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Original Article

IN-VITRO IN-VIVO STUDIES OF LAMOTRIGINE TABLETS PREPARED BY HOT MELT EXTRUSION TECHNIQUE

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ABSTRACT

Objective: Present study deals with improvement in dissolution and bioavailability of poorly water soluble Lamotrigine (Lamo), an antiepileptic drug (AED) of phenyltriazine class. Formulation of poorly water soluble drug for oral delivery is one of the biggest challenge. Amongst all the approaches, the novel solid dispersion (SD) technique known as hot melt extrusion (HME) has found to be the most widely used method in improving dissolution and bioavailability.

Methods: Dissolution enhancement of Lamo were done by HME technology where crystalline form of API is converted to amorphous form using hydrophilic polymer Kollidon VA64. Plasticizers like Polyethylene glycol (PEG 4000), polyoxyl 35 castor oil (Cremophor EL) and Sorbiton monolaurate (Montane 20PHA) were used. Physical blends of drug, polymer and plasticizer were prepared in the ratio of 1:1:0.1. These physical mixtures were subjected to melt and the resultant formulations were subjected to physical characterization, dissolution, permeability and in vivo testing. Pharmacokinetics of Lamo was studied in rats. Drug efflux pump like P-glycoprotein (P-gp) was recognized to posses' functional role in determining the pharmacokinetics of drugs.

Results: Drug release showed the similar profile for all the HME formulations while the permeability studies showed improved permeability of formulations containing Montane 20PHA. In comparison to Non HME, HME formulations showed a significant enhancement in permeability. SD prepared by Cremophor EL resulted in 765.22% enhancement in extent of absorption.

Conclusion: HME technology could be a promising formulation approach to enhance the dissolution and bioavailability of Lamo.

Keywords- Lamo, HME, *In vivo*, Kollidon VA64, Permeability.

INTRODUCTION

Lamo is an AED of the phenyltriazine class. Its chemical name is 3, 5-diamino-6-(2,3-dichlorophenyl)-as-triazine [1], Lamo is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M Hydrochoric acid (HCl) (4.1 mg/mL at 25ºC) [1]. Lamo belongs to the biopharmaceutical classification system (BCS) Class II, [2] for such hydrophobic compound, poor solubility would result in a slow dissolution and hence low oral bioavailability, which may limit its further clinical application.

Majority of the drugs are administered by the preoral route. Many hurdles starting from drug dissolution in gastrointestinal fluid to first pass metabolism are due to various physicochemical and biopharmaceutical problems. It was recently identified that drug efflux pumps like P-gp are playing major role in altering the pharmacokinetics of various drugs and particularly associated with poor bioavailability in co-ordination with gut wall metabolism. Thus, a deep insight and thorough understanding of P-gp, its physiological and biochemical role in effluxing drugs is worthwhile, in order to have an opportunity to improve the bioavailability of drugs restricted by P-gp [3].

Improved clinical efficacy of various drugs observed by P-gp inhibition, P-gp inhibitors are gaining recognition to improve bioavailability by inhibiting P-gp in intestine, brain, liver and kidneys. P-gp can be inhibited (i) by blocking drug binding site either competitively. Non-competitive or allosterically; (ii) by interfering ATP hydrolysis; and (iii) by altering integrity of cell membrane lipids [3].

The bioavailability enhancement of poorly water soluble drugs by use of Pgp inhibitors finds to be improving by use of various plasticizers. Out of all the plasticizers of this study Cremophor EL [4] have been used as Pgp inhibitor for this study. Lamo is a strong substrate of Pgp activity. Inhibition of Pgp activity improves intestinal absorption and tissue distribution while reducing the substrate metabolism and its elimination. SD technique namely the HME was used for the preparation of formulations which were further subjected to pharmacokinetic study. Plasticisers are included to the polymers to facilitate thermal processing, to modify drug release from polymeric system and enhance mechanical properties and surface appearance of dosage form. When plasticisers are added to the polymers the flexibility of the polymers is increased by increasing the intermolecular separation of polymer molecules which results in reduction in glass transition temperature (Tg), polymer melt viscosity and tensile strength [5].

