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Research Article

FORMULATION AND EVALUATION OF LIPID BASED FORMULATION OF VALSARTAN

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ABSTRACT

Valsartan (VAL) 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 VAL. LBF classified into different four types. Among them Type I formulation and Type IV formulation was prepared. The solubility of VAL was determined in different oil, surfactant and co-surfactant. The optimized Type I formulation contained VAL (25mg) and Capmul MCM C8 (500 mg). LBFs were further evaluated for its percentage transmittance, Robustness to dilution, stability and drug content. The optimized formulation of VAL-loaded LBF exhibited complete *in vitro* drug release in 120 minas compared the plain drug. These results suggest the potential use of LBF to improve dissolution of poorly water soluble VAL.

Keywords: Dissolution, Valsartan, Poor water solubility, Lipid Based Formulation

INTRODUCTION

Valsartan (VAL) is a non peptide, orally active and specific angiotensin II antagonist acting on the AT1 receptor subtype. The VAL heart failer trial demonstrated that the use of VAL was associated with reduced rate of heart failure related hospitalizations and mortality as well as shorter duration of hospitalization (Smith et al, 2005) VAL 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 bioa vailability of about 23%. Peak plasma concentrations of VAL occur 2 to 4 h after an oral dose and 94% to 97% of the drug is bound to plasma proteins (Brookman et al, 1997). 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 VAL 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 (Cappello et al, 2006). 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 (Charman et al, 2000). Some efforts have been made to enhance the solubility of VAL to understand its effect on the bioavailability of the drug, and valsartan/hydroxypropyl-ß - cyclodextrin complex has been reported to significantly increase the solubility and decrease the rate of valsartan degradation (Cappello et al, 2006). A gelucire 50/13-based dispersion granule formulation has also been reported very recently (Shrivastava et al, 2009). 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 valsartan Type I and IV lipid based formulation to improve upon the solubility of the valsartan 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 (Pouton et al, 2008).

MATERIAL AND METHOD

Valsartan 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.

Solubility Studies

The solubility of VAL 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 VAL. After sealing, the mixture was heated at 40^{0}C in a water-bath to facilitate the solubilization using a vortex mixer. Mixtures were shaken with shaker at 25^{0}C for 48 h. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min, and excess insoluble VAL was discarded by filtration using a membrane filter (0.45 µm, 13 mm, Whatman, USA). The concentration of VAL was quantified by U. V. Spectrophometer at 251nm (Bok et al, 2004).

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.

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±2ºC) 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 (Shen et al, 2006).

Robustness to dilution

Robustness of formulation to dilution was studied as per Date and Nagarsenker's method with slight modification (Date et al, 2007). 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.

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

Formulation	Batch	Ingredient
Type I	S_1	Capmul MCM + 25 mg VAL
Type I	S_2	Capmul MCM C8 + 25 mg VAL
Type I	S_3	Sunflower oil + 25 mg VAL
Type IV	S_4	Acrysol K 140 +25mg VAL
Type IV	S_5	Tween 80 +25mg VAL
Type IV	S_6	Acrysol K 140: Transcutol-P (1:1)+ 30 mg VAL
Type IV	S_7	Tween 80: Transcutol-P (1:1)+ 30 mg VAL

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 LBF (Ghosh et al, 2004).

***In vitro* release of VAL**

In vitro drug release of VAL from optimized LBF was performed by a conventional method. A hard gelatin capsule size "0" filled with percentage (equivalent to 10 mg VAL) and pure drug (10 mg) separately ware put into each of the 900 ml phosphate buffer pH 6.8 at 37±0.5^{0}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 (Zhang et al, 2008).

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: (Moore et al, 1996)

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

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

VAL from optimized lipid formulation was extracted in methanol using the sonication technique. The methanolic extract was analyzed for VAL content spectrophotometrically at a wavelength of 251 nm after suitable dilution (Bok et al, 2004).

