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# ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF OLMESARTAN MEDOXOMIL USING SYLYSIA

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## ABSTRACT

Olmesartan Medoxomil used as antihypertensive drug belongs to BCS class II. It has less aqueous solubility and high permeability. Due to less aqueous solubility it exhibits low oral bioavailability i.e. 26% only. The primary objective of the present research was to improve the aqueous solubility and in vitro dissolution rate of Olmesartan Medoxomil using different grades of porous carrier sylysia i.e. sylysia 350, sylysia 550 and sylysia 730. The FT-IR and DSC study confirmed no interaction between drug and sylysia. The solid dispersions were prepared by solvent evaporation method. The solid dispersions exhibited desirable flow properties for processing into tablet dosage forms. In vitro dissolution study of all solid dispersions showed highest dissolution rate for sylysia 550(98.2) based solid dispersions. The solid dispersion with highest solubility was compressed into immediate release tablet with sodium starch glycolate as super disintegrating agents. The tablets with 25% of sodium starch glycolate showed quick disintegration and similar dissolution rates as that of the optimized solid dispersion.

**KEYWORDS:** solubility, porous carrier and tablet.

## INTRODUCTION

Various drug delivery systems, such as liposomes, micelles, emulsions, polymeric micro/nanoparticles have been showing great promise in controlled and targeted drug delivery. Among these systems porous materials are emerging as a new category of host/guest systems. Greater attention has been focused on the development of porous materials as controlled drug delivery matrices because of possessing several alternatives

features such as stable uniform porous structure, high surface area, tunable pore sizes with narrow distribution and well defined surface properties. These materials possess vast amounts of Nano pores that allow the inclusion of drugs. These features allow them to adsorb drugs and release them in a more reproducible and predictable manner. The use of mesoporous, microporous and nanoporous carriers used for drug delivery is a part of growing research.

Sylysia is available in different grades like 350, 550 and 730. These are dry, white micronized porous powder for adsorption of a high proportion of drug. It is used primarily as a tablet excipient to improve the ease of powder flow through the tableting process, which provides more accurate dosages. It can be also used for powdering liquids, to increase the viscosity of liquids and gels, or to protect sensitive compounds from moisture. It is used in research as a drug carrier in solid dispersions to improve dissolution. Spray-drying indomethacin and Sylysia resulted in an amorphous form of indomethacin in a solid dispersion, probably due to its incorporation into mesopores that inhibit crystallization of the drug. This amorphous structure was stable for at least 2months at elevated temperature and humidity. Similar results (dissolution rate improvement and amorphous drug structure in the dispersion) were also obtained with tolbutamide and spironolactone.

In the present study, olmesartan was selected as the model drug for the above research. It is an antihypertensive, angiotensin-II receptor antagonist. Olmesartan is also used to treat mild or moderate liver or kidney disease, renal artery stenosis and disease of heart valve and heart muscles. This drug exhibits low oral bioavailability i.e. 26%. It is BCS Class II drug exhibiting poor solubility and high permeability. The Primary objective of present work was to improve the solubility and In-Vitro dissolution rate of olmesartan medoxomil by preparing solid dispersion using different grades of porous carrier sylysia and to formulate this into tablet dosage form.

**MATERIALS USED**

Olmesartan Medoxomil was obtained as gift sample from Cadila Pharm Ltd, Ahamdabad. Sylysia 350,550 and 730 were obtained as gift samples from Fuji Sylysia, Japan. Acetone was procured from Merck, India). Other chemicals used in this study are of analytical grade.

## METHODS

### Preparation of solid dispersions

The compositions of solid dispersions are shown in table 1. Olmesartan medoxomil was dissolved in acetone. The drug solution was added to porous powder sylysia and mixed till complete evaporation of acetone.

