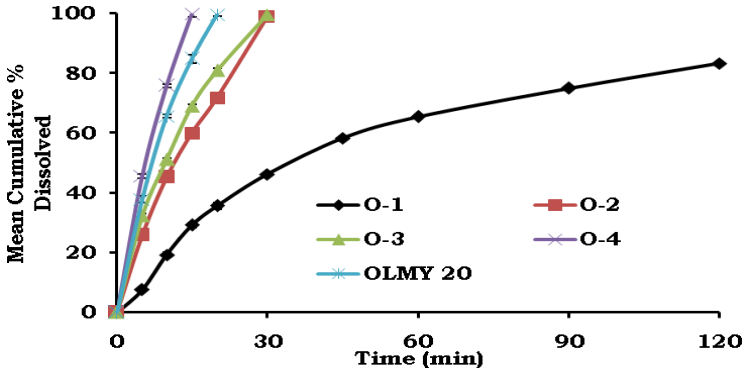

Figure 6: Comparitive *in vitro* dissolution profiles of OLM tablet formulations

Accelerated stability studies

Accelerated stability studies were carried out for optimized formulations i.e V-4 and O-4 by storing at 40 ± 2^0 C and 75 ± 5 % RH for three months. Tablets were evaluated for drug content, hardness, friability, and disintegration time and drug percent dissolved at 15 minutes (DP15). From the data obtained, tablets were stable for three months at 40 ± 2^0 C and 75 ± 5 % RH. The results with regarding to drug content, hardness, friability, disintegration time and DP15 were found to be within the specified limits for both the drug formulations.

CONCLUSION

Both the Valsartan (VAL) and Olmesartan medoxomil (OLM) are widely prescribed anti-hypertensive agents with angiotensin II type I receptor antagonistic activity. Both VAL and OLM are type of BCS class II drugs and having a low and variable oral bioavailability. Recrystallization of VAL and OLM from different organic solvents improved its aqueous solubility and thereby *in vitro* dissolution properties. In the present investigation, tablets containing VAL, OLM and recrystallized products were prepared by direct compression method and evaluated for drug content, uniformity of weight, hardness, friability, disintegration time and dissolution properties. Overall, tablet formulations of recrystallized VAL and OLM products with crosspovidone as super disintegrant showed, superior dissolution properties when compared to drugs alone and marketed products. Accelerated stability studies indicated the stability of optimized formulations i.e V-4 and O-4 at 40 ± 2^0 C and 75 ± 5 % RH for three months.

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Conflict Of Interest: Nil

REFERENCES

1. Flesch G, Lloyd P, Müller PH. Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist. Eur J Clin Pharmacol., 1997; 52:115-120. https://doi.org/10.1007/s002280050259
2. Nadeem S, Asif H, Lakshita C, Shamsher MA, Mitra M, Parminder SB. Pharmacological and Pharmaceutical Profile of Valsartan: A Review. Journal of Applied Pharmaceutical Science, 2011; 01(04):12-19.
3. Warner GT, Jarvis B. Olmesartan Medoxomil. Drugs, 2002; 62:1345-53. https://doi.org/10.2165/00003495-200262090-00005
4. Laeis P, Puchler K, Kirch W. The pharmacokinetic and metabolic profile of olmesartan medoxomil limits the risk of clinically relevant drug interaction. J. Hypertens. Suppl., 2001; 19:21-32. https://doi.org/10.1097/00004872-200106001-00004
5. Sarwar B, Suryakanta S, Rizwan Md, Irfanuddin Md, Shobha DM. Bioavailability Enhancement Strategies: Basics, Formulation Approaches and Regulatory Considerations. Current Drug Delivery, 2011; 8(6):691-702. https://doi.org/10.2174/156720111797635504
6. Dixit AR, Rajput SJ, Patel SG. Preparation and Bioavailability Assessment of SMEDDS Containing Valsartan. AAPS Pharm Sci Tech, 2010; 11(1):314-321. https://doi.org/10.1208/s12249-010-9385-0
7. Yana YD, Sunga JH, Kima KK, Kimb DW, Kima JO, Leec BJ, Yonga CS, Choi HG. Novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes. International Journal of Pharmaceutics, 2012; 422(1-2):202-210. https://doi.org/10.1016/j.ijpharm.2011.10.053
8. Qiuping M, Hongrui S, Erxi C, Xin Z, Tongying J, Changshan S, Siling W. Uniform nano-sized valsartan for dissolution and bioavailability enhancement: Influence of particle size and crystalline state. International Journal of Pharmaceutics, 2012; 441 (1-2):75-81. https://doi.org/10.1016/j.ijpharm.2012.12.025
9. De Matos Jensen CE, Dos Santos RAS, Denadai AML, Santos CFF, Braga ANG; Sinisterra RD. Pharmaceutical Composition of Valsartan: β-Cyclodextrin: Physico-chemical characterization and anti-hypertensive evaluation. Molecules, 2010; 15:4067-4084. https://doi.org/10.3390/molecules15064067
10. Chirag R, Neha J, patel J, Upadhyay UM. Enhanced Oral Bioavailability of Olmesartan by using Novel Solid Self Emulsifying Drug Delivery System. International Journal of Advanced Pharmaceutics, 2012; 2(2):82-92.
11. Kang MJ, Hyung SK, Jeon HS, Park JH, Lee BS, Byeong KA. In Situ Intestinal Permeability and In Vivo absorption Characteristics of Olmesartan Medoxomil in Self-Micoremulsifying Drug Delivery System. Drug Development and Industrial Pharmacy, 2011; 38(5):587-596. https://doi.org/10.3109/03639045.2011.619194
12. Hetal PT, Bindesh VP, Sneha PT. Development and Characterization of Nanosuspensions of Olmesartan Medoxomil for Bioavailability Enhancement. J Pharm Bioallied Sci., 2011; 3(3):426-434. https://doi.org/10.4103/0975-7406.84459
13. Amit C, Upendra N, Neha G, Sharma VK, Khosa RL. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. Journal of Advanced Pharmacy Education & Research, 2012; 2(1):32-67.
14. Nalluri BN, Ramya KM, Rao TP, Peter AC. Effect of Recrystallization on the Pharmaceutical Properties of Valsartan for Improved Therapeutic Efficacy. Journal of Applied Pharmaceutical Science, 2012; 2(10):126-132. https://doi.org/10.7324/JAPS.2012.21025
15. Rao TP, Murali B, Devala RG, Srinivas BP. Improvement of Pharmaceutical Properties of Olmesartan by Recrystallization Technique. Journal of Chemical and Pharmaceutical Sciences, 2014; 7(2):162-164.