RESULTS AND DISCUSSION

Solubility Study (Screening of Oil)

Solubility studies were aimed at identifying a suitable oily phase for development of VAL LBF. Identifying the suitable oil having a maximal solubilizing potential for the drug under investigation is very important to achieve optimum drug loading (Pouton et al, 2006). Solubility of VAL 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 VAL (76.5 mg) in relatively quantity of 1gm. The experiment was repeated in triplicate and the result represents the mean value (mg/gm ± SD).

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, who demonstrated increased AUC and Cmax for orally administered digoxin in rats when co-administered with Cremophor®. Solubility of VAL 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 VAL (95.4 mg) in relatively quantity of 1gm. The experiment was repeated in triplicate and the result represents the mean value (mg/gm ± SD).

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. The experiment was repeated in triplicate and the result represents the mean value (mg/gm ± SD).

Table 2: Solubility of VAL in different oil

Oil	Solubility (mg/gm)
Captex 100	5.91 ± 1.98
Captex 200	7.54 ± 1.21
Capmul MCM	29.65 ± 1.78
Capmul MCM C8	76.51 ± 3.24
Sunflower oil	73.48 ± 2.89
Cotton oil	62.78 ± 3.23
Cotton seed oil	67.24 ± 3.11
Olive oil	43.96 ± 2.98

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

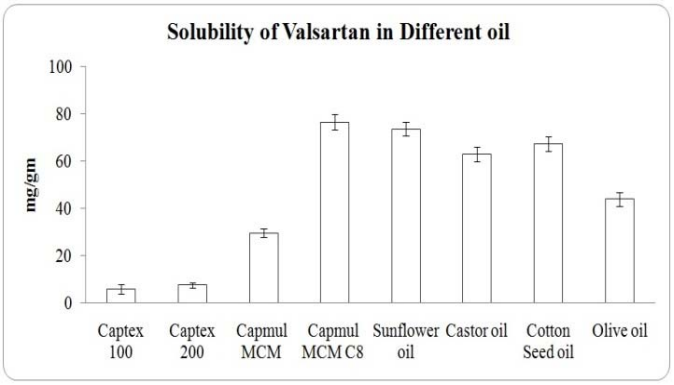

Fig. 1: Show the solubility of VAL in different oil

Table 3: Solubility data of VAL in different surfactant

Surfactant	Solubility (mg/gm)
Acrysol K 140	94.56 ± 2.51
Acrysol K 135	87.91 ± 1.45
Tween 20	69.73 ± 2.38
Tween 80	76.57 ± 2.67
Span 20	65.41 ± 1.23
Span 80	69.57 ± 1.98
Labrasol	54.52 ± 1.23

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

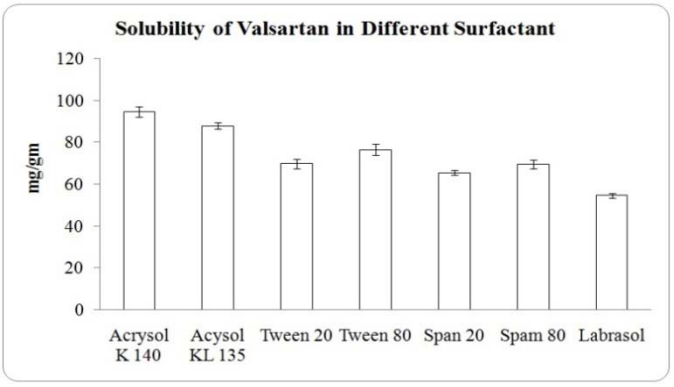

Fig. 2: Show the solubility of VAL in different Surfactant

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

Co-surfactant	Solubility (mg/gm)[a]
Transcutol P	319.51 ± 4.67
PG	109.23 ± 3.21
PEG	83.91 ± 2.89