Various approaches are available to improve dissolution rate of poorly water-soluble drug, including the use of surfactants, inclusion complexation, drug micronization into an amorphous form and SD. [6] In the SD, the drug may be dispersed or solubilized within a polymeric carrier at molecular levels or in the amorphous state, and provide a large surface which leads to significant enhancement in the dissolution process. The improvement in dissolution is mainly attributed to the reduction in particle size, increase in surface area and reduction in crystallinity. Furthermore, no energy is required to breakup the crystal lattice of a drug during the dissolution process, and drug solubility and wettability may be improved by surrounding hydrophilic polymers used in SD. In comparison with traditional methods for preparation of SD, HME is a promising novel technology [7] for improving the bioavailability of water insoluble drugs, and presents many advantages for pharmaceutical applications. It can be used as a continuous process with the absence of aqueous or organic solvents and subsequent drying steps, which makes scaling up easier. In addition, intense blending and agitation during the process prevents the aggregation of drug particles suspending in the molten polymer, leading to a more homogeneous dispersion of fine particles. However, not all the thermal plastic polymer carriers are compatible with the drugs and suitable carriers as well, the drug/polymer ratio for a specific drug need to be optimized. In the present studies, we attempted to improve dissolution and bioavailability of Lamo by preparation of SD with HME technique. Hydrophilic polymer with certain Tg and backbones will be used to

prepare SD. Further pharmacokinetics of Lamo in rats was investigated to evaluate the in vivo performance of prepared SD.

MATERIALS AND METHODS

Materials

Lamo was obtained as a gift sample from Emcure Pharmaceuticals ltd (Pune) and all other chemicals were obtained from the college source.

Animals: Wistar Rats ranging from about 230-290g body weight approximately were used in the study.

Prior consent approval was taken from the animal ethical committee. In vivo study protocols were approved by the Institutional Animal Ethics Committee (Regd. No RCPIPER/IAEC/07-2013-14).

Methods

Optimization of drug: polymer ratio

Solubility of Lamo and polymer was checked in different solvents such as methanol, ethanol and water. Both the drug and polymer were soluble in ethanol and hence selected as solvent for optimization of drug: polymer ratio. Drug and polymer (1:1 to 1:5) were solubilized in ethanol. The obtained solution was then poured into petri plates and films were cast [8] by the solvent evaporation method and were observed after 24 hrs at room temperature for their appearance.

Preparation of HME and NHME formulation

Different concentrations of plasticizers in the range of 10%w/w - 30%w/w of polymer quantity were studied. Physical mixture of drug, polymer and plasticizer were subjected to melt extrusion process. The HME process was carried out using Thermo Scientific Prism Lab Model co-rotating intermeshing twin screw extruder with L/D of 40/1. [9] The screw speed was adjusted to 100 rpm resulting in residence time in the extruder of less than 1 min along with the barrel (melting zone) temperature of 220ºC [11]. Physical mixtures of various formulations were passed through the hot melt extruder. Melt extrudates were cooled at room temperature. Extrudes were milled using the hammer mill, involving coarse milling, fine milling and screening. Milled HME granules were then lubricated and subsequently compressed into tablets. NHME formulation was prepared by direct compression method.

Solubility

Solubility of Lamo was measured in distilled water. An excess amount of the drug was added to 50 ml conical flask and was kept under shaking for 72 hrs (Rotary shaker, Biomedica). Saturated solution was filtered through 0.45 µ membrane filter, absorbance of filtered solutions were determined and amount of drug solubilized was calculated.

Dissolution [12]

Tablets were evaluated for dissolution testing using:

Medium: 0.1 N HCl; 900 mL

Apparatus 2: 50 rpm

Time: upto 45 min

Permeability studies

The prepared tablets were subjected to in vitro permeability test using dialysis membrane LA401 [13, 14]. Where the tablets were placed in the dialysis membrane along with the dissolution medium. This membrane tube was then introduced into the vessel just above the paddle and below the upper level of dissolution medium.

