Available online on 15.10.2023 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Development and Evaluation of Microemulsion Formualatons of Valsartan for Solubility Enhancement

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Article Info:

Article History:

Received 09 July 2023
Reviewed 19 August 2023
Accepted 27 Sep 2023
Published 15 Oct 2023

Cite this article as:

Kumari P, Kumar K, Joshi A, Chauhan V, Rajput V, Development and Evaluation of Microemulsion Formualatons of Valsartan for Solubility Enhancement, Journal of Drug Delivery and Therapeutics. 2023; 13(10):117-120
DOI: http://dx.doi.org/10.22270/jddt.v13i10.5990

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Abstract

Microemulsions have attracted considerable amount of interest as potential drug delivery vehicles largely due to their simple method of preparation, stability and their abilities to incorporate a wide range of drugs of varying solubility. O/W microemulsion is expected to increase the solubility by dissolving low water solubility compounds into its dispersed phase and to enhance the oral bioavailability by protecting the drug increasing the rate of absorption and wettability due to surfactants induced permeability changes and smaller droplet size (< 100 nm) and most importantly able to target lymphatic system.

In the present study, the drug delivery system contains Valsartan, a hydrophilic component, a lipophillic component, surfactants and co-surfactants. The objective is to provide an increased release of valsartan and increased bioavailability of valsartan. Prepared microemulsion formulations by phase-titration method were evaluated for viscosity, drug content, thermodynamic stability studies and in-vitro dissolution. Resultant microemulsion optimized formulation (ME5) shows drug release (88.2±0.16%.%). Hence, micro-emulsion of valsartan was successfully developed and evaluated.

Keywords: Microemulsion, Valsartan, solubility, evaluation.

INTRODUCTION

Microemulsions are thermodynamically stable, fluid, optically clear dispersions of four component mixtures consisting an oil phase, a water phase, surfactant and co-surfactant. When a mixture of surfactant and co-surfactant is added to a biphasic system, a thermodynamically stable, optically transparent or translucent, low viscous and isotropic microemulsion is formed[1].

Structurally, microemulsions have normal micelles solutions, reverse micelles, cores or droplets of water and oil[2].

Unlike conventional emulsions, microemulsion domains fluctuate in size and shape and undergo spontaneous coalescence and breakup. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions[3].

In 1943, Hour and Schulman visualized the existence of small emulsion like structures by electron microscopy and subsequently coined the term “microemulsions”. They prepared the first microemulsions by dispersing oil in an aqueous surfactant solution and adding an alcohol as a co-surfactant, leading to a transparent, stable formulation[4]. Formation of monophasic/biphasic system is confirmed by visual inspection. In case turbidity appears followed by a phase separation, the samples shall be considered as biphasic[5]. The area covered by these points is considered as the microemulsion region of existence. The phase behavior of surfactants, which form microemulsion in absence of co-surfactant, can be completely represented by ternary diagram[6].

Valsartan belongs to the angiotensin II receptor blocker (ARB) family of drugs, which also includes telmisartan, candesartan, losartan, olmesartan, and irbesartan. ARBs selectively bind to angiotensin receptor 1 (AT1) and prevent the protein angiotensin II from binding and exerting its hypertensive effects, which include vasoconstriction, stimulation and synthesis of aldosterone and ADH[7]. Overall, valsartan's physiologic effects lead to reduced blood pressure, lower aldosterone levels, reduced cardiac activity, and increased excretion of sodium[8].

In the present study an attempt was made to increase solubility of Valsartan by the use of different oils, surfactants and co-surfactants for the preparation of microemulsion formulatoins and their evaluation.

MATERIALS AND METHODS

Materials: Valsartan was a gift sample from UANFARMA, Maharashtra (India), Tween 60, PEG 200, PEG 400, Tween 80, Span 80, Labrasol, Sodium Hydroxide pellets, Octanol, HCl, Di-Sodium Hydrogen Phosphate AR, Propylene glycol & Iso propyl alcohol were from vendor Sweta Scientific, Lucknow, Uttar Pradesh and Castor Oil, Soyabean Oil & Peanut oil were from vendor Jindal Refineries Ltd, Uttarakhand and Capmul Pg-12 was from CDH, Delhi and Linseed oil, Cottonseed oil were from S L Enterprises, Uttarakhand.

Selection of the oil phase: Selection of the oil phase was based upon the maximum solubility of the drug. Different oils including castor oil, Capmul Pg-12, soyabean oil, Kollisolv GTA, MCT were taken for solubility studies. Based on the solubility Capmul Pg-12 was selected as the oil phase.

Selection of surfactants and co surfactant: Solubility of Valsartan was checked in different surfactants and co surfactants. Emulsification efficiency of surfactants and co-surfactants were examined to check their ability to emulsify selected oil. To determine the emulsification ability, equal amount of surfactant was mixed with drug and after proper dilution, it was monitored for transmittance at 638nm using UV-Vis spectrophotometer. Similarly co-surfactant was selected based on their ability to form stable and clear micro emulsion at a minimum concentration[9].

