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# LABRAFAC WL1349 AIDED LYOPHILIZE SOLID DISPERSION OF OLMESARTAN MEDOXOMIL

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**Keywords:**

Solid dispersion, Dissolution, Olmesartan medoxomil, HPMC, PVP, labrafac WL1349

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**ABSTRACT:** Water solubility is the rate limiting step in dissolution and bioavailability. Olmesartan medoxomil is BCS class-II drugs having low water solubility. Olmesartan medoxomil acts on cardiovascular system and used in the treatment of hypertension as antihypertensive agent. Olmesartan medoxomil have low water solubility and low bioavailability as 26%. In this research study we made Olmesartan medoxomil solid dispersion for increasing water solubility of Olmesartan medoxomil. HPMC and PVP were used as hydrophilic polymer while Lyophilization technique was used as a method of preparation of solid dispersion. We evaluated the effects of freeze drying in process yield, solubility and total Olmesartan content of the solid dispersion. This solubility study shows significant increase in solubility of solid dispersion of Olmesartan medoxomil than pure Olmesartan medoxomil. Dissolution study illustrate that, there was improved dissolution rate when compared to plain Olmesartan. The result and conclusion of this research suggest that the solid dispersion prepared in this research has successfully improved the solubility of Olmesartan medoxomil.

**INTRODUCTION:** Therapeutic activity or effect of drug is depending on the solubility and bioavailability of drug. The widely used and most convenient route for drug administration is oral route. Solubility plays an important role in oral bioavailability because it is rate limiting step. Water solubility of insoluble drugs is always creating challenges in formulation and development of drug. Poor solubility and inappropriate dissolution rate of dissolution are the reasons to compromise the therapeutic effect of drug; hence to increase the solubility of poorly soluble drug is important.

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There are several techniques for increasing solubility of drugs e.g., Solubilisation, Complexation, reduction in particle size, and formation of salt *etc*. Sekiquchi and Obi in 1961, introduced a technique for increasing solubility and bioavailability of water insoluble drug, the technique is named as "Solid Dispersion". Olmesartan medoxomil is US FDA approved drug used in the treatment of hypertension as antihypertensive agent.

Olmesartan medoxomil is either used alone or in combination. The oral bioavailability of Olmesartan medoxomil is 26% and plasma protein binding is 99%. Metabolism of Olmesartan is happen in liver whereas the elimination half-life is 13 hrs. In this research study, it has been proved that solubility and rate of dissolution of Olmesartan medoxomil is increased by using hydrophilic polymer like PVP and HPMC.

The prepared Olmesartan medoxomil solid dispersion were evaluated for rate of dissolution, drug content, interaction between drug and polymers using DSC and IR, and solubility study [1, 2, 3].

**MATERIALS AND METHODS:** Olmesartan medoxomil was obtained as a gift samle from Ajanta Pharma, Aurangabad, India. PVP K14 were obtained from Fine chem. Industries, Mumbai. HPMC were obtained from Vishal chem., Mumbai. Labrafac WL1349 were collected from Fineorganics, Mumbai. Other required chemicals used were of analytical grade.

**Preformulation Studies:**

**Organoleptic Properties:** The samples of Olmesartan, HPMC & PVP were subjected for study of organoleptic properties like colour, odour, and appearance.

**Melting Point:** The melting point of Olmesartan, HPMC & PVP was determined by capillary method.

**Solubility:**

**Procedure:** The solubility of pure Olmesartan, physical mixture of drug and polymer and prepared solid dispersion were examined in distilled water and pH 6.8 phosphate buffer. Required quantities of pure Olmesartan, physical mixture of Olmesartan and polymer and prepared solid dispersion were added in 25ml distilled water in 250 ml conical flask.

The conical flask was shaken rotary flask shaker for 72 hrs at room temperature. In entire procedure all the samples were protected from direct light by covering the flask with aluminium foil. After 72 hrs the absorbance of resulting solution was determined by using UV spectrophotometer at 257nm [4].

**UV Spectroscopy:**

**Determination of ʎmax:** Stock solution (100µg/ml) of Olmesartan was prepared in methanol. This solution was then carefully diluted with the methanol to obtain a desired concentration. The UV spectrum of the resulting solution was recorded in the range 200-800 nm on Lab-India, double beam spectrophotometer and the wavelength showing maximum absorption (ʎmax) was determined.