Medium: 0.1 N HCl; 900 mL

Apparatus 2: 50 rpm

Time: up to 7 hrs

In vivo studies

pharmacokinetics evaluation of Lamo+Kollidon VA64+PEG4000 (1:1:0.1), Lamo+Kollidon VA64+ Cremophor EL (1:1:0.1) and Lamo+Kollidon VA64+Montane 20PHA (1:1:0.1) optimised SD were used for in vivo studies in rats weighing 230-290 gm (n=4) of either sex at a dose equivalent to 50 mg/kg Lamo in comparison to Lamo pure drug. In vivo study protocols were approved by the Institutional Animal Ethics Committee (Regd. No RCPIPER/IAEC/07-2013-14).

Collection of blood sample: [15]

200 µL blood samples were collected (into eppendorf tubes containing 20 µL of heparin solution) through tail vein from rats under light ether anesthesia at 30 min, 1 hour, 3 hour, 5 hour and 8 hour after oral administration.

Drug solution

Lamo 10 mg/mL suspension in 0.5% carboxy methyl cellulose (CMC*) was prepared immediately before administration. Polymeric formulations were prepared as 20 mg/mL suspensions in 0.5 % CMC* immediately before administration.

Dose

50mg/kg of Lamo oral (As in Table 1)

Table 1: Lamo doses to rats

Rat No	Body weight (G)	Dose (ml) at 50 mg/kg	Study group
1.	267	1.34	Lamo
2.	248	1.24	Lamo
3.	254	1.27	Lamo
4.	243	1.22	Lamo
5.	276	1.38	FormulationL1
6.	255	1.28	FormulationL1
7.	268	1.34	FormulationL1
8.	274	1.37	FormulationL1
9.	244	1.22	FormulationL2
10.	250	1.25	FormulationL2
11.	278	1.39	FormulationL2
12.	267	1.34	FormulationL2
13.	245	1.23	FormulationL3
14.	263	1.32	FormulationL3
15.	264	1.32	FormulationL3
16.	254	1.27	FormulationL3

Table 2: Preparation of standard solution in plasma

Std drug solution (prepared in Methanol) (µg/ml)	Amt of plasma (µl)	Amount added (µl)	Final concentration in Plasma (µg/ml)
200	995	5	1
200	990	10	2
200	975	25	5
200	963.5	37.5	7.5
2000	995	05	10
2000	990	10	20

Collection of blood samples

200 µL blood samples were collected (into eppendorf tubes containing 20 µL of heparin solution) through tail vein from rats under light ether anesthesia at 30 min, 1 hour, 3 hour, 5 hour and 8 hour after oral administration.

Calibration curve: (As in figure 4)

Calibration curve was done using plasma concentrations of 1, 2, 5, 7.5, 10 and 20µg/ml.

Preparation of standard solutions in plasma: (As in Table 2)

Extraction procedure for the plasma samples and calibration curve related samples was as follows

Extraction procedure

Blood samples were set aside for 20 minutes for coagulation. Coagulated blood samples were centrifuged at 1500 rpm for 10 minutes for separation of serum. To 75 µL of serum sample, 10 µL of internal standard (100 ppm methylparaben solution in methanol) and 30 µL of 1.0 N NaOH were added and this mixture was extracted with 2.5 mL ethyl acetate twice. After addition of ethylacetate, each time the samples were vortexed for 5 minutes. The vortexed samples were centrifuged at 2000 rpm for 10 minutes. Ethylacetate layers were pooled and dried at room temperature. The dried ethylacetate extracts were reconstituted in 200 µL mobile phase, filtered through 0.2 µ filter and processed for HPLC analysis as stated below.

HPLC analysis: [15]

The HPLC system is Agilent 1200 HPLC, a gradient quaternary system (having four ports/reservoirs for mobile phase), a manual rheodyne injector of 20 µm loop with DAD detector (diode array detector system).

