Otra Kumar et al. / Journal of Pharmacy Research 2012,5(12),5464-5466

Research Article
ISSN: 0974-6943

Available online through
www.jpronline.info

Formulation and evaluation of Olmesartan dispersable tablets by using solid dispersion method

Otra Kumar*[1], A. Prameela Rani[2]

[1]*Drugs Control Administration, Eluru, West Godavari District, A.P , ,India.*

[2]*Principal, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, A.P - 522 510,India.*

Received on:14-07-2012; Revised on: 19-08-2012; Accepted on:17-09-2012

ABSTRACT

Olmesartan is a novel and widely prescribed antihypertensive drug which belongs to BCS Class II (Biopharmaceutics Classification System), i.e. having good permeability and poor aqueous solubility. The objectives of present study is to enhance the solubility of Olmesartan by preparing solid dispersion by using carriers such as PVP, PEG, Mannitol and formulate solid dispersion dispersable tablets.

Key words: Olmesartan, PVPK30, PEG6000, Mannitol, Solid dispersion method.

INTRODUCTION:

Olmesartan acts by blocking the action of a hormone called angiotensin II receptor. Hypertension (HTN) or high blood pressure, sometimes arterial hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. In 90-95% of cases are categorized as "Primary Hypertension" which means high blood pressure with no obvious underlying medical cause. The remaining 5-10% of cases is caused by other conditions that affect the kidneys, arteries, heart or endocrine system. Hypertension is a major risk factor for stroke, myocardial infarction (heart attacks), heart failure, aneurysms of the arteries.[1]

The presence of other cardiovascular risk factors is taken into account when decisions are made regarding drug treatment[2]. Recent international hypertension guidelines have also created categories below the hypertension range to indicate the risks with higher blood pressures in the normal range which uses the term prehypertension for blood pressure in the range of 120-139 mmHg systolic and/or 80-90 mmHg for diastolic. The ESH-ESC Guidelines (2007) use optimal, normal and high normal categories to subdivide pressures below 140 mmHg systolic and 90 mmHg diastolic[3].

Solubility is defined as the amount of a substance that dissolves in a given volume of solvent at a specified temperature. A solution is a mixture of two or more components that form a single phase which is homogeneous down to the molecular level. The component that determines the phase of the solution is termed the solvent and usually constitutes the largest proportion of the system[4]. The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system[5]. More than 90% of the drugs arrowed since 1995 are poor solubility; poor permeability and more than 40% of new chemical entities have little or no water solubility. Absorption of drug into systemic blood circulation by dermal, pulmonary, nasal, sublingual or gastro intestinal administration involves transport of dissolved drug molecules through absorbing membrane.

EXERIMENTAL SECTION:

Olmesartan was obtained from M/s. Dr. Reddy's Laboratories LTD and PVPK30, PEG6000 and Mannitol was purchased from M/s. Swastik Pharmaceuticals. All the Chemicals, solvents and carriers used were of analytical grade.

***Corresponding author.**
Otra Kumar
[1]Drugs Control Administration,
Eluru, West Godavari District,
A.P , ,India.

Construction of Standard Calibration Curve:

Olmesartan can be estimated spectrophotometrically at 257nm as it obeys, Beer-Lamberts Law. Stock solution can be done by dissolving 100 mg of Olmesartan in 10ml of methanol and made upto 100 ml with 0.1M HCl of pH 1.2. From stock solution dilutions are made whose concentration ranging from 2 to 20 μg/ml. The absorbance was measured at 257 nm by using UV Spectrophotometer. A plot of concentration of drug versus absorbance was plotted. The linear regression analysis was done on absorbance data points and given in figure 1.