**Construction of Calibration Curve (Beer-Lambert's Plot) of Olmesartan:** An accurately weighed required quantity (100mg) of Olmesartan was added and dissolved in 10 ml methanol in 100 ml volumetric flask and the final volume was adjusted to make 100 ml by using methanol.

From the resulting solution 10ml was transferred to 100 ml volumetric flask and the final volume was adjusted to make 100 ml by using methanol to get stock solution (100µg/ml). From the prepared stock solution further, serial dilutions were prepared by using methanol (1-10µg/ml). The absorbance of the prepared dilution samples was taken at **ʎmax** (257nm) using UV visible spectrophotometer against methanol as blank.

**Fourier Transform Infrared Spectroscopy (FTIR):** Fourier Transform Infrared Spectroscopy (FTIR) study of Olmesartan and polymer were obtained on Agilent Cary 630 by using KBr pellet technique. The study was done over the wave number range from 4000 to 400 cm.

**Compatibility Testing:**

**Fourier Transform Infrared Spectroscopy (FTIR):** FTIR study was done to examine possible interaction among the Olmesartan and Polymer. The compatibility study was done on FTIR over the range from 4000 to 400 $cm^{-1}$. The spectra of Olmesartan and polymers, were comparatively studied to determine the interaction if any between Olmesartan and polymers.

**Differential Scanning Colorimetry (DSC):** The any possible interaction between Olmesartan medoxomil and polymers while making of solid dispersion was examined by thermal analysis of solid dispersion with pure Olmesartan by using DSC. Shimadzu TA-60 was used for DSC analysis. Different samples were subjected for heating in open aluminium pan. The heating rate were 10°C per minute and the temperature range was 25°C to 300°C under 50ml perminute nitrogen flow.

**Preparation of Solid Dispersion by Lyophilization:**

**Preliminary Study:** Trial runs were carried out to select the various parameters for freeze drying. The parameters selected and the reason for their selection is as given.

**Olmesartan:**

**Polymers Ratio:** The different ratios are to be taken as SD1=1:0.5:0.5, SD2=1:1:1, SD3=1:2:2. The solid dispersion according to this ratios were prepared but Olmesartan showed enhanced solubility in water with combination polymer (HPMC: PVP) concentration SD3=1:2:2. So 1:2:2 ratio of Olmesartan: polymers was selected for further work.

**Actual Experimentation:** Each solution for Lyophilization was prepared by mixing predetermined ratio of Olmesartan and polymer to 50ml of labrafac WL1349. A solution for solid dispersion was prepared by dissolving 2gm of polymers in 50ml labrafac WL1349 which was then subjected for sonication for 10 minutes. 1gm of Olmesartan medoxomil was added to resulting solution.

The solution then subjected for Lyophilization by using Labultima LU222. The resulting dried products were collected and subjected for thorough evaluation process like Process Yield (PY), Solubility (S), and Total Olmesartan content [5].

**Evaluation of Solid Dispersion:**

**Process Yield (PY):** The total yield of solid dispersion was calculated by taking the ratio of the weight of collected solid dispersion from freeze dryer to the total initial weight of raw material taken for Lyophilization. The process yield was calculated in form of percentage by using formula [6].

PY (%) = (Weight of Solid Dipsersion) / (Weight of raw material) × 100

**Total Olmesartan Content:** The total olmesartan content were calculated by taking solid dispersion equivalent to 10mg Olmesartan and mixing it in 2ml methanol and then subjected make up the volume up to 10ml. the solution was then filtered and diluted carefully with 10ml pH 6.8 phosphate buffer. The drug content was analysed at 257 nm by UV Spectrophotometer [6].

**Dissolution Study:**

**Procedure:** *In-vitro* dissolution study of pure olmesartan medoxomil and olmesartan solid dispersion was performed by using USP rotating paddle apparatus (Type-II). The paddle rotation speed was 50 RPM. pH 6.8 phosphate buffer was used as dissolution medium.

During dissolution study the temperature was maintained at 37°C±0.5°C. 6 hard gelatin capsules were filled by solid dispersion equivalent to 20mg of Olmesartan and subjected for dissolution study. At time interval of 15, 30, 45, 60, 90 and 120 minutes the samples were collected. The collected samples were suitably diluted by using appropriate blank. The absorbance was measured at 257 nm by using UV Spectrophotometer [7, 8].