**Table 1: Composition of solid dispersions Olmesartan Medoxomil.**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| DRUG | 0.5g | 0.5g | 0.5g | 0.5g | 0.5g | 0.5g | 0.5g | 0.5g | 0.5g |
| SYLYSIA 350 | 0.5g | 1g | 1.5g | - | - | - | - | - | - |
| SYLYSIA 550 | - | - | - | 0.5g | 1g | 1.5g | - | - | - |
| SYLYSIA 730 | - | - | - | - | - | - | 0.5g | 1g | 1.5g |
| Acetone | 6ml | 8ml | 12ml | 2ml | 5ml | 5ml | 2ml | 2ml | 5ml |

## CHARACTERIZATION OF SOLID DISPERSIONS

### 1. Solubility

Excess amount of drug & the formulations was added to 1ml of distilled water and were kept in digital shaker for 24 hours. Then these mixtures were centrifuged for 2-3 minutes. After centrifugation 1mL of the supernatant was collected, suitably diluted and analyzed spectrophotophotometrically at 235nm. The result of solubility study of pure drug and formulations is given in table no.2 and bar graph has shown in fig.1.

### 2. Drug content

Samples from each formulation equivalent to 10 mg of olmesartan medoxomil was weighed and added to 5 mL of 0.1 N HCl. The samples were sonicated for 10 min, filtered, suitably diluted and analyzed spectrophotometrically at 235nm. Whose results are given in table no.2.

### 3. Micromeritic properties

Pure drug and solid dispersions were subjected to measurement of densities (bulk and tap densities), angle of repose, Carr's index and Hausner's ratio, determined as per standard procedures. The results were shown in table.2.

### 4. Fourier Transform Infrared (FT-IR) Spectroscopy

Olmesartan and sylysia interactions were assessed by FT-IR spectroscopy. FT-IR spectra of selected drug and its physical mixtures (1:1) were recorded on IRAffinity-1, (Shimadzu, Japan) using KBr discs. The instrument was operated under dry air purge and the scans were

collected at a scanning speed of 2 mm/s with resolution of 4 $cm^{-1}$over the region 4000–400$cm^{-1}$. Different IR peaks are shown in fig.4.

**5. Differential Scanning Calorimetry (DSC)**

The DSC measurements were performed on a DSC-60(Shimadzu, Japan) with a thermal analyzer. All samples(about 2 mg of olmesartan medoxomil) were placed in sealed aluminum pans before heating under nitrogen flow (20 mL/min)at a scanning rate of 10 1C/min from 25 to 250 1C. An empty aluminum pan was used as reference. DSC measurements were also performed for physical mixtures of drug and sylysia (1:1) to study the drug–polymer interaction. DSC analysis measures the amount of energy absorbed or released by a sample when it is heated or cooled, providing quantitative and qualitative data on endothermic (heat absorption) and exothermic (heat evolution) processes. The results of DSC study are shown in fig.5.

**6. In-Vitro dissolution study**

In vitro dissolution studies were performed using USP dissolution apparatus II. The dissolution test for the prepared solid dispersions was carried out in 900 mL. Of 0.1N HCl at 37$^{o}$C and 50 RPM for 2 h. At specific time intervals, 5 mL of samples were withdrawn, filtered and analysed for their concentration using UV spectrophotometer. The withdrawn samples were replaced by equal amounts of the dissolution media to maintain constant volume. The dissolution profile of solid dispersions and immediate release tablets are shown in fig. 2 & 3 respectively.

**Table 2: Solubility, drug content and micromeritic properties of solid dispersions.**

| FORMULATION | Carr's Index | Hausner's Ratio | Angle of Repose (Θ) | Solubility (µg/mL) | Drug Content |
|---|---|---|---|---|---|
| **Olmesartan Medoxomil** | 0.26 | 1.353 | 41 | 359.375 | - |
| **F1** | 0.282 | 1.348 | 23 | 5500 | 92.5 |
| **F2** | 0.260 | 1.352 | 20 | 1281.25 | 98.6 |
| **F3** | 0.259 | 1.355 | 18 | 1125 | 97.5 |
| **F4** | 0.22 | 1.252 | 28 | 3968.75 | 94.6 |
| **F5** | 0.185 | 1.235 | 21 | 4453.125 | 96.5 |
| **F6** | 0.182 | 1.213 | 18 | 5750 | 99.5 |
| **F7** | 0.274 | 1.434 | 22 | 1906.25 | 98.2 |
| **F8** | 0.268 | 1.458 | 21 | 1468.75 | 97.5 |
| **F9** | 0.263 | 1.449 | 19 | 1500 | 94.5 |