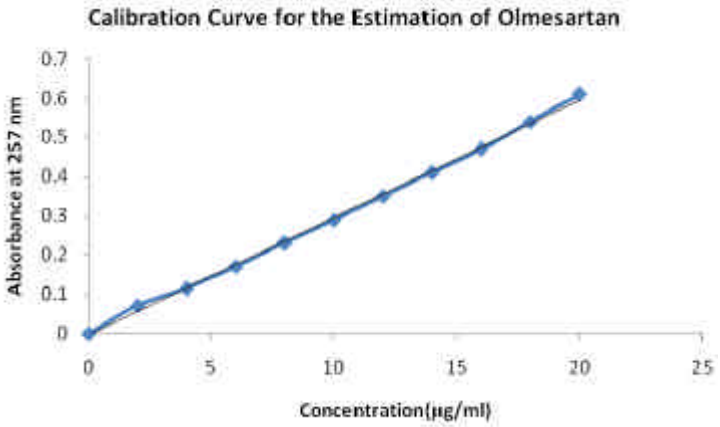

Fig 1: Calibration Curve for the Estimation of Olmesartan:

Preparation of Olmesartan Solid Dispersion:

Solid dispersion was prepared by solvent evaporation method. Methenol is used as a solvent and different Drug – PVPK30, Drug-PEG 6000, and Drug-Mannitol ratios (1:1, 1:2, 1:3 & 1:4) are used to prepare olmesartan solid dispersions. The respective amount of PVPK 30, PEG 6000, Mannitol was dissolved in a required amount of methanol taken in a conical flasks to get a clear complete soluble polymer in methanol solution. A magnetic stirrer was used for this purpose. Then the weighed amount of Olmesartan was added to this solution carefully. Constant stirring was continued until the drug is completely incorporated in solvent. The solvent was completely removed by drying in sunshade. The mass obtained was further dried in desiccators overnight, crushed, pulverized and seived[6,7].

Evaluation of Solid Dispersion:

Saturation Solubility study:
Solid Dispersion equivalent to 20mg and Olmesartan was dissolved in 10ml of methanol. The solution was filtered and diluted with 0.1 M HCl and analyzed at 257nm.

***In vitro* Drug Release Studies for Olmesartan Solid Dispersions:**
Accurately weighted amount of sample was taken for dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release while measuring the solution.

Table 2: Drug content of Olmesartan

S.No.	Composition	Amount of Drug Present in Solid Dispersion (mg)	Drug Content
1	D:Mannitol (1:1)	19.560	99.65
2	D:Mannitol (1:2)	19.970	99.70
3	D:Mannitol (1:3)	19.70	99.50
4	D:Mannitol (1:4)	20.0	100
5	D:PVP (1:1)	19.80	99
6	D:PVP (1:2)	19.84	99.15
7	D.PVP (1:3)	19.90	99.65
8	D.PVP (14)	20.0	100
9	D:PEG (1:1)	19.80	99.15
10	D:PEG(1:2)	20.0	100
11	D:PEG (1:3)	19.84	99.05
12	D:PEG (1:4)	20.0	100

Flow Properties of Solid Dispersions:
The powder substances of Olmesartan solid dispersing and other excipients used for the formulation of Olmesartan dispersible tablets were evaluated.

Table 3: Saturation Solubility Studies for Olmesartan and Olmesartan Solid Dispersion

S.No.	Composition	Amount of Drug (mg/100ml)
1	Drug (D)	0.5012
2	D:Mannitol (1:1)	0.6550
3	D:Mannitol (1:2)	0.7910
4	D:Mannitol (1:3)	0.8960
5	D:Mannitol (1:4)	1.0640
6	D:PVP (1:1)	0,7240
7	D:PVP (1:2)	0.9210
8	D.PVP (1:3)	1.0322
9	D.PVP (14)	1.3428
10	D:PEG (1:1)	0.7981
11	D:PEG(1:2)	1.2410
12	D:PEG (1:3)	1.4727
13	D:PEG (1:4)	1.960

From the above obtained values Olmesartan: PEG 6000(1:4) was concluded as the best solubility enhancer and dissolution studies were performed on this solid dispersion which is compared with the drug dissolution.