**Solubility:**

**Procedure:** The solubility of pure Olmesartan, physical mixture of drug and polymer and prepared solid dispersion were examined in distilled water and pH 6.8 phosphate buffer. Required quantities of pure Olmesartan, physical mixture of Olmesartan and polymer and prepared solid dispersion were added in 25ml distilled water in 250 ml conical flask.

The conical flask was shaken rotary flask shaker for 72 hrs at room temperature. In entire procedure all the samples were protected from direct light by covering the flask with aluminium foil. After 72 hrs the absorbance of resulting solution was determined by using UV spectrophotometer at 257nm [9, 10].

## RESULT AND DISCUSSION:

**Preformulation Study:**

**Organoleptic Properties:** Olmesartan and polymer were studied for organoleptic properties as shown in **Table 1.**

**TABLE 1: ORGANOLEPTIC PROPERTY OF OLMESARTAN HPMC AND PVP**

| Sr. no. | Parameter | Olmesartan | HPMC | PVP |
|---|---|---|---|---|
| 1 | Colour | White | White or creamy white | Off-white |
| 2 | Odour | Characteristic Odour | Characteristic Odour | Characteristic Odour |
| 3 | Appearance | Crystalline powder | Granular powder | Amorphous powder |

**Melting Point:** Melting point of olmesartan and polymers are shown in **Table 2.**

**TABLE 2: MELTING POINT OF OLMESARTAN, HPMC AND PVP**

| Sr. no. | Sample | Melting point | |
|---|---|---|---|
| | | Observed | Reported |
| 1 | Olmesartan | 175–180°C | 178°C |
| 2 | HPMC | 225-230°C | 225°C |
| 3 | PVP | 150-180°C | 159°C |

## UV Spectroscopy:

**Determination of ʎmax:** In UV spectroscopy study, wavelength of maximum absorbance (ʎmax) of olmesartan in methanol was found to be 257nm shown in **Fig. 1**. The reported ʎmax of olmesartan in methanol is 257nm. The various concentration and absorbance's are shows the Beer–Lambert law in **Table 3** and **Fig. 2.**

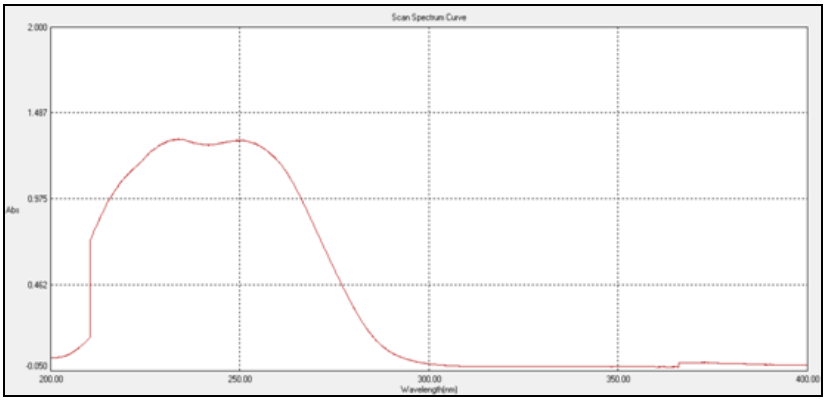


**FIG. 1: UV SPECTRUM OF OLMESARTAN IN METHANOL**

## Construction of Calibration Curve (Beer-Lambert's plot) of Olmesartan:

**TABLE 3: CONCENTRATION AND ABSORBANCE VALUES FOR OLMESARTAN IN METHANOL (ʎMAX- 257NM)**

| Sr. no | Concentration (ug/ml) | Absorbance |
|---|---|---|
| 1 | 10 | 0.412 |
| 2 | 20 | 0.622 |
| 3 | 30 | 0.834 |
| 4 | 40 | 1.027 |
| 5 | 50 | 1.197 |

