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Formulation and Assessment of Lipid Based Formulation of Olmesartan Medoxomil

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Abstract

Olmesartan Medoxomil (OLM) is an angiotensin II receptor blocker antihypertensive agent. The aim of the present study investigation was to develop a Lipid Based Formulation (LBF) to enhance the dissolution as well as the oral bioavailability of poorly water soluble OLM. LBF classified into different four types. Among them Type I formulation and Type IV formulation was prepared. The solubility of OLM was determined in different oil, surfactant and co-surfactant. In Type I formulation, OLM (25mg) was dissolved in Capmul MCM C8 (500 mg) and sunflower oil (500 mg). LBFs were further evaluated for its percentage transmittance, Robustness to dilution, stability and drug content. The optimized formulation of OLM-loaded LBF exhibited complete *in vitro* drug release in 120 min compared the plain drug. These results suggest the potential use of LBF to improve dissolution of poorly water soluble OLM.

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Introduction

Olmesartan medoxomil (OLM) is a non peptide, orally active and specific angiotensin II antagonist acting on the AT1 receptor subtype. OLM is poorly soluble and aqueous solubility is reported to be less than 1 mg/ml. The drug is rapidly absorbed following

oral administration, with a bioavailability approximately 26%. Peak plasma concentrations of OLM occur 1 to 2 h after an oral dose and are highly bound to plasma proteins (99%) [1]. Rapid onset of action is desirable to provide fast relief in the treatment of heart failure. Therefore, it is necessary to enhance the aqueous solubility and dissolution rate of OLM to obtain faster on set of action, minimize the variability in absorption, and improve its overall oral bioavailability. The various formulation strategies reported in the literature include the use of surfactants, cyclodextrin complexes, nanoparticles, solid dispersions, micronization, lipids, and permeation enhancers [2]. There has been increasing focus on the utility of lipid-based formulations are reported to assist the absorption of poorly soluble drugs by reducing the inherent limitation of slow and incomplete dissolution [3]. In addition to all these approaches, preparation of lipid-based formulation was tried to make formulation process easier. The main aim of the study was to develop Olmesartan Medoxomil Type I and IV lipid based formulation to improve upon the solubility of the Olmesartan Medoxomi which will have some bearing on the bioavailability. Type I systems are mixtures of lipophilic materials which have little or no solubility in water. Typically they are blends of food glycerides derived from vegetable oils, which are safe for oral ingestion, rapidly digested, and absorbed completely from the intestine. Because Type I systems do not contain surfactant they have very limited ability to self-disperse in water. Although precipitation may sometimes be a problem, Type I formulations are an excellent option if the drug is sufficiently soluble in mixed glyceride oils. Bioavailability may be as good from Type I formulations as Type II and Type III formulations, and Type I formulations certainly have advantages, in relation to safety and drug stability. Type IV systems are essentially pure surfactants or mixtures of surfactants and co-solvents. It is generally accepted that formulation of poorly water-soluble drugs in pure co-solvents is likely to result in precipitation of the drug. The only advantage that could be gained is the possibility that the drug precipitates as a suspension of very fine crystalline or amorphous particles [4].

Material and Method:

Material

Olmesartan Medoxonil was a kind gift from Torrent Research Centre, Ahmedabad, India. Gift samples of Acrysol K 140 (polyoxyl 40 hydrogenated castor oil) and Acrysol El 135 (Polyoxyl 35 castor oil) from Corel Pharma chem., ahmedabad, India. Captex 100 (Propylene glycol dicaprate ester), Captex 200 (Mixed diesters of caprylic / capric acid), Capmul C8 (Glycerol mono-dicaprylate), and Capmul MCM C8 was obtain from Abitec Corporation, USA as a gift sample. Transcutol P (Diethylene glycol monoethyl ether) and Labrasol (Caprylocaproyl macrogol-8 glycerides) were gifted from Gattefosse, france. Sunflower oil, Castor oil, Cotton seed oil and olive oil were purchased from market. Tween 80 (polysorbate 80), Tween 20 (polysorbate 80), Span 20, Span 80, PEG 400 (Polyethylene glycol), PG (Propylene glycol) and Methanol were procured form S. D. Fine Chemicals, Mumbai, India. All other chemicals were of analytical grade.

