ISSN: 0975-766X
CODEN: IJPTFI
Available Online through *Research Article*
www.ijptonline.com

DRUG INTERACTIO OF OLMESARTAN MEDOXOMIL COMPLEXES IN ALBINO MALE RABBITS

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Received on: 12-05-2017 *Accepted on: 15-06-2017*

Abstract

The study aimed to develop inclusion complexes of the olmesartan medoxomil and evaluate the physicochemical parameters of the inclusion complexes, The absolute bioavailability is about 26%,and an extent of about 99 % bound to plasma proteins , So there is strong need to enhance aqueous solubility of hydrophobic drug by different methods like solid dispersion, inclusion complexation etc. Hence the study aimed to develop inclusion complexes of the olmesartan medoxomil and evaluate the physicochemical parameters of the inclusion complexes, and in-vivo pharmacokinetic studies and in-vivo pharmacokinetic performance of olmesartan. However, further studies are required for comprehensive, systematic, multi-disciplinary evaluation of various claims to make effective use of these products.

Key words: Olmesartan medoxomil, Pharmacokinetics, XRD, FTIR.

Introduction

Inclusion Complex:

When a small molecule that can enter the cavity interacts with macrocyclic compound possessing an intramolecular cavity of molecular dimension then an Inclusion complex is formed. The macrocyclic molecule is called the ‘host’ and the small included molecule is called the “guest”. [Sanjula Baboota, 1990]. When water is typically the solvent of choice complexes can be formed either in solution or in the solid state and, inclusion complexation can be accomplished in with some non-aqueous solvents and co-solvent systems.

Drug Profile

Olmesartan medoxomil (prodrug) is the P-glycoprotein substrate and angiotensin II receptor antagonist. once-daily dosing is the Potential advantages of this drug , there are no adverse reactions,[Vikas A Saharan, 2009] a well-

tolerated side-effect profile, and a cost-effective average wholesale price. Soluble in methanol, slightly soluble in ethanol, insoluble in water. oral bioavailability average is 26% and no food interferes with absorption.

Materials

Chemicals:

1. **DRUG:** olmesartan medoxomil
2. **POLYMERS:** β-cyclodextrin
3. **OTHER CHEMICALS:** Naringin, HPLC grade Methanol, Double distilled water etc,.

Experimental Animals

- From the Teena Biolabs Pvt. Ltd. (Reg, no. 177/99 CPCSEA), Hyderabad, Andhra Pradesh. Healthy, , and Healthy six male albino rabbits, weighing 1.2-1.5kg six male wistar rats weighing 200-220g, were procured. Vaagdevi Institute of Pharmaceutical Sciences, (1533/PO/a/11/CPCSEA) Warangal. Approved animal houses were used.
- The standard laboratory condition is provided for animals (12 hr light and 12 hr dark cycle) and had free access to commercial pellet diet (Vyas labs Ltd, Hyderabad, India) with libitum and water.
- Ethical norms were strictly followed during all experimental procedure.
- Institutional Animal Ethical Committee of University college of Pharmaceutical Sciences, dated (14/03/2012).approved the study.

Methodology: These are the following stages in which the proposed work was carried out in following stages:[Li-Ping Ryan2005 Anuj kumar2011]

A. Preformulation studies.

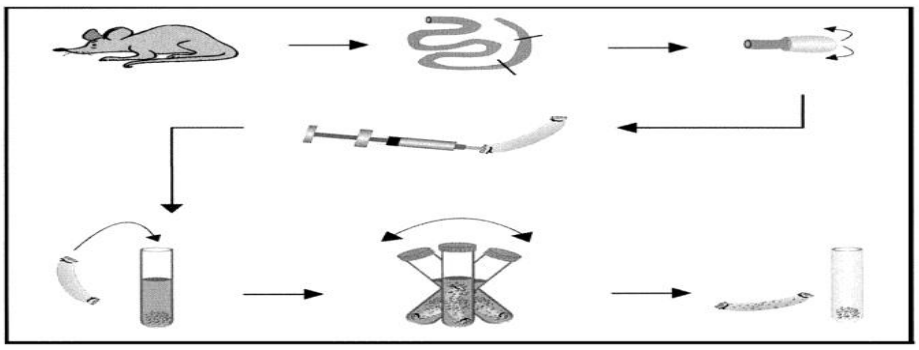
B. Drug-polymer inclusion complexes.