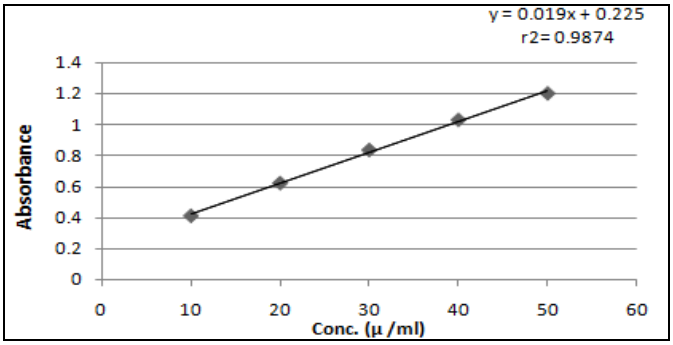


**FIG. 2: BEER-LAMBERTS PLOT OLMESARTAN IN METHANOL (λMAX- 257nm)**

**FT-IR Study:** An IR spectrum of pure Olmesartan medoxomil is shown in **Fig. 3**. Pure Olmesartan medoxomil spectra showed in sharp characteristic peaks at 3712.97, 3589.53 and 673.16cm$^{-1}$at **Table 4**. The above distinctive peaks appear in the spectra of all physical mixture that is HPMC shown in **Fig. 4** & **Table 5** as well as PVP shown in **Fig. 5** & **Table 6** at the same wave number indicating no interaction between the drug and the HPMC & PVP. The final result suggested that there was no interaction between of Olmesartan Medoxomil Solid Dispersion and physical mixture (HPMC & PVP). The results are given in **Fig. 6** & **Table 7.**

## Fourier Transform Infrared Spectroscopy (FTIR):


**FIG. 3: FTIR SPECTRUM OF OLMESARTAN MEDOXOMIL**

**TABLE 4: FT IR SPECTRA RANGE FOR OLMESARTAN MEDOXOMIL**

| Sr. no. | Assignment | Wave number (cm$^{-1}$) |
|---|---|---|
| 1 | O-H (Stretching) | 3712.97 |
| 2 | O-H (Stretching) | 3589.53 |
| 3 | C-H (Bending) | 673.16 |

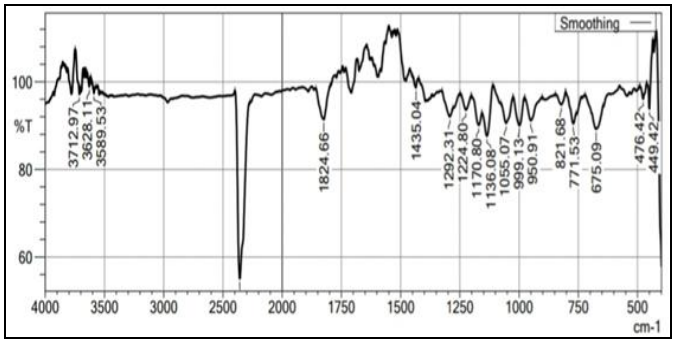


**FIG. 4: FTIR SPECTRUM OF PHYSICAL MIXTURE (OLMESARTAN MEDOXOMIL+ HPMC)**

**TABLE 5: FT-IR SPECTRA RANGE FOR OLM+HPMC**

| Sr. no. | Assignment | Wave number ($cm^{-1}$) |
|---|---|---|
| 1 | Free O-H( Stretching) | 3712.97 |
| 2 | N-H | 3589.53 |
| 3 | -C-F (Stretching) | 1224.80 |
| 4 | =C-H (Bending) | 1055.07 |
| 5 | =C-H (Bending) | 999.13 |
| 6 | -C-H (Bending) | 675.09 |

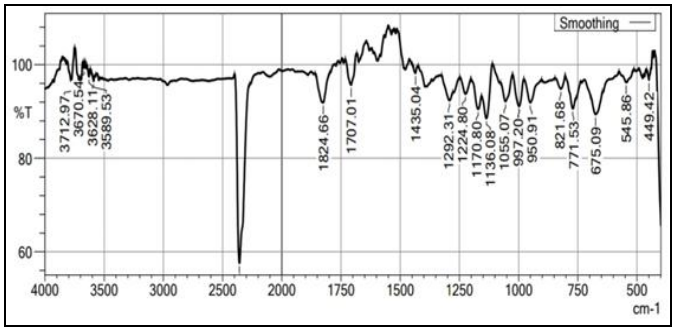


**FIG. 5: FTIR SPECTRUM OF PHYSICAL MIXTURE (OLMESARATAN MEDOXOMIL+ PVP)**

**TABLE 6: FT-IR SPECTRA RANGE FOR OLM+PVP**

| Sr. no. | Assignment | Wave number ($cm^{-1}$) |
|---|---|---|
| 1 | O-H Stretching | 3712.97 |
| 2 | -N-H | 3589.53 |
| 3 | -C=O | 1707.01 |
| 4 | C=C | 1435.04 |
| 5 | C-F | 1292.31 |
| 6 | =C-H (Bending) | 1055.07 |
| 7 | =C-H (Bending) | 997.20 |
| 8 | -C-H (Bending) | 675.09 |