Method:

Solubility Studies

The solubility of OLM in various oils, surfactants, and co-surfactants was determined, respectively. 3 gm of each of the selected vehicle were added to each cap vial containing an excess of OLM. After sealing, the mixture was heated at 40°C in a water-bath to facilitate the solubilization using a vortex mixer. Mixtures were shaken with shaker at 25°C for 48 h. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min, and excess insoluble OLM was discarded by filtration using a membrane filter (0.45 µm, 13 mm, Whatman, USA). The

concentration of OLM was quantified by U. V. Spectrophometer at 257nm [5].

Formulation of Type I and IV Lipid Based Formulation (LBF)

Type I and IV Lipid based formulation was made by using different oil and different type and concentration of surfactant and co-surfactant. Different formulation was tabulated in table 1. All formulation contain 500mg ingredient respectively.

Table 1: Different formulation of Type I & Type IV LBF.

Formulation	Batch	Ingredient
Type I	S_1	Capmul MCM + 25 mg OLM
Type I	S_2	Capmul MCM C8 + 25 mg OLM
Type I	S_3	Sunflower oil + 25 mg OLM
Type IV	S_4	Acrysol K 140 +25mg OLM
Type IV	S_5	Acrysol EL 135 +25mg OLM
Type IV	S_6	Acrysol K 140: Transcutol-P (1:1)+ 30 mg OLM
Type IV	S_7	Acrysol El 135: Transcutol-P (1:1)+ 30 mg OLM

Macroscopic Evaluation

Macroscopic analysis was carried out in order to observe the homogeneity of lipid formulations. Any change in color and transparency or phase separation occurred during normal storage condition (37±2°C) was observed in optimized lipid formulation.

Transmission test

Stability of optimized lipid formulation with respect to dilution was checked by measuring transmittance through U.V. Spectrophotometer (UV-1700 SHIMADZU). Transmittance of samples was measured at 650nm and for each sample three replicate assays were performed [6].

Robustness to dilution

Robustness of formulation to dilution was studied as per Date and Nagarsenker's method with slight modification [7]. Formulation was diluted to 100 and 1000 times with various media viz. water, pH 1.2 buffer and pH 6.8 buffer. The diluted formulation were stored for 12 h and observed for any signs of phase separation or drug precipitation.

Stability

Temperature Stability

Shelf life as a function of time and storage temperature was evaluated by visual inspection of the lipid formulation at different time period. Lipid formulation was diluted with purified distilled water and to check the temperature stability of samples, they were kept at three different temperature range (2-8°C (refrigerator), Room temperature) and observed for any evidences of phase separation, flocculation or precipitation.

Centrifugation

In order to estimate metastable systems, the optimized lipid based formulation was diluted with purified distilled water. Thenformulation was centrifuged (Remi Laboratories, Mumbai, India) at 1000 rpm for 15 minute at 0°C and observed for any change in homogeneity of microemulsions [8].

***In vitro* release of OLM**

In vitro drug release of OLM from optimized LBF was performed by a conventional method. A hard gelatin capsule size "0" filled with percentage (equivalent to 10 mg OLM) and pure drug (10 mg) separately ware put into each of the 900 ml phosphate buffer pH 6.8 at 37±0.5°C with 50 rpm rotating speed. Samples (10 ml) were withdrawn at

regular time intervals (5, 10, 15, 30, 45, 60, 90 and 120 min) and filtered using a 0.45µm filter. An equal volume of the respective dissolution medium was added to maintain the volume constant. The drug content of the samples was assayed using UV visible spectrophotometric method. All measurements were performed in triplicate from three independent samples [9].

Statistical analysis

The U.S FDA's guidance for industry on dissolution testing of Immediate release (IR) solid oral dose forms (1997), as well as SUPAC-IR (1995), SUPAC-MR (1997) and bioavailability and bioequivalence study guidance for oral dosage forms, describes the model independent mathematical approach proposed by Moore and Flanner for calculating a dissimilarity factor *f1* of dissolution across a suitable time interval. The similarity factor *f2* is a measure of similarity in the percentage dissolution between two dissolution curves and is defined by following equation: [10]

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t \left(R_t - T_t \right)^2 \right]^{-0.5} x100 \right\}$$

Where n is the number of withdrawal points, r_t is the percentage dissolved of the reference at the point t (marketed product of LOV) and t_t is the percentage dissolved of the test at the time point t (SMEDDS formulation). A value 100% for the similarity factor (*f2*) suggests that the test and reference profiles are identical. Value between 50 to 100 indicate that the dissolution profile are similar value imply and increase in dissimilarity between release profile.

Determination of drug content

OLM from optimized lipid formulation was extracted in methanol using the sonication technique. The methanolic extract was analyzed for OLM content spectrophotometrically at a wavelength of 257 nm after suitable dilution [5].