C. Characterization of prepared complexes.

D. Intestinal permeability studies using rat everted sac model.

E. Pharmacokinetic studies in rabbits.

Intestinal Permeability Studies



Pharmacokinetic Evaluation

- Study Design: between the doses with a crossover design with a washout period of 10 days Sample Size: Six albino male Rabbits.
- Route of administration: Oral route
- Treatment: single dose (10mg/Kg)
  - Pure drug(Olmesartan medoxomil)
  - Solid dispersion without and with Naringin
  - Inclusion complex without and with Naringin
- Sampling: Blood samples will be collected pre-dose (0 hr) and pre-determined post dose at various time points (0, 0.5, 1, 1.5,2,3,4,6,8 hrs) through a marginal ear vein into anticoagulant-treated polypropylene tubes after drug administration.
- Blood samples collected were centrifuged immediately at 10,500rpm to separate the plasma. The plasma samples collected were stored at −4°C.

Sample Extraction [Daryl Norwood 2002]

- To 1000 µL of plasma samples in a borosilicate glass tube were added 5 mL of HPLC grade acetonitrile. After vortex mixing at room temperature for 10 min , the samples were centrifuged at 10,500 rpm for 10 min. [Mohamed Ali Lassoueda2011]
- The upper organic layer was transferred to a glass container and evaporated inside a vacuum oven at 40°C.
- In 1 ml of mobile phasethe dry residue was dissolved in . 20 µL of this solution was injected into liquid chromatography after the mixture was sonicated well for 10 min.

Standard Sample Preparation

- Standard samples were prepared by spiking blank plasma with known amounts of valsartan (internal standard 10ug), olmesartan medoxomil and range of 10-80µg/mL used for calibration curve construction.[SK Shah, AJ Asnani2011].

Data Analysis

Phase Solubility: The solubility constant (Kc) was calculated from the slope

$$K = \frac{\text{slope}}{S_0(1 - \text{slope})}$$

Where, So is the solubility of the drug.

- **Drug content:**

$$\text{Actual OLM content in weight} = \frac{\text{quantity of inclusion complex}}{\text{theoretical amount of OLM in inclusion complex}} \times 100$$

- **Calculation of the apparent permeability coefficients:** Apparent permeability coefficient (Papp) was determined according to the formula:

$$Papp = \frac{dQ}{dt} \times \frac{1}{ACo}$$

Where Papp (cm/s) is the apparent permeability coefficient, dQ/dt (mg/s) is the amount of drug transported across the membrane per unit of time, A (cm2) is the surface area available for permeation and C0 (mg/ml) represents the outside everted gut sacs the initial concentration of the drug.

- The percentage of drug recovery (R %) was :

$$R\% = \frac{Cr,end \times Vr + Cd,end \times Vd}{Co \times Vr} \times 100$$

where Cr, end and Cd, end (mg/ml) are the drug concentrations measured at the end of the experiment inside and outside the sacs, respectively; Cd,0 (mg/ml) is the initial concentration of the drug outside the everted gut sacs; Vr and Vd (ml) are the volumes of the mucosal and the serosal media, respectively.

- The percentage of drug retained (Ad%) on the intestinal tissues was determined according to the formula:

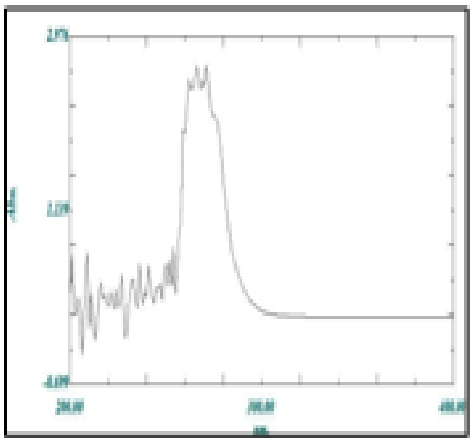
$$Ad\% = 100 - R\%$$

Statistical Analysis

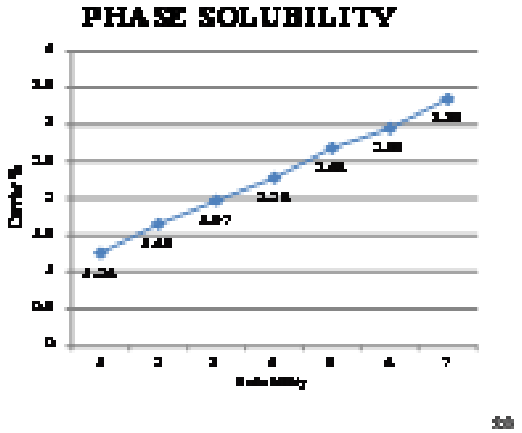
- The pharmacokinetic parameters of the in-vivo absorption studies were computed using KINETICA software and the model was non-compartmental extravascular.
- The apparent permeability average values (P_{app}) and the in-vivo absorption studies values were compared for each sample using one way analysis of variance (ANOVA) test.
- The difference was considered significant at $p \leq 0.05$.

Results and Discussion

Determination of Absorption maxima

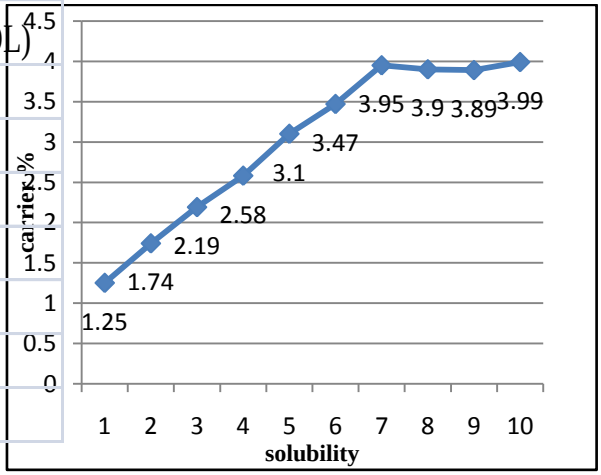


Phase Solubility Profile of Olmesartan and β-cyclodextrin



GIBBS FREE ENERGY TRANSFER($\Delta G^{o}tr$) FOR SOLUBLIZATION PROCESS OF OLMESARTAN MEDOXOMIL IN AQUEOUS SOLUTION OF β-CYCLODEXTRIN AT 37°C

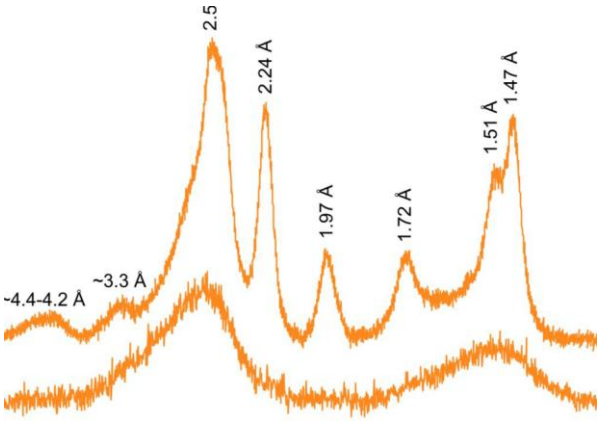
Percentage of β-CD in water	$\Delta G^{0}tr$(KJ/MOL)
0.2	-4.567
0.4	-9.345
0.6	-12.358
1	-20.569
1.5	-32.659
2	-35.485
3	-39.378