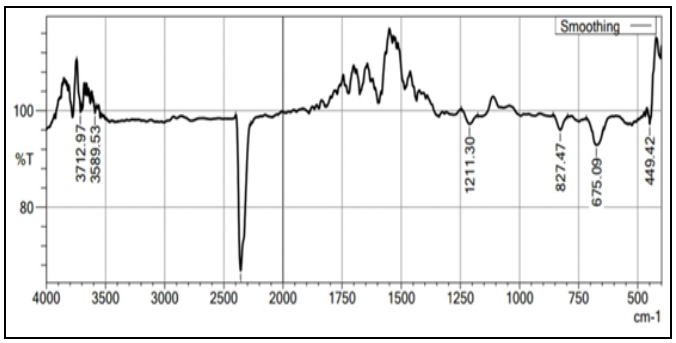


**FIG. 6: ATR SPECTRUM OF OLMESARTAN MEDOXOMIL SOLID DISPERSION**

**TABLE 7: FTIR SPECTRA RANGE FOR OLM SOLID DISPERSION**

| Sr. no. | Assignment | Wave number ($cm^{-1}$) |
|---|---|---|
| 1 | Free-OH (Stretching) | 3727.97 |
| 2 | -N-H | 3589 |
| 3 | Aromatic C-F (Stretching) | 1211 |
| 4 | C=N | 2348 |
| 5 | =C-H(Bending) | 827.47 |
| 6 | -C-H(Bending) | 675.09 |

**Differential Scanning Colorimetry (DSC):** Pure olmesartan DSC thermogram and olmesartan-polymer mixture DSC thermogram are shown in **Fig. 7** and **Fig. 8** respectively. The DSC thermogram of olmesartan shows sharp exothermic peak at 178.3°C corresponding to its melting point 175-178°C. For olmesartan with polymer the sharp peak observed at 110°C.

The above result shows that there was no significant shift in exothermic peak. From this it can be concluded that there was no interaction between Olmesartan and Polymers. Hence Olmesartan medoxomil found to be compatible with selected polymers.

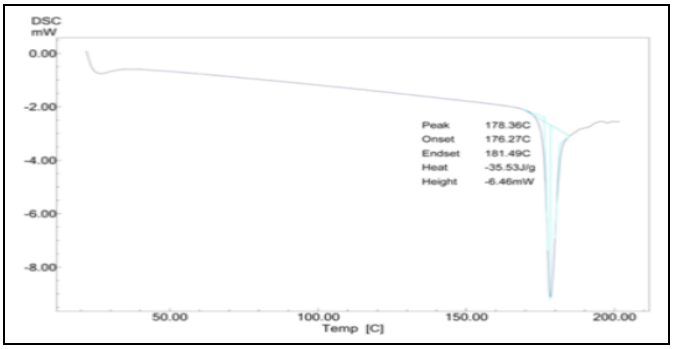


**FIG. 7: DSC SPECTRA OF OLMESARTAN MEDOXOMIL**

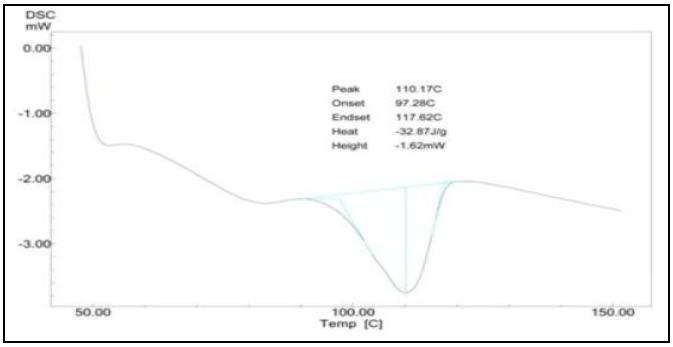


**FIG. 8: DSC SPECTRA OF SOLID DISPERSION**

**Evaluation of Solid Dispersion:**

**Process Yield (PY):** Maximum Process Yield was reported to be 98.78% in formulation SD 1:2:2.

**Dissolution Study:** Release of Olmesartan from solid dispersion found in pH 6.8 buffer. There was almost increase in the release of olmesartan than plain drug shown in **Fig. 9** and **Table 8**.