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

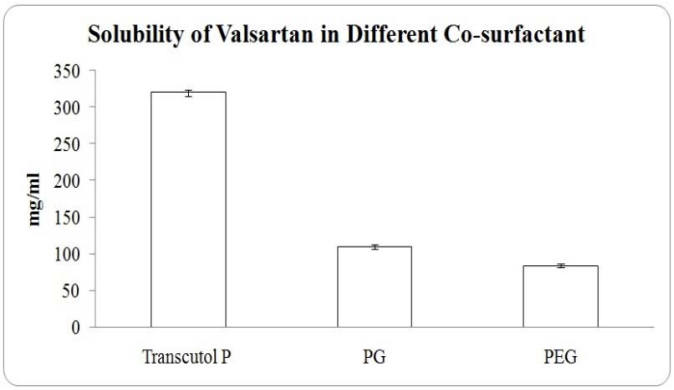

Fig. 3: Show solubility of VAL in different co-surfactant

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	14.09 ± 0.005	14.09 ± 0.005	14.09 ± 0.005	14.09 ± 0.005	14.09 ± 0.005	14.09 ± 0.005
S_2	12.99 ± 0.006	12.99 ± 0.006	12.99 ± 0.006	12.99 ± 0.006	12.99 ± 0.006	12.99 ± 0.006
S_3	16.83 ± 0.004	16.83 ± 0.004	16.83 ± 0.004	16.83 ± 0.004	16.83 ± 0.004	16.83 ± 0.004
S_4	45.78 ± 0.008	45.78 ± 0.008	45.78 ± 0.008	45.78 ± 0.008	45.78 ± 0.008	45.78 ± 0.008
S_5	39.05 ± 0.005	39.05 ± 0.005	39.05 ± 0.005	39.05 ± 0.005	39.05 ± 0.005	39.05 ± 0.005
S_6	67.85 ± 0.007	67.85 ± 0.007	67.85 ± 0.007	67.85 ± 0.007	67.85 ± 0.007	67.85 ± 0.007
S_7	56.76 ± 0.003	56.76 ± 0.003	56.76 ± 0.003	56.76 ± 0.003	56.76 ± 0.003	56.76 ± 0.003

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.

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	
	2-8^{0}C	Room temperature	2-8^{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 Seen	Not Seen	Not Seen	Not 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

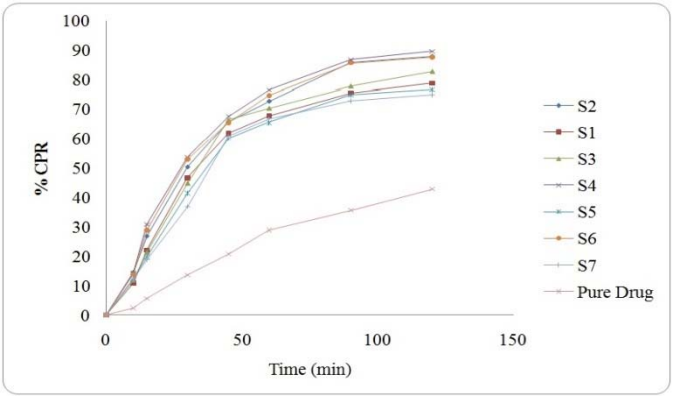

Fig. 4: Show *in vitro* drug release from VAL LBF

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 VAL (*f2* values 23.36 and 22.16).

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

Batch	Similarity factor (f_2)
S_1	26.91
S_2	23.36
S_3	25.60
S_4	22.16
S_5	28.27
S_6	22.98
S_7	28.95

***In-vitro* release of VAL**

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 87% drug release within 120 min while release rate is very slow in case of pure drug, i.e. 42% within 120 min and S_4 (Type IV) release more than 89% drug release within 120 min. It is confirmed that any of these factors affect the bioavailability of drug.

Determination of drug content

Drug content of the optimized formulation was found to be 99.34 ± 0.56 % (mean ± SD, n=3).

CONCLUSION

In this study, LBF (Type I and Type Iv) of VAL 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 VAL formulations.

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