- The HPLC column used in this study was Luna C 18 (2) stationary phase with 25 cm length, 4.6 mm internal diameter and 5 µm particle size.

HPLC analysis of standard mixture of Lamo and methyl paraben

The different methods were tried to obtain Lamo peak well resolved from the peak of internal standard Methyl Paraben. It is necessary that the standard mixture of Lamo and Methyl Paraben should pass the system suitability parameters like capacity factor, number of theoretical plates, tailing factor and resolution. With the optimized chromatographic parameters (stationary phase, mobile phase, flow rate, detection wavelength, volume of injection applied) the standard mixture of Lamo and Methyl Paraben was well resolved.

- Initially, the sample of Lamo and Methyl Paraben were dissolved in Methanol (as all the compounds are soluble in Methanol).
- Then, dilution of all the samples made with mobile phase [Lamo (5 ppm) + Methyl Paraben (5 ppm)] was performed.
- The column was saturated with mobile phase with 1 mL/min flow rate.

HPLC instrument

Instrument Name: Agilent 1200 series with photodiode array detector

HPLC details and procedure

Column: Luna C18 (2) New Column

Mobile Phase: Methanol: Water (80:20, v/v)

Flow rate: 1 mL/min

Wavelength of detection: 286 nm

RESULTS AND DISCUSSION

Based on film casting method 1:1 ratio of Drug: Polymer was optimized as no recrystallization of API was observed in the film after 48 hours of storage. Recrystallization was observed in sample of pure drug only. Based on the observations it can be concluded that 1:1 drug: polymer ratio was sufficient to hold the amorphous form of API in solid solution. The use of 10%w/w concentration of plasticizers gave same solubility enhancement as compared to 20%w/w and 30%w/w concentration. So 10%w/w concentration of plasticizer was optimized in the formulations and only these formulations were subjected for further study like dissolution, permeability and in vivo study. Foremost objective of this study is to enhance solubility of Lamo, complete melting of drug in polymeric matrix is necessary, so temperature of melting zone was set at 220ºC as API melting point is 216ºC - 218ºC. Polymer can't degrade at HME processing temperature as its degradation temperature is above 230ºC. HME processing time was maintained less than 1 min with the help of screw speed so as to avoid degradation of drug and polymer as residence time is directly related to degradation.

Kollidon VA 64 is a hydrophilic polymer and form a gel on the surface of tablet when comes in contact with dissolution media. Tablets prepared with HME technology shows disintegration pattern by erosion mechanism.

The disintegration time (DT) of these tablets was two times more than DT of NHME formulation. At first time point dissolution of HME formulations was slower than NHME formulations, due to higher DT of tablets, thereafter both approaches shows similar dissolution profiles.

As Lamo is slightly soluble in 0.1N HCl, complete release (Figure 1) was observed at 45 min time point. Different types of plasticizers did not show any effect on dissolution rate or present dissolution method was unable to discriminate the formulation changes (types of plasticizers) in dissolution profile. So, author had taken support of in vitro permeability study to evaluate the effect of type of plasticizers.

Dissolution results are interpreted with the help of different dissolution models.

Table 3: Solubility studies

10 % Plasticizer				
Sample	Drug	HME with PEG 4000	HME with Cremophor EL	HME with Montane 20 PHA
Solubility (µg/mL)	70.15	100.09	370.91	310.66

Solubility of formulation containing 10% cremophor EL shows maximum improvement in solubility followed by Montane 20PHA and PEG4000.