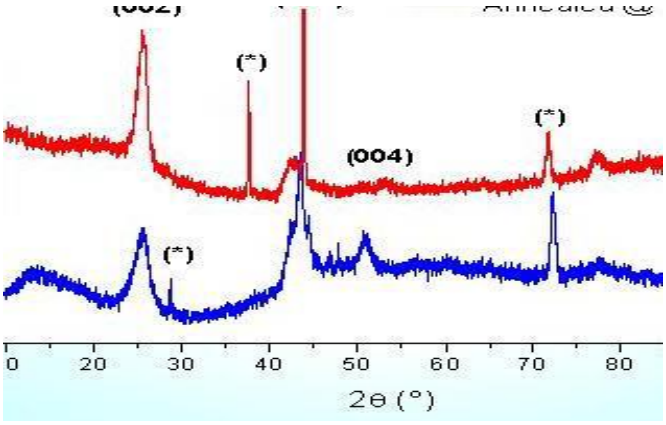


Saturation solubility of Olmesartan medoxomil inclusion complexes

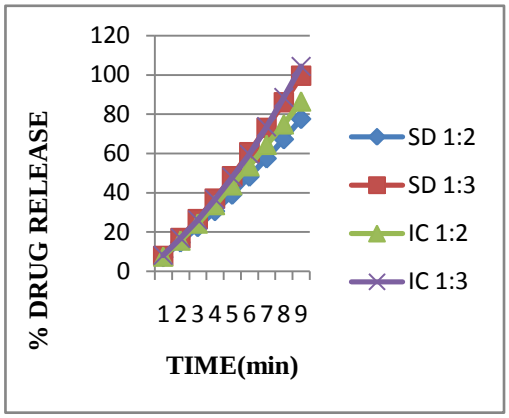
Formulation code	% Drug content(ug/ml)
PM1	37.28±0.836
PM2	62.96±0.767
PM3	94.67±0.878
SD1	59.85±0.507
SD2	117±0.191
SD3	118±0.66
IC1	89.56±0.67
IC2	99.81±0.78
IC3	107.11±0.89

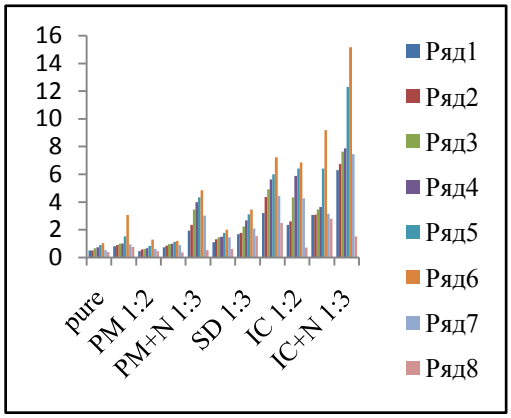
XRD Diffractogram



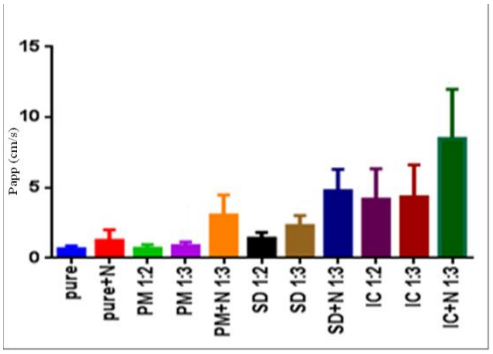


DISSOLUTION PROFILE OF DIFFERENT COMPLEXES OF APPARENT PERMEABILITY CO-EFFICIENT OF COMPLEXE OLMESARTAN AND β-CYCLODEXTRIN