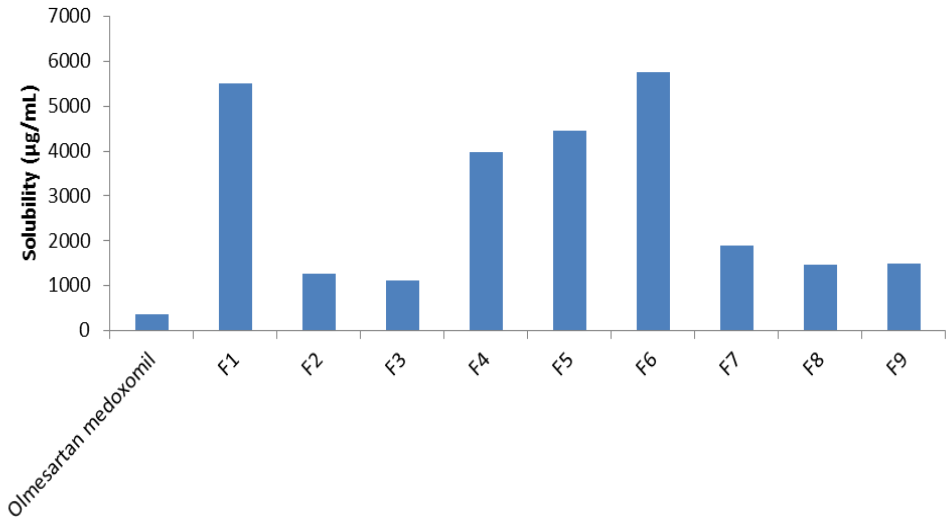


**Figure 1:- Solubility profile of Solid dispersions.**

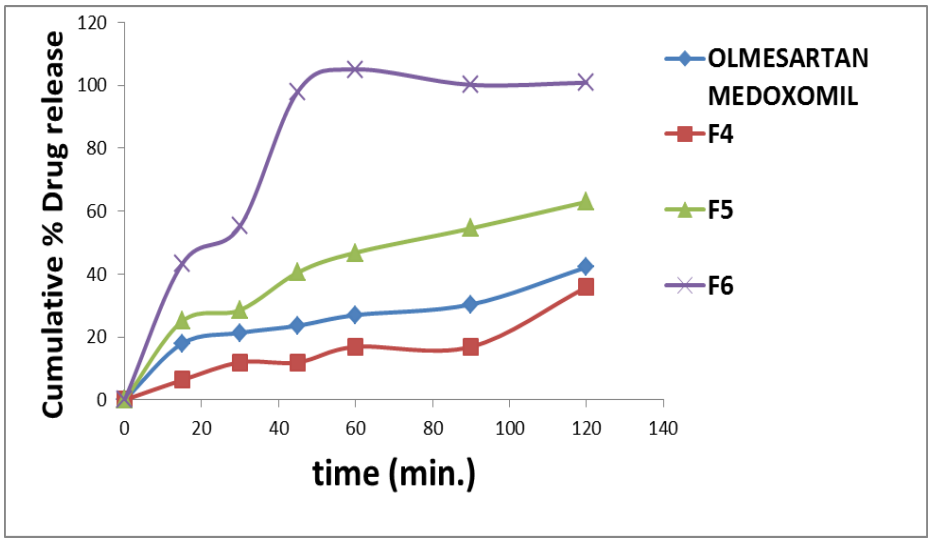


**Figure 2:- Dissolution profile of Sylysia 550 based solid dispersions.**

**Table 3: Composition of Olmesartan medoxomil immediate release tablets.**

| Ingredients | F10 | F11 | F12 |
|---|---|---|---|
| Solid dispersions (F6) | 100 mg (drug =25 mg and 75 mg of sylysia 550) | 100 mg (drug =25 mg and 75 mg of sylysia 550) | 100 mg (drug =25 mg + 75 mg of sylysia 550) |
| Sodium starch glycolate | 2 mg | 3 mg | 4 mg |
| TOTAL | 102 mg | 103 mg | 104 mg |