**TABLE 8: DISSOLUTION PROFILE OF VARIOUS BATCHES OF SOLID DISPERSION**

| Time (min.) | (%) Drug Release | | | |
|---|---|---|---|---|
| | Drug | SD1 | SD2 | SD3 |
| 00 | 00 | 00 | 00 | 00 |
| 15 | 4.68 | 5.58 | 7.9 | 13.77 |
| 30 | 12.06 | 12.78 | 18.5 | 36.48 |
| 45 | 19.26 | 23.45 | 47.3 | 73.1 |
| 60 | 25.94 | 33.48 | 74.0 | 84.5 |
| 90 | 31.52 | 54.56 | 77.3 | 93.15 |
| 120 | 38.36 | 61.80 | 89.9 | 103.55 |

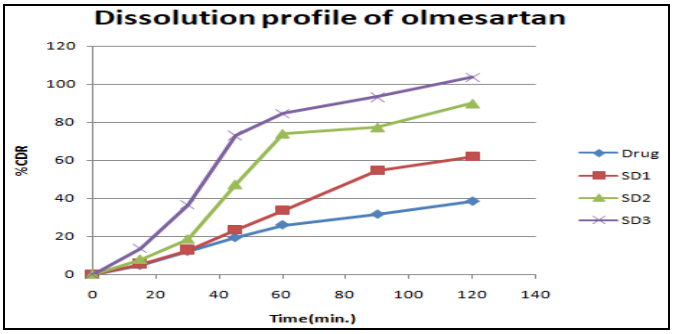


**FIG. 9: DISSOLUTION PROFILE OF VARIOUS BATCHES OF SOLID DISPERSION**

**Solubility (S):** Solubility of plain Olmesartan in water is a very low whereas significant increase in its solubility was observed with various concentrations of polymers.

Solid dispersion developed in the ratio of 1:3 drug polymer show significant increase in solubility than the other drug polymer ratio shown in **Fig. 10** and **Table 9**.

**TABLE 9: SOLUBILITY OF OLMESARTAN AS SOLID DISPERSIONS**

| Sr. no. | Formulation | Distilled water(ug/mL) | Buffer pH (6.8) (ug/mL) |
|---|---|---|---|
| 1 | Pure drug | 0.173 | 0.184 |
| 2 | Physical mixture | 1.178 | 1.435 |
| 3 | Solid dispersion (1:3) | 1.395 | 1.788 |

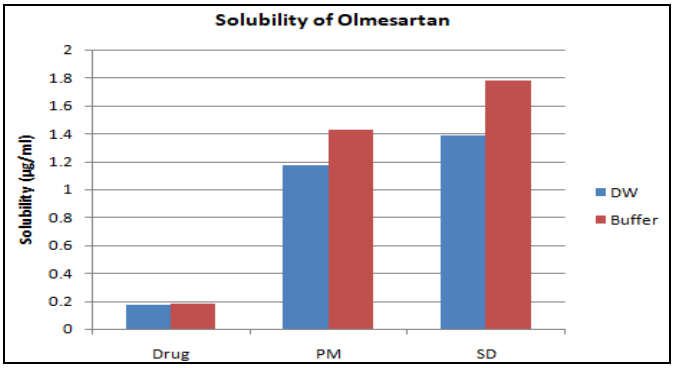


**FIG. 10: SOLUBILITY OF OLMESARTAN**

**Total Olmesartan Content:** All the batches of olmesartan solid dispersion show good olmesartan content. The Olmesartan content was found in the range from 93.45 ± 0.45 to 96.30 ± 0.54 shown in **Table 10**.

**TABLE 10: TOTAL OLMESARTAN CONTENT**

| Sr. no. | Formulation | Drug content |
|---|---|---|
| 1 | SD1 | 93.45 ± 0.45 |
| 2 | SD2 | 94.60 ± 0.53 |
| 3 | SD3 | 96.30 ± 0.54 |

**CONCLUSION:** The physical properties and spectra of Olmesartan were matched and found to be similar to standard which is given in analytical profile of olmesartan. The polymers PVP & HPMC and the drug Olmesartan were examined for compatibility by FTIR and DSC. From the FTIR and DSC study Olmesartan found to be compatible with PVP and HPMC. Dissolution study of SD3 show increase in dissolution rate than pure Olmesartan.SD3 show higher aqueous solubility than pure Olmesartan and other Solid Dispersions.

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**CONFLICTS OF INTEREST:** The authors have no conflict of interest to declare.

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