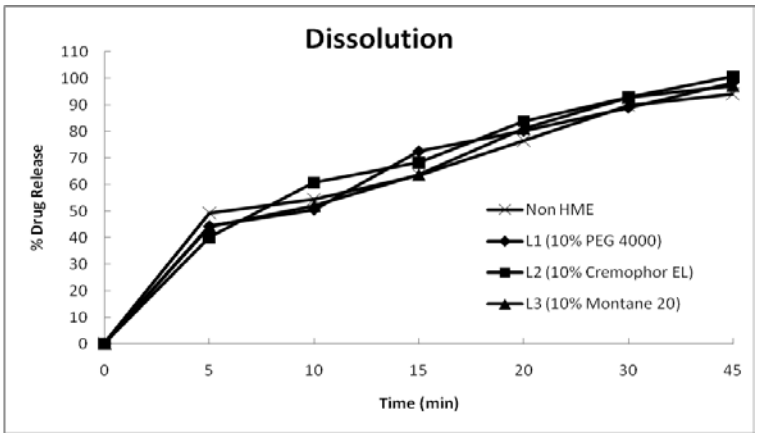

Fig. 1: Dissolution comparison of HME and NHME formulations

Table 4: Model fitting

	L1 (10% PEG 4000)			L2 (10% CREMOPHOR EL)			L3 (10% MONTANE 20)		
	R	**K**	**n**	**R**	**K**	**n**	**R**	**K**	**n**
Matrix	0.8736	0.0402	-	0.8818	0.0408	-	0.8787	0.0401	-
T-test	4.015	passes	-	4.181	passes	-	4.116	(Passes)	-
Peppas	0.9797	0.1062	0.1951	0.9926	0.1039	0.2071	0.9784	0.1049	0.1978
T-test	10.927	passes	-	18.219	passes	-	10.576	(Passes)	-

Where R=regression coefficient, k= kinetic constant, n= diffusion exponent

In Peppas model when the release exponent n ≤ 0.5 by Fickian diffusion release from slab (non swellable matrix) means that drug release followed, by both diffusion and erosion controlled mechanisms [16, 17]. Same drug release pattern has been observed in present study for tablets prepared by HME technology.

Table 5: Comparative values of plasticizers

	ST (mN/m)	**Hydroxyl value**	**HLB**
(PEG 4000)	44([20])	25-32([20])	18.5([20])
(Cremophor EL)	40.9 ([19])	65-78([19])	12-14([19])
(Montane 20PHA)	28([18])	159-169 ([18])	8.6 ([18])

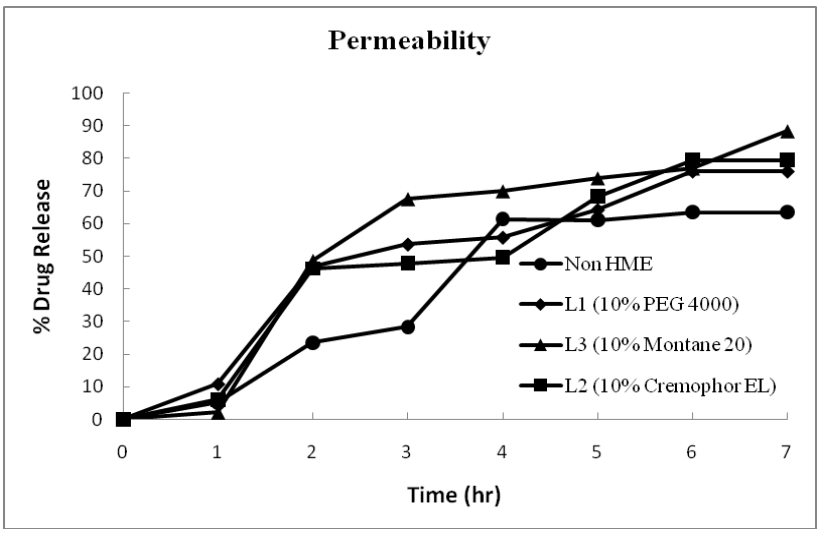

Fig. 2: Permeability comparison HME and NHME formulations

Formulation with 10% Montane 20PHA shows improvement in, in vitro permeability as compared to formulations containing 10% Cremophor EL and 10% PEG 4000. NHME formulation shows lower permeability than all HME formulations. Surprisingly in vitro permeability enhancement was observed in formulation prepared by 10% Montane 20 irrespective of lower Hydrophlic Lipophilic