Solubility Analysis: About 10gm of oil was accurately weighed in 25ml glass beaker and 100mg of Valsartan was added into it, followed by stirring on magnetic stirrer at moderate speed to dissolve the drug. When drug was dissolved completely another 10mg Valsartan of was added and stirring was continued. Addition of drug was continued until the saturated solution is obtained. Finally, the total amount of drug consumed was determined by using UV-spectrophotometer at 250nm. In the similar way solubility of Valsartan was checked in different surfactants and co-surfactants[10].

Preparation of drug loaded microemulsion: Formulations were developed using phase titration method. A predetermined amount of Valsartan (100) mg was dissolved in the required quantity of Capmul Pg-12 (oil). Tween-80**:** (surfactant) and Propylene glycol (co-surfactant) were added to the above mixture in different ratio. Distilled water was added gradually with continuous stirring, which resulted in the formulation of a transparent and homogenous microemulsion[11].

Characterization of micro emulsion

Percentage Transmittance: Transparency of micro emulsion formulation was determined by measuring percentage transmittance through U.V. Spectrophotometer at 638 nm with distilled water taken as blank and three replicates were performed for each sample[12].

pH determination: The apparent pH of all micro emulsions was determined at 25°C by immersing the electrode directly into the micro emulsion using a digital pH meter[13].

Refractive index: Refractive indexes of the prepared micro emulsions were determined at 25°C by Abbe's refractometer by placing one drop of micro emulsion on the slide[14].

Viscosity measurement: The viscosity of the prepared micro emulsion was measured at 25°C at 60 rpm by LV spindle no. 63 using a Brookfield viscometer[15].

Determination of Drug Content: The drug content of the micro emulsion formulation was determined by dissolving 1 ml (equivalent to 10 mg drug) of the formulation in 10ml of methanol. After suitable dilutions with methanol, absorbance was determined using the UV spectrophotometer keeping blank micro emulsion as control at wavelength 250 nm and three replicates were performed for each sample[16].

Drug solubility study: Valsartan was added in excess to the optimized microemulsion formulation as well as each individual ingredient of the formulation. After continuous stirring for 4 hours at room temperature, samples were withdrawn and centrifuged for 10 minutes. The amount of drug soluble in optimized formulation as well as each individual ingredient of the formulation was calculated by subtracting the drug in the sediment from the total amount of drug added. The solubility of drug in microemulsion was compared with respect to its individual ingredients[17].

***In-vitro* drug release:** The diffusion study was carried out on a modified Franz diffusion cell of volume 20ml. The receptor compartment was filled with 20 ml of Phosphate buffer (pH 7.4). The donor compartment was fixed with cellophane membrane (Cut Off weight = 1000 Da) contains Valsartan microemulsion formulation (equivalent to 5 mg of drug) and plain drug solution separately. At predetermined time intervals samples were withdrawn from receptor compartment and analyzed for drug content by UV Spectrophotometer at 250 nm[18].

Drug release kinetic data analysis: Release data was evaluated through PCP disso software for the kinetic models. First, and Peppas and Korsmeyer model were studied[19].

RESULTS

Table 1: Solubility of Valsartan in various oils, surfactants and co-surfactants.

Oils	Solubility mg /ml	Surfactant	Solubility mg/ml	Co-surfactant	Solubility mg/ml
Castor Oil	1.33±0.20	Span 80	10.65±2.31	PEG 200	18.64±0.57
Soyabean Oil	0.54±0.01	Tween 80	13.43±0.77	PEG 400	7.65±0.61
Peanut oil	0.684±0.0091	Labrasol	12.63±0.31	Propylene glycol	25.97±1.05
Capmul Pg-12	14.3443±0.0182	Tween-60	11.55±2.31	Iso propyl alcohol	0.95±0.03
Linseed oil	1.3453±0.0122				
Cottonseed oil	0.749±0.0095				

Table 2: Emulsification efficiency with surfactants and selected oil (Capmul Pg-12).

Surfactant	% Transmittance	HLB Value
Tween-60	86.147±0.0172	14.9
Tween-80	87.127±0.0241	15
Labrasol	75.271±0.0218	14

Table 3: Emulsification efficiency with co surfactants and selected surfactant (Tween-80).

Co surfactant	% Transmittance	HLB Value
PEG 200	71.151±0.0158	5-6
PEG 400	73.132±0.0141	8-9
Propylene glycol	79.263±0.0231	11.6

Table 4: Composition of batches for Valsartan micro emulsion.

Formulation code	Smix ratio	% w/w composition		
		% Oil	% Smix	% Water
ME1	1:1	30	60	10
ME2	1:2	60	35	5
ME3	1:3	35	60	10
ME4	2:1	50	40	10
ME5	3:1	40	55	5

Table 5: Evaluation parameters of prepared Valsartan micro emulsion formulations.