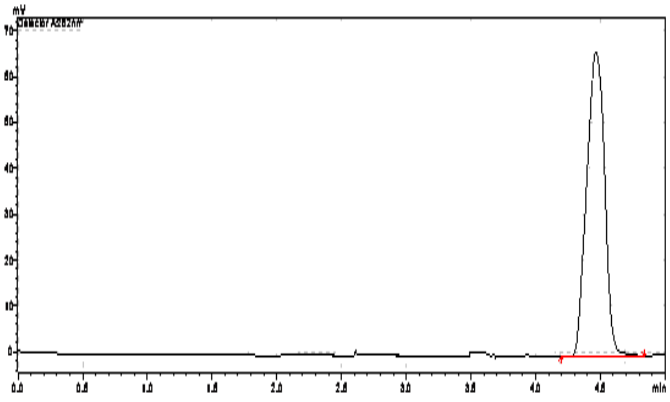


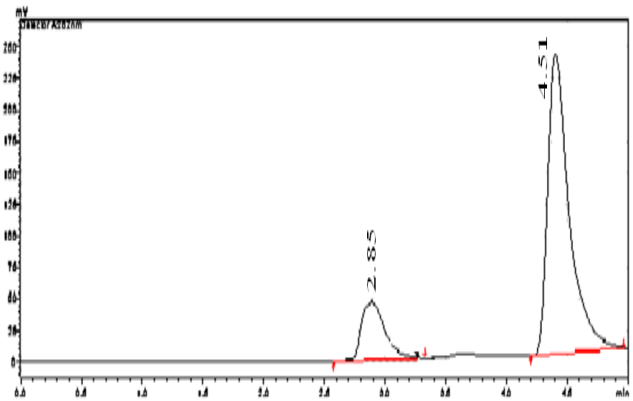


ONE WAY ANOVA INTESTINAL PERMEABILITY STUDIES DATA

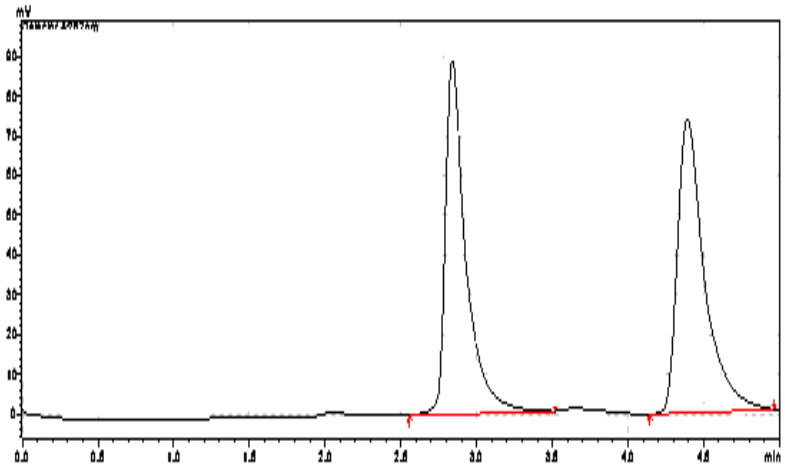


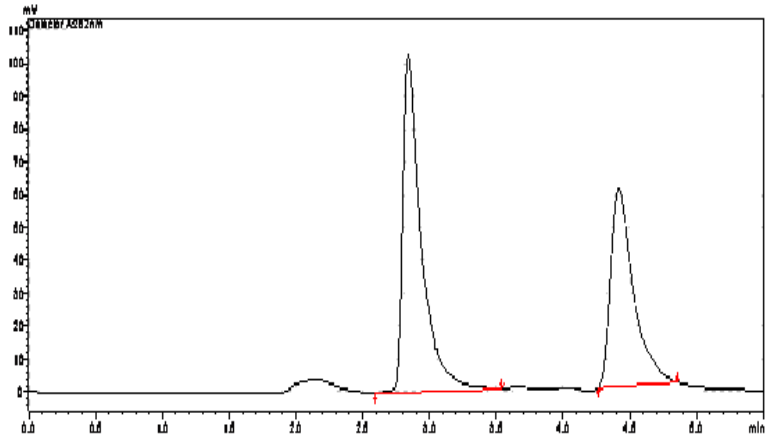
HPLC CHROMATOGRAPH





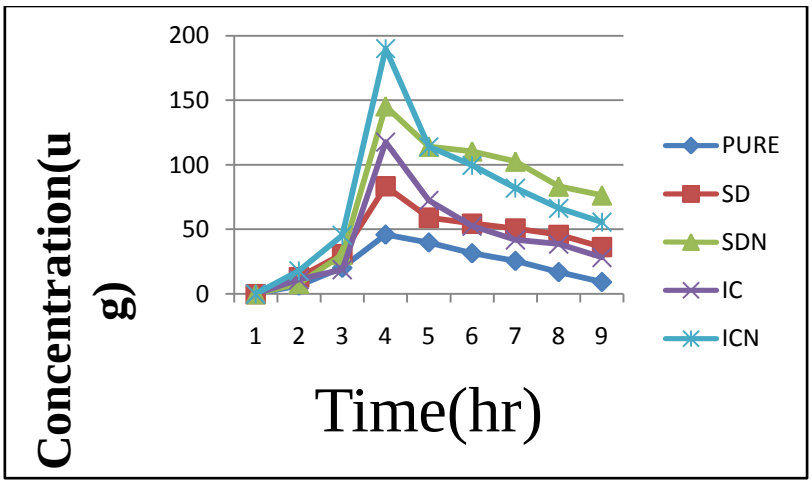
HPLC CHROMATOGRAM





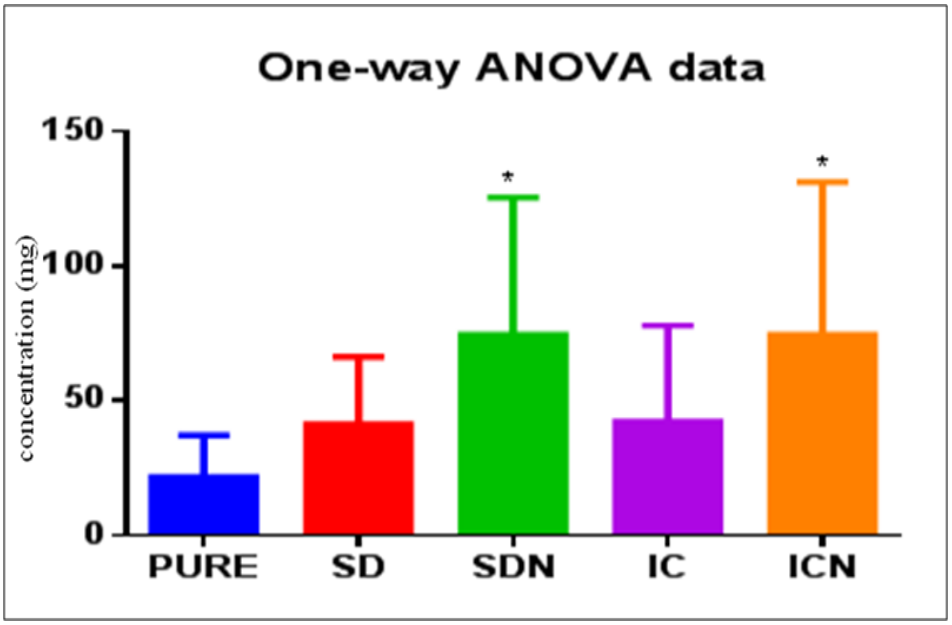
PHARMACOKINETIC PROFILE OF OLMESARTAN

PHARMACOKINETIC PARAMETERS



SL.NO	PARAMETERS	FORMULATIONS ADMINISTERED				
		PURE DRUG	SD	SDN	IC	ICN
1	Cmax	45.98	83.26	145.42	117.5	189.99
2	Tmax	1	1	1	1	1
3	AUClast	0.1861	0.3004	0.7084	0.345	0.647
4	AUCextra	0.0379	1.054	1.591	0.267	0.569
5	AUCtotal	0.224	0.613	1.126	1.354	2.299
6	Clearance	0.2532	0.043	0.048	0.105	0.097
7	t½	2.7368	15.973	14.43	6.56	7.086
8	MRT	4.785	23.276	21.164	9.6	10.466
9	Kel	0.2089	0.0429	0.047	0.104	0.095
10	R^2	0.988	0.989	0.992	0.988	0.998

One Way Anova



Conclusion

The present study showed the suitability of β-cyclodextrin as a carrier to prepare Olmesartan medoxomil inclusion complexes. As demonstrated by both XRD and FTIR the amorphization of Olmesartan medoxomil offered an explanation for better dissolution rate with the enhancement of oral absorption.

It revealed that naringin (P-glycoprotein inhibitor) can be used a pharmaceutical excipient for inclusion complex to increase in intestinal permeability and in-vivo pharmacokinetic performance of olmesartan.

However, further studies are required for comprehensive, systematic, multi-disciplinary evaluation of various claims to make effective use of these products.

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