**Table 4:- Quality control tests for immediate release tablets of olmesartan medoxomil.**

| Tests | F10 | F11 | F12 |
|---|---|---|---|
| Drug Content (%) | 97.6 | 98.5 | 96.5 |
| Hardness (Kg/cm$^2$) | 5.3 | 5.1 | 5.4 |
| Weight variation | 102 ± 3 | 103 ± 2 | 104 ± 2 |
| Friability (%) | 0.5 | 0.7 | 0.3 |
| Disintegration Time (min) | 12 | 8 | 5 |

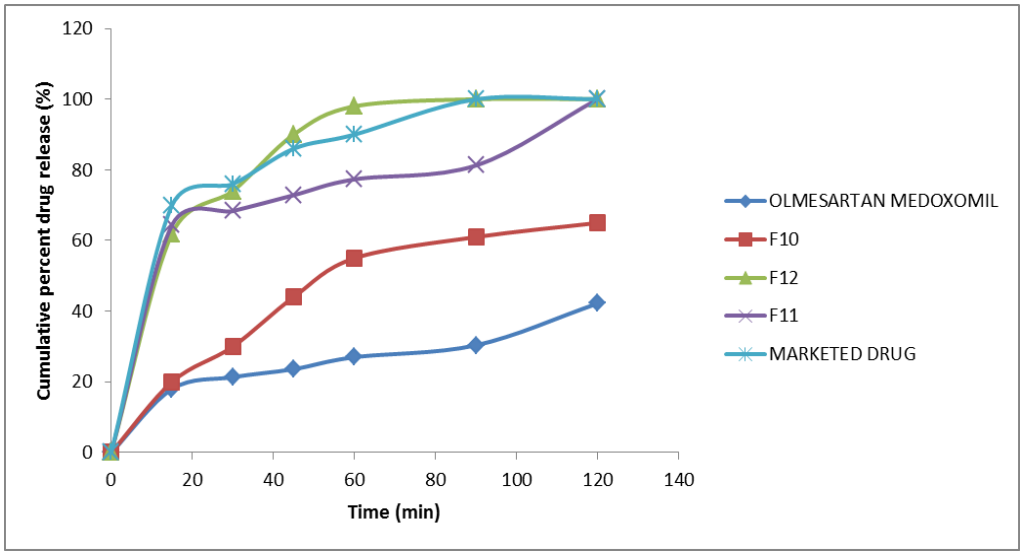


**Figure 3:- Dissolution profile of pure drug, formulated tablet and marketed tablets.**

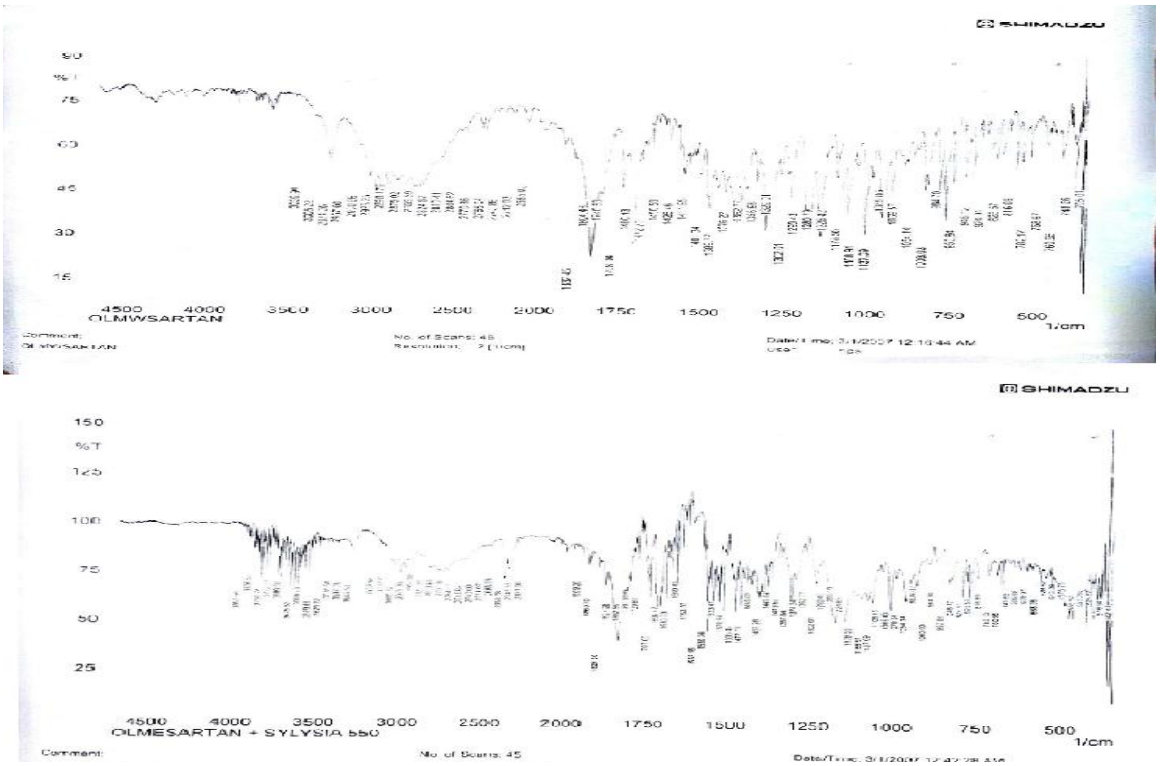


**Figure 4:- FT-IR of Olmesartan medoxomil and its physical mixtures with sylysia 550.**

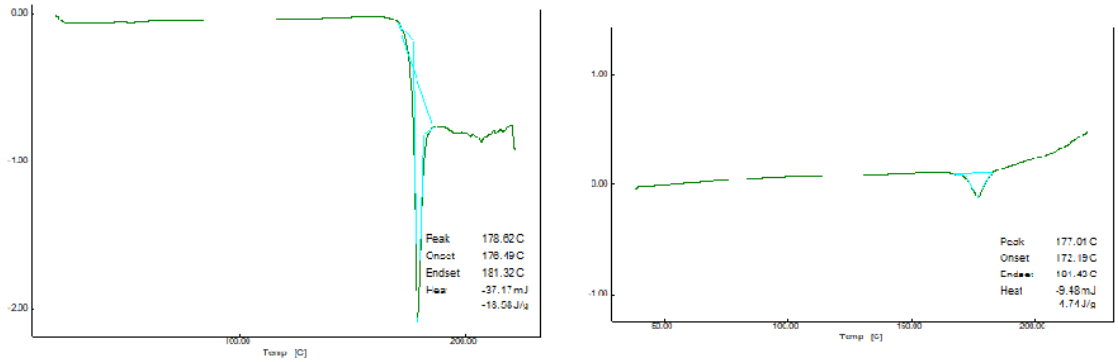


**Figure 5:- DSC thermogram of olmesartan medoxomil and its physical mixtures with sylysia 550.**

## RESULTS AND DISCUSSION

### Solubility studies

- The solubility study of the pure drug olmesartan medoxomil showed very low solubility i.e. 359.375µg/ml. All the solid dispersion formulations prepared with SYLYSIA 350, 550 & 730 exhibited improvement in solubility. But solid dispersions prepared with SYLYSIA 550 (F4, F5 & F6) showed better solubility enhancement. F6 showed maximum solubility (5750µg/ml) i.e. 16 times more soluble than pure drug. So further evaluations were performed only for SYLYSIA 550 based solid dispersions. (Kenneth E. Ezealisiji,et al,471-476,6, 2015).