Batch	Transmittance (%)	pH	Refractive index	Viscosity (cp)	Drug content (%)	Solubility mg/ml
ME1	99.26 ± 0.08	4.16 ± 0.18	1.3628±0.008	65.23±0.8	98.57± 0.18	26.67±0.07
ME2	99.32 ± 0.11	3.86 ± 0.12	1.3530 ± 0.005	66.46±0.7	99.42 ± 0.14	27.47±0.12
ME3	99.53 ± 0.23	3.92 ± 0.21	1.3618 ± 0.003	71.56±0.77	99.11 ± 0.03	28.57±0.07
ME4	98.47 ±0.09	3.74 ± 0.08	1.3720 ± 0.008	69.43±0.34	99.62 ± 0.12	26.37±0.05
ME5	98.71 ± 0.21	4.22 ± 0.22	1.3218±0.016	70.36±0.74	98.43 ± 0.14	30.77±0.05

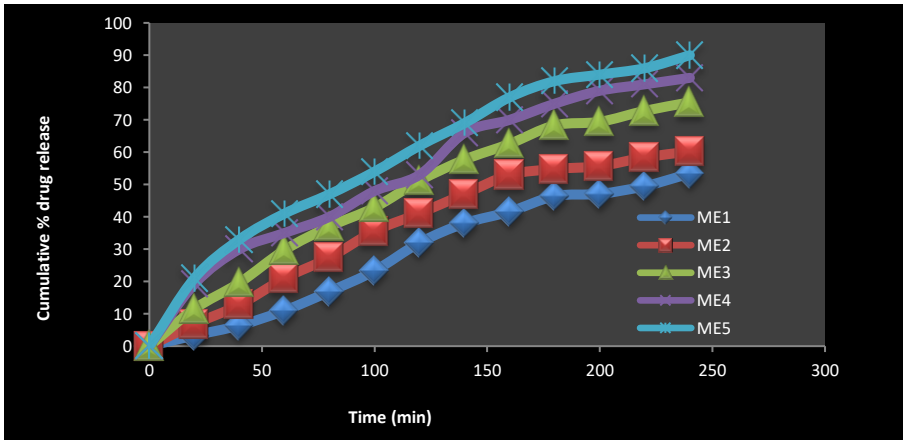

Figure 1: *In vitro* study of prepared Valsartan micro emulsion formulations.

Table 6: Different release models for Valsartan micro emulsion formulations.

Batch	Kinetic model	Parameters
ME1	Peppas and Korsmeyer	R = 0.941, K1 = 4.334, n = 0.860
ME2	Peppas and Korsmeyer	R = 0.964, K1 = 4.247, n = 0.754
ME3	First order	R = 0.942, K1 = 5.39, n = 0.850
ME4	Peppas and Korsmeyer	R = 0.954, K1= -0.080
ME5	Peppas and Korsmeyer	R = 0.973, K1 = 7.812, n = 0.872

DISCUSSION

For present study Valsartan was obtained as a Gift sample from UANFARMA, Maharashtra India. The drug was authenticated by different test i.e. solubility, melting point, test according to IP and analytical methodology was performed on sample to justify the authenticity of sample. The m.p. detected was in the range of 115-117°C.

Phase behavior investigations of this system demonstrated the suitable approach to determine the water phase, oil phase, surfactant concentration, and co surfactant concentration with which the transparent, one-phase, low-viscous micro emulsion system was formed[20,21].

Characterization of the micro emulsion formulations

Total five formulations were developed to enhance the solubility of the Valsartan. Prepared formulations were further studied for different parameters including percent transmittance, drug content, pH determination, refractive index, viscosity, drug release.

Refractive index: The refractive index for the micro emulsion formulations was found to be in the range of 1.3218±0.016 to 1.3720 ± 0.008.

Drug Content: The drug content was found to be in the range of 98.43 ± 0.14 to 99.62 ± 0.12 % in the micro emulsion formulations.

Viscosity: The Viscosity was found to be in the range of 65.23±0.8 to 71.56±0.77 % in the micro emulsion formulations. The viscosity of the micro emulsion increased with increasing concentration of the surfactant[22].

Percentage Transmittance: The percent transmission carried out on UV spectrophotometer at 250 nm was found to be in the range of 98.47 ±0.09 to 99.53 ± 0.23 % for all which confirms good transparent nature of formulations.

pH determination: For the micro emulsion formulations, the pH value was found to be in the range of 3.74 ± 0.08 to 4.22 ± 0.22.

Drug release studies: It was seen that after 4 hours of diffusion, the drug released from the formulation ME5 faster and more than that of the other ratios i.e., 88.2±0.16%.

Kinetic modeling for transdermal patches: In present study PCP disso Version 2 software was used in for the estimation of release pattern. *In-vitro* release data were plotted in 2 different models i.e. first and Korsemeyer peppas. It was observed that release was governed by the diffusion process[23].

CONCLUSION:

In present study different formulations of Valsartan was formulated as microemulsion with an aim of solubility enhancement. On basis of different properties micro emulsion formulations of ME5 batch was found to be optimum. Study concludes that by the means of micro emulsion formulations solubility of Valsartan can be enhanced.

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