Preparation of Dispersible Tablets:
Dispersible tablets containing Olmesartan solid dispersion were prepared by direct compression method[8]. Olmesartan solid dispersion and excipients mixture was prepared by homogeneously mixing with microcrystalline cellulose (binder) in a glass mortar for 15 minutes. Before direct compression, the powder was screened through a 60 µm sieve and thoroughly blended[9]. The blend was lubricated with magnesium stearate for 3-5 min. The mixture (200 mg) was then compressed using an 8mm diameter die in a 9-station rotary punching machine of M/s. Cadmach Pharma Pvt. Ltd., Ahmedabad).

Table 4: Composition of Dispersible Tablets of Olmesartan:

S.No.	Ingredients	Category	Quantities in mg. F1	F2	F3	F4	F5
1	Olmesartan+ PEG6000(1:4)	Solid Dispersion	100	100	100	100	100
2	Microcrystalline Cellulose	Binder	42	42	42	42	42
3	Lactose	Diluent	42	42	42	42	42
4	Crospovidone	Super Disintegrant	-	10	2.5	5	7.5
5	Sodium Starch Glycolate	Super Disintegrant	10	-	7.5	5	2.5
6	Talc	Glidant	3	3	3	3	3
7	Magnesium Stearate	Lubricant	3	3	3	3	3
	Total Weight		200	200	200	200	200

Evaluation of dispersible tablets:
Thickness of the tablet was determined using a vernier Caliper

Weight Variation:
20 Tablets of each formulation were weighed by using an electronic balance and the test was performed as per official method.

Hardness:
Hardness of the tablet was determined by using hardness testing apparatus CM TT/R-736 (Cadmach Machines, Ahmadabad)

Friability:
The friability of the tablet was measured in a Roche Friabilar FT00/Campbell Electronics, Mumbai.)

Disintegration Test:
Disintegration Test was carried using Disintegration Apparatus (Model-USP Campbell Electronics, Mumbai)

Drug Content:
Three tablets were powdered and powder equivalent to weight of one tablet (200 mg) was transferred to 100ml flask containing 10 ml Methanol and dilute with 0.1 M HCl filtered. Absorbance measured at 257nm.

***In vitro* dissolution studies:**
In vitro dissolution study was performed using USP Type 2 Dissolution Apparatus (VDA-6DR Veego Industries, Mumbai) at 100 rpm.

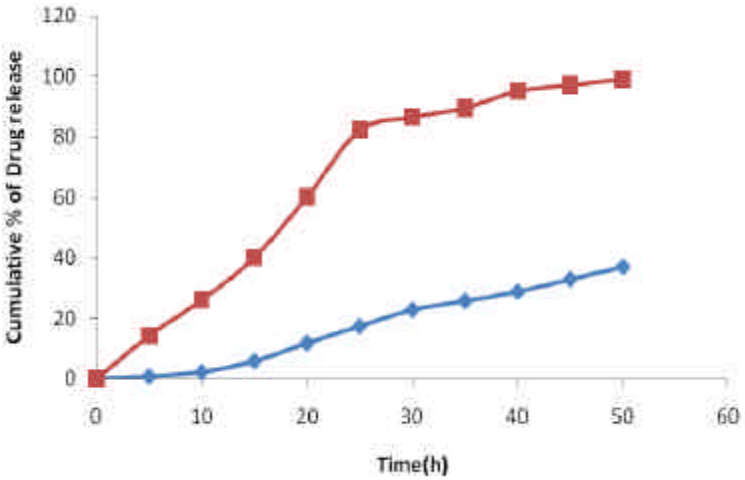

***Figure 2: In vitro* Drug Release Studies for Olmesartan and Olmesartan Solid Dispersion D: PEG (1:4)**

***In Vivo* Drug Absorption Studies:**

A healthy rabbit weight 2.5 to 3 kg was taken and checked for absence of any disease. The fore limbs and hind limbs were fixed so as to rabbit was not in dorsal position. The animal dose was calculated and its equivalent weight in tablet was calculated and it was mixed with 5ml of water and this dispersion was administered orally with the help of needles syringe. Dextrose solution was administered orally with given continuously throughout the period of study. Periodically 1 ml of blood sample was taken using a syringe which contained 1 ml of heparin solution to prevent blood clotting. These blood samples were centrifuged at 2500 rpm for about 30 mins. One ml. of the supernatant was taken, and after suitable dilution, analyzed at 257 nm by spectrophotometrically. The value obtained denotes amount of drug absorbed in rabbits. (CPCSEA Approval number-1243-bc/08)