### Drug Content

- Drug content for all solid dispersions were more than 90 % indicating that the drug was uniformly mixed with the porous carrier sylysia. (Odon Planinsek, et al, 406, 41–48, 2011).

### Micromeritic Properties

- Pure drug olmesartan medoxomiland solid dispersion formulations (F4) showed poor flow property. Formulations F5 & F6 showed good flow property as observed from angle of repose carr's index and hausner's ratio. The improvement in solubility can be attributed to the free flowing characteristics of sylysia. (Hirofumi Takeuchi, et al, 293, 155–164, 2005).

### FT-IR Study

- The FT-IR study for the pure drug Olmesartan Medoxomil showed the peaks at 2974,3005,1140,2972 for the following functional groups primary amine groups,

secondary amine groups, C-N, C-O-C respectively. All the above peaks are also retained in the mixture of drug and sylysia. Hence there is no interaction between drug and sylysia. (Kwang-Ho Cha, et al, 7, 5565–5575, 2012).

**DSC Study**

- DSC study for the pure drug olmesartan medoxomil showed a sharp endothermic peak at $178^0$C with onset and end set temperature of $176^0$C to $181^0$C respectively. The physical mixture of drug with Sylysia showed a melting endotherm at $178^0$C. Hence there is interaction between drug and Sylysia.(Kwang-Ho Cha, et al, 7, 5565–5575, 2012).

**Dissolution Study**

- From the dissolution study of pure drug olmesartan medoxomil it was observed that only 40% of drug was dissolved in 2 hours. Powder formulations (F4) also exhibited similar type of dissolution profile indicating that 1:1 ratio of drug & sylysia 550 was not sufficient for improvement in dissolution rate. As the ratio of sylysia 550 increased to 1:2(F5) and 1:3(F6) the dissolution rate increased significantly. Powder formulation F6 showed nearly 100% drug dissolution in 45 mins. This improvement in dissolution rate can be attributed to the porous nature of SYLYSIA 550. However when these powder formulations were compressed into tablets a decrease in dissolution rate was observed.

- In vitro dissolution study for tablets revealed that when the formulation F6 was compressed into a tablet the dissolution rate decreased significantly. This can be attributed to slow disintegration of tablets. Incorporation of super disintegrant to the tablet formulations reduced the disintegration time to 5 min and also showed a similar dissolution profile as that of marketed tablet. (Odon Planinsek, et al, 406, 41–48, 2011).

**CONCLUSION**

From the above research project it was concluded that sylysia 550 can be used as a porous carrier for improvement in solubility and dissolution rate of olmesartan medoxomil. It can also be concluded that compression into tablet also can exhibit similar improvement in dissolution rate with incorporation of sodium starch glycolate as super integrant (4%).

**REFERENCES**

1. Odon Planinsek, Borut Kovacic, Franc Vrecer, "Carvedilol dissolution improvement by preparation of solid dispersions with porous silica" International Journal of Pharmaceutics, 2011; 406: 41–48.
2. Hirofumi Takeuchi, Shinsuke Nagira, Hiromitsu Yamamoto, Yoshiaki Kawashima, "Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method" International Journal of Pharmaceutics, 2005; 293: 155–164.
3. Meer Tarique Ali, Ritesh Fule, Ajay Sav, and Purnima Amin, "Porous Starch: a Novel Carrier for Solubility Enhancement of Carbamazepine" AAPS Pharm Sci Tech, 2013; 14(3): 919–926.
4. Kenneth E. Ezealisiji, Chika J. Mbah, Patience O. Osadebe, "Aqueous Solubility Enhancement of Mirtazapine: Effect of Cosolvent and Surfactant" Pharmacology & Pharmacy, 2015; 6: 471-476.
5. Kwang-Ho Cha, Kyung-Jin Cho, Min-Soo Kim, Jeong-Soo Kim, Hee Jun Park, Junsung Park1, Wonkyung Cho1, Jeong-Sook Park, Sung-Joo Hwang, "Enhancement of the dissolution rate and bioavailability of fenofibrate by a melt-adsorption method, 2012; 7: 5565–5575.