RESULTS AND DISCUSSION

Solubility Study (Screening of Oil)

Solubility studies were aimed at identifying a suitable oily phase for development of OLM LBF. Identifying the suitable oil having a maximal solubilizing potential for the drug under investigation is very important to achieve optimum drug loading [11,12]. Solubility of OLM in various oily phases is presented in Table 2 and Figure 1. Among the various oily phases that screened, Capmul MCM C8 could solubilize the target amount of OLM (87.89 mg) in relatively quantity of 1gm. The experiment was repeated in triplicate and the result represents the mean value (mg/gm ± SD)

Table 2: Solubility of OLM in different oil

Oil	Solubility (mg/gm)
Captex 100	10.78 ± 1.34
Captex 200	13.45 ± 1.09
Capmul MCM	37.89 ± 2.78
Capmul MCM C8	87.89 ± 4.56
Sunflower oil	94.45 ± 3.67
Cotton oil	53.78 ± 2.30
Cotton seed oil	34.65 ± 1.89
Olive oil	36.76 ± 2.78

[a] Data expressed as mg/gm ± SD (n=3)

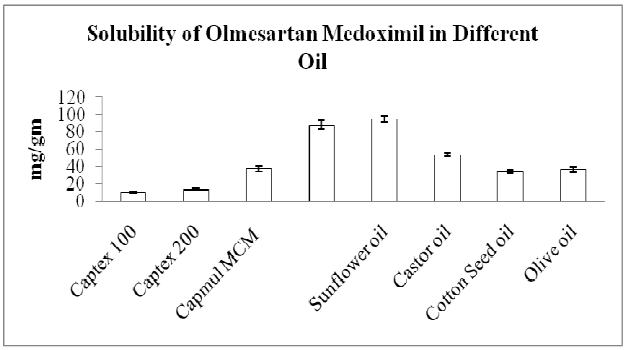

Figure:1 Show the solubility of OLM in differentoil

Screening of Surfactant

Nonionic surfactants are generally considered less toxic than ionic surfactants. They are usually accepted oral ingestion. In this study, the five nonionic surfactants (Tween 80, Tween 20, Acrysol K 140. Acrysol El 135, Span 20, Span 80 and Labrasol) were selected, of which some are reported

to have bioactive effects, like lymphotropic characters by Tween 80, Tween 20, and Span 80 and inhibitory effect on p-gp and CYP enzyme such as Acrysol K 140. Acrysol El 135. These findings were confirmed by Zhang et al., 2003 [13], who demonstrated increased AUC and Cmax for orally administered digoxin in rats when co-administered with Cremophor®. Solubility of OLM in various surfactant phases is presented in Table 3 and Figure 2. Among the various non-ionic surfactants that screened, Acrysol K 140 could solubilize the large amount of OLM (110.56 mg) in relatively quantity of 1gm. The experiment was repeated in triplicate and the result represents the mean value (mg/gm ± SD).

Table 3: Solubility data of OLM in different surfactant

Surfactant	Solubility (mg/gm)
Acrysol K 140	110.56 ±3.67
Acrysol K 135	108.67 ± 2.35
Tween 20	65.43 ± 2.38
Tween 80	76.52 ±2.67
Span 20	55.76 ± 1.23
Span 80	71.56 ± 2.67
Labrasol	54.5 ± 1.23

[a] Data expressed as mg/gm ± SD (n=3)

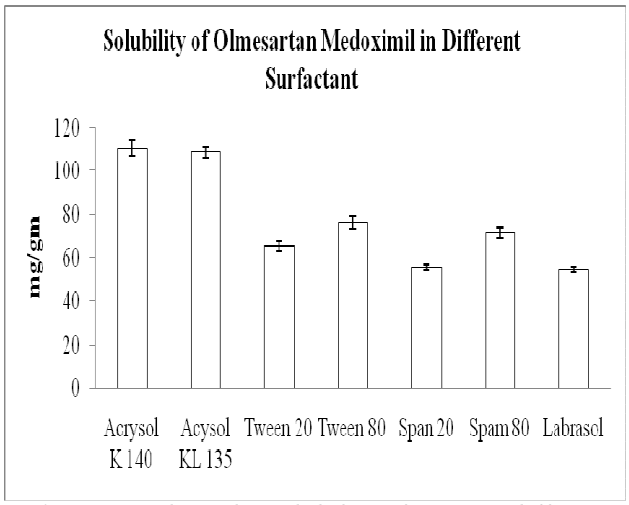

Figure 2: Show the solubility of OLM in different Surfactant

Screening of Co-surfactant

Co-surfactant is required with surfactant in LBF Type IV for reported to improved dispersibility and drug absorption from the formulation[6]. In view of the current investigation, three co-surfactant, namely PEG 400, PG and Transcutol P, as depicted in table 4, Transmuctol-P exihibited good emulsification with Acrysol K 140 and Acrysol EL 135. The experiment was repeated in triplicate and the result represents the mean value (mg/gm ± SD).