Table 5: Time Plasma Concentration Data

S.No.	Time (min)	Plasma drug concentration (μg/ml)
1	0	0
2	5	0.94
3	10	1.89
4	15	3.90
5	20	5.65
6	25	9.15
7	30	10.05
8	35	11.10
9	40	11.15
10	60	9.85
11	120	9.65
12	180	8.95

Table 7: In Vivo Drug Absorption Data

S.No.	Time (min)	*In-vivo* % drug absorbed
1	0	0
2	5	6.9
3	10	13.9
4	15	29.7
5	20	47.6
6	25	61.6
7	30	80.2
8	35	83.0

Stability Studies:

The accelerated stability studies was carried out according to ICH Guidelines by storing the tablets in amber coloured rubber stoppered vials and kept in stability chamber maintained at $40^0 \pm 2^0$ C / 75 ± 5 % RH for 90 days. Samples were withdrawn on 90th day and were analysed for physical stability, drug content and dissolution studies. Results were analyzed by One-way ANOVA followed by Tukeys' Test[11]. The results indicate that the prepared formulation was stable.

RESULTS AND DISCUSSION:

The Calibration Curve was obtained with a good regression (r^2). The infra red spectra of the drug, excipients and prepared solid dispersions reveal that there is no interaction between the drug and excipients, as shown in table 1 and figure 1.

Olmesartan and carriers were characterized for angle of repose, bulk density, compressibility, moisture uptake and solubility. The results were satisfactory. The solid dispersion was prepared by solvent evaporation method. The results showed that the prepared solid dispersion were well within the limits for further studies. The solubility of Olmesartan solid dispersions were found highest in this solvent evaporation method.

The dispersible tablets of the selescted Olmesartan solid dispersions were prepared using the formula shown in table 4. The prepared dispersed tablets of Olmesartan were evaluated for average weight, Friability, hardness, drug content, *In vitro* dissolution studies and *In Vivo* Drug Absorption Studies. The drug release from Olmesartan solid dispersions tablets was found to be 97.50% within 50 min. Mannitol, PVPK30, PEG6000 in four different concentrations (20mg, 40mg, 60mg & 80mg) were used to increase the solubility of Olmesartan, among them PEG6000(80mg) was shown tremendous increase in solubility of Olmesartan.

Olmesartan dispersible tablets were prepared by direct compression method using two different super disintegrants Crospovione and Sodium starch glycolate, lactose as diluents and microcrystalline cellulose as binder. Drug-polymer compatibility studies by FTIR indicates there is no possible interactions between the drug and polymer and prepared tablets were characterized for their physico-chemical characteristics, whose results were within the limits of pharmacopoeia in all formulations(Fl -F5).

Olmesartan solid dispersion D:PEG (100mg) micro crystalline cellulose (42mg), Lactose (42mg), Crospovidone (7.5mg),Sodium Starch Glycolate (2.5mg), Magnesium Stearate (3mg), Talc (3mg) was the best formulation (F5) as the said formulation shows rapid dissolution and it is very good. The results of stability studies indicate that the prepared formulation was stable.

CONCLUSION:

Olmesartan solid dispersion tablets was shown the maximum % of drug release which was much more than 90%. From the *In vitro* drug release it was found that the solid dispersion complex of drug was giving good dissolution property. Hence, it can be concluded that the dispersible tablets of Olmesartan solid dispersions may be giving better therapy. This in turn can be reduce the dose of Olmesartan, which is expected to reduce dose related adverse effects and cost of therapy. It is worthwhile for further investigations on long time stability and bioavailability evaluations in human subjects can be confirmed the optimal formula.

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Source of support: Nil, Conflict of interest: None Declared