Balance (HLB) value, which can be justified based on the other properties of plasticisers like hydroxyl value and surface tension (ST). Hydroxyl value of plasticizers may play an important role in Critical Micelle Concentration (CMC). Higher is the hydroxyl value more will be the hydrophilicity of plasticizer. Montane 20PHA has a higher hydroxyl value of 159-169 than hydroxyl value of Cremophor EL of 67-78 and PEG 4000 of 25-32 [19, 20] which may play an important role to improve solubility and ultimately permeability. K values of Matrix and Peppas models passes. Based on R value it can be concluded that Peppas is the best fitted model for all the 3 formulations. Also lower ST of plasticizer can help the drug penetration in solvent or media to enhance solubility.

Lower the melt viscosity of polymer more will be the mixing efficiency of API and polymer. Use of plasticizers in formulation lower the Tg of polymer with increased intermolecular separation in polymer chains which ultimately improves the molecular level dispersion of API in polymer bed. NHME tablets shows lower in vitro permeability compared to all HME formulations (Figure 2), even though having almost similar profile in dissolution study. Increase in, in vitro solubility and permeability by HME technology may increase the in vivo bioavailability which may lead to reduction in some fold of dose.

Linearity of the method was in the concentration range 1- 20 µg/mL of Plasma (Figure 3).

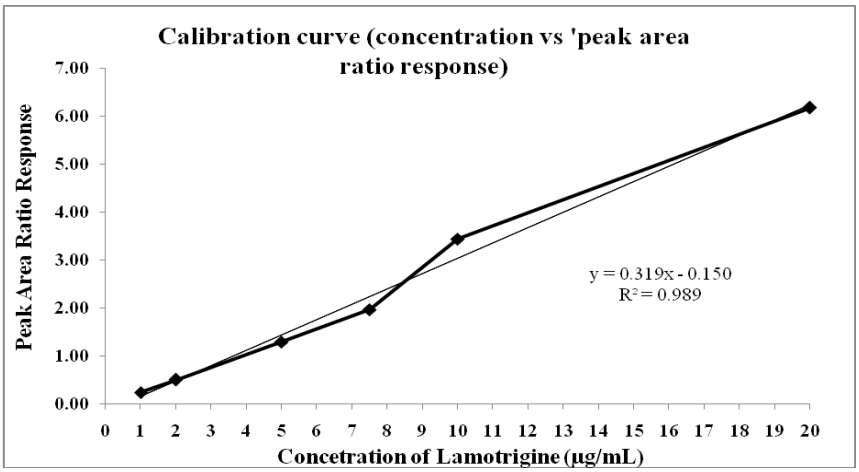

Fig. 3: Calibration curve

Plasma concentrations of lamo following the oral administration of pure drug and its solid dispersions prepared by HME technology is shown in Fig. 4.

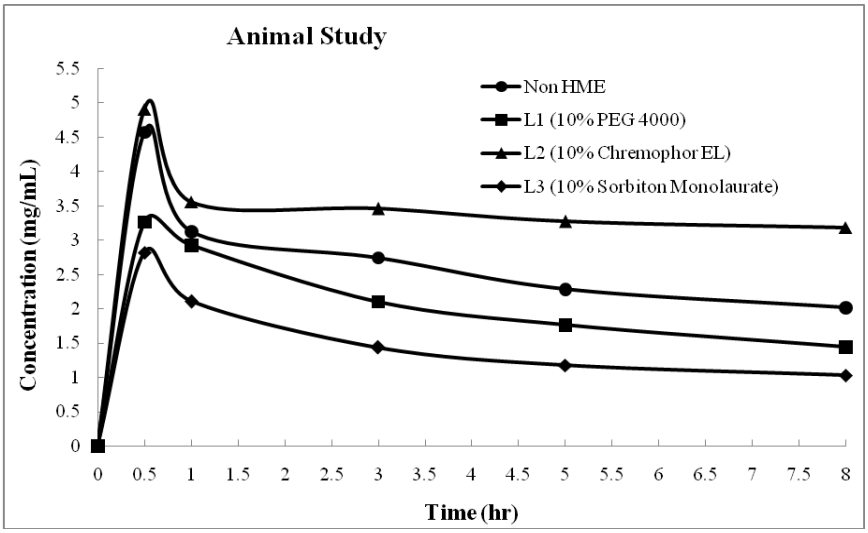

Fig. 4: Animal study

Pharmacokinetics parameters estimated are summarized in Table 6.