Table 4: Solubility data of OLM in different co-surfactant

Co-surfactant	Solubility (mg/gm)[a]
Transcutol P	135.89 ± 5.78
PG	85.34 ± 3.54
PEG	67.90 ± 2.76

[a] Data expressed as mg/gm ± SD (n=3)

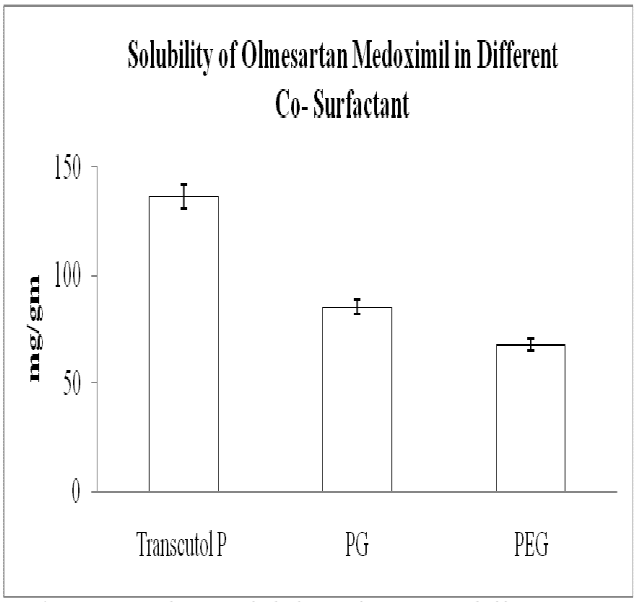

Figure 3: Show solubility of OLM in different co-surfactant

Transmission test

LBF are diluted with different medium like Water, pH 1.2 buffer and pH 6.8 buffer for 50 times and 100 times. Samples are analyzed at 650 nm. The results of transmittance value are shown in Table 5.

Table 5: Show % transmittances result of different LBF upon dilution with Water, pH 1.2 buffer and pH 6.8 buffer

Batch No.	Transmittance (%) ± S.D.					
	50 Times Dilution With Water	100 Times Dilution With Water	50 Times Dilution With 0.1 N HCL	100 Times Dilution With 0.1 N HCL	50 Times Dilution With Ph 6.8 Buffer	100 Times Dilution With Ph 6.8 Buffer
S_1	12.34 ± 0.002	13.42 ± 0.005	11.87 ± 0.004	14.23 ± 0.007	12.56 ± 0.002	13.89 ± 0.007
S_2	11.24 ± 0.002	13.49 ± 0.002	10.99 ± 0.003	12.99 ± 0.006	12.46 ± 0.009	13.34 ± 0.003
S_3	17.33 ± 0.006	18.83 ± 0.004	16.83 ± 0.003	19.39 ± 0.009	17.63 ± 0.002	20.10 ± 0.005
S_4	39.78 ± 0.007	42.68 ± 0.003	38.78 ± 0.005	43.40 ± 0.002	38.28 ± 0.003	44.43 ± 0.006
S_5	45.06 ± 0.004	48.05 ± 0.007	43.45 ± 0.006	47.46 ± 0.004	42.78 ± 0.004	46.76 ± 0.003
S_6	69.15 ± 0.002	70.85 ± 0.004	67.85 ± 0.007	69.43 ± 0.003	71.85 ± 0.002	72.54 ± 0.005
S_7	62.73 ± 0.002	65.69 ± 0.003	59.64 ± 0.002	61.89 ± 0.004	60.00 ± 0.005	65.76 ± 0.006

In Type I lipid based formulation containing only oil and Type IV type containing surfactant and co-surfactant. So, transmittance is not achieving 100 but in formulation containing 1:1 surfactant and co-surfactant then transmittance is increase than formulation containing only oil and surfactant.

Robustness to dilution

Diluted LBF did not show any precipitation or phase separation on storage in various dilutions medium. This revels that all media were robust to dilution.

Stability

Stability studies of the LBF samples were carried out by subjecting them to temperature stability and centrifugation. The temperature stability study was carried out by keeping the sample at two different temperatures (2-8^{0}C, Room temperature) for two months and visual inspection was carried out by drawing samples at monthly intervals for the subsequent months. As per the results shown in Table no 6 & 7 evidence of phase separation or any flocculation or precipitation was observed in some LBF. The few of formulation show no sign of phase separation when subjected to centrifugation at 1000 rpm for 15 minutes. Thus, it was concluded that the few of LBF was stable thermally as well as under stressful conditions.

Table 6: Temperature stability study of LBF samples for different time intervals

Batch	Phase Separation, Flocculation, precipitation			
	After 1 month		After 2 month	
	28^{0}C	Room Temperature	28^{0}C	Room Temperature
S_1	Not Seen	Not Seen	Seen	Seen
S_2	Not Seen	Not Seen	Not Seen	Not Seen
S_3	Not Seen	Not Seen	Not Seen	Not Seen
S_4	Not	Not Seen	Not	Not Seen

	Seen		Seen	
S_5	Not Seen	Not Seen	Not Seen	Not Seen
S_6	Not Seen	Not Seen	Not Seen	Not Seen
S_7	Not Seen	Not Seen	Not Seen	Not Seen

Table 7 : Centrifugation stability study of LBF samples for different time intervals

Batch	Phase Separation	
	After 1 month	After 2 month
S_1	Not Seen	Seen
S_2	Not Seen	Not Seen
S_3	Not Seen	Seen
S_4	Not Seen	Not Seen
S_5	Not Seen	Not Seen
S_6	Not Seen	Not Seen
S_7	Not Seen	Not Seen

***In-vitro* release of OLM**

A dissolution study was performed for the LBF formulation in buffer pH 6.8 and the result was compared with pure drug. The release pattern was shown in figure 4. The release pattern shows that drug release from Type I and Type IV LBD formulations faster than pure drug. Moreover, S_2 (Type I) release more than 76.89% drug release within 120 min while release rate is very slow in case of pure drug, i.e. 43.78 % within 120 min and S_4 (Type IV) release more than 89.67% drug release within 120 min. It is confirmed that any of these factors affect the bioavailability of drug.

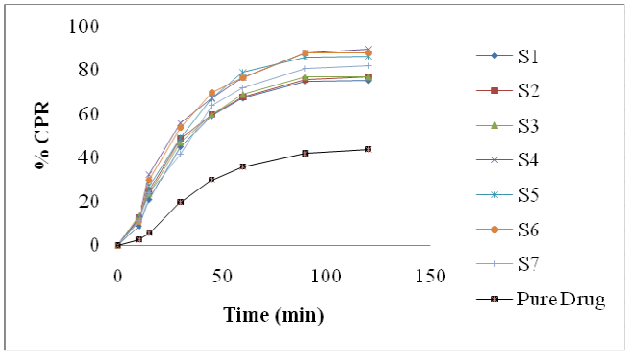

Fig.4: Show *in vitro* drug release from OLM LBF A value of 100% for the similarity factor (f_2) suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar whilst smaller values imply an increase in dissimilarity between release profiles (Moore & Flanner, 1996). Calculated *f2* values are presented in Table 8 from this Table, it is evident that the release profile of S_2 and S_4 is highly different from Pure OLM (*f2* values 30.38 and 24.46).

Table 8: Similarity factor (f_2) for release profiles of Pure OLM and all LBF in buffer pH 6.8

Batch	Similarity factor (f_2)
S_1	31.83
S_2	30.38
S_3	30.31
S_4	24.46
S_5	25.84
S_6	24.81
S_7	28.88

Determination of drug content

Drug content of the of the optimized formulation was found to be 98.76± 0.56 % (mean ± SD, n=3).

Conclusion

In this study, LBF (Type I and Type Iv) of OLM were prepared and evaluated for their *in vitro* behavior. In Type I formulations are prepared by using lipid component (oil phase) only and Type IV formulations containing surfactant and combination of surfactant and co-surfactant. Formulation S_2 and S_4 exhibited faster release profile compared to other formulation and pure drug and also stable up to 2 month. No sign of phase separation and flocculation in different temperature and centrifugal effect. But in formulation S_4 is Type IV formulation so may be sometime may be irritant and poorly tolerated in the gastrointestinal tract. Thus Type I formulation (S_2) can be regarded as a novel and commercially

feasible alternative to the current OLM formulations.

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