Table 6: Pharmacokinetic parameters of Lamo

Parameters Samples	Tmax (hr)	Cmax (µM)	AUC_{last} (hr*µM)	AUC_{inf} (hr*µM)	MRT_{inf} (hr)
Lamo	0.5	2.8	10	23	12
L1 (10% PEG 4000)	0.63	3.3	14	30	11
L2 (10% Cremophor EL)	0.5	4.9	24	199	55
L3 (10% Montane 20 PHA)	0.5	4.6	18	44	13

Lamo was found to be absorbed rapidly when given orally, and a highest peak plasma concentration (Cmax) 4.9 µg/mL was observed at 0.5 hrs after administration of L2 formulation (10% Cremophor EL).

All the pharmacokinetics parameters namely Cmax, Tmax and $(AUC)_{0-\infty}$ indicated rapid and higher absorption of Lamo when administered as solid dispersion (L2) prepared using 10% Cremophor EL. $AUC_{0-\infty}$ was also much higher in case of SD prepared with 10% Cremophor EL when compared to NHME and other HME formulations. $AUC_{0-\infty}$ was increased from 23 hr*µM (for pure drug) to 30 hr*µM, 199 hr*µM and 44 hr*µM for L1, L2 and L3 respectively. Extent of absorption was increased by 30.43%, 765.22% and 91.30% in L1, L2 and L3 formulations respectively. Noticeable boost in absorption of L2 formulation was observed due to p-gp inhibition activity by Cremophor EL. Lamo is a strong substrate of P-gp activity, so P-gp inhibitor like Cremophor EL enhanced its in vivo bioavailability to great extent. As a measure of hydroxyl groups in a surfactant, the hydroxyl value is an indicator of the hydrophilic character [21]. In this study, it has been observed that solubility of drug increases as hydroxyl value increases. In, in vivo study the extent of absorption increases as hydroxyl value of plasticizers increases. Plasticizers like Montane 20 PHA and PEG 4000 improved the solubility and permeability of Lamo as compare to pure drug due to HME technology. The bioavailability enhancement of Lamo in L2 formulation is a cumulative effect of HME technology and P-gp activity of Cremophor EL. So it is difficult to calculate the exact improvement in bioavailability due to HME technology.

CONCLUSION

SD prepared using 10% Montane 20 PHA and 10% Cremophor EL improved the in vitro permeability and bioavailability of Lamo respectively. This study reveals the solubility enhancement by HME technology and bioavailability enhancement was mainly achieved by plasticizer having P-gp inhibition activity. Other plasticizers like PEG 4000 and Montane 20PHA improved the solubility and bioavailability due to HME technology only. HME technology improved the physicochemical and pharmacokinetic parameters which confirmed the versatile application of this technology in pharmaceutical development of poorly water soluble drugs.

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CONFLICT OF INTEREST

There is no conflict of interest.

ABBREVIATIONS

S. No.	Word	Abbreviation
1	Lamotrigine	Lamo
2	Antiepileptic Drug	AED
3	Solid Dispersion	SD
4	Hot Melt Extrusion	HME
5	Polyethylene Glycol	PEG
6	Paraglycoprotein	P-gp
7	Biopharmaceutical Classification system	BCS
8	Hydrochloric Acid	HCl
9	Glass Transition temperature	Tg
10	Carboxy Methyl Cellulose	CMC*
11	Critical Micelle Concentration	CMC
12	Surface Tension	ST
13	Hydrophilic Lipophilic Balance	HLB

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