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Original Article

ENHANCEMENT OF SOLUBILITY OF POORLY SOLUBLE DRUG LANSOPRAZOLE

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ABSTRACT

Objective: To improve the solubility of lansoprazole with solid dispersion (SD) method by using hydrophilic polymer PEG 6000, PEG 15000 and amphiphilic polymer solupus.

Methods: Solid dispersions of lansoprazole were prepared with polymers PEG 6000, PEG 15000 and amphiphilic polymer soluplus, using three methods of preparation–1) solvent melting 2) solvent evaporation and 3) microwave heating method along with different drug: carrier ratios. Performance of the prepared formulations were evaluated for solubility, fourier transform infrared (FTIR) spectroscopy, and differential scanning calorimetry (DSC) parameters.

Results: All SDs showed enhancement in solubility of lansoprazole. Solubility and also carrier concentration showed a positive effect on solubility. The lansoprazole-soluplus solid dispersion 1:3 in concentration showed enhanced aqueous solubility when formulated with a solvent melting procedure.

Conclusion: The studies indicated that PEG 6000, PEG 15000 and Soluplus inhibite crystallization of lansoprazole, subsequently form amorphous state in solid dispersion, which is, confirmed via FTIR and DSC results of lansoprazole solid dispersion.

Keywords: Lansoprazole, Solubility enhancement, PEG, Solid dispersion, Soluplus

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INTRODUCTION

Lansoprazole, BCS-II class, belongs to be antacid, which inhibit proton pump and act as an antisecretory compound. Lansoprazole is effective and safe for the symptomatic relief or treatment option for disorders GERD (gastroesophageal reflux disease), peptic ulcer, lesions produced by nonsteroidal anti-inflammatory drugs [1-6].

Poorly aqueous soluble drugs have a limited absorption, which causes the decrease in dissolution and affects the biological action of the drug. To overcome this drawback, solubility enhancement is the major concern nowadays. Enhancement of solubility is the most challengeable in pharmaceutics. There are various pharmaceutical approaches are available to manipulate the solubility of drugs. Solid dispersion (SD) is mixture two different components generally, a hydrophilic/amphiphilic matrix act as carrier and a hydrophobic drug [7].

As lansoprazole has low aqueous solubility, will absorbs slowly and causes the decreased rate of dissolution, which affect the rapid efficacy of drug. Therefore, there is a need to enhance the solubility of lansoprazole, which can be achieved by lansoprazole SD with hydrophilic, and amphiphilic carriers, which ultimately increase their rate of dissolution. By preparing the solid dispersion, the particle size of drug is reduced and the wettability, and dispersibility of drug increased; therefore, dissolution of drug was improved [8].

The goal of this research project is to formulate lansoprazole SDs with three different concentrations of hydrophilic matrix like polyethylene glycol 6000, polyethylene glycol 15000 and amphiphilic matrix soluplus with three different methods like solvent melting, solvent evaporation method and microwave oven method to enhance the lansoprazole aqueous solubility.

MATERIALS AND METHODS

Lansoprazole was received as a gift sample from Cipla Ltd. Verna, Goa. Polyethylene glycol 6000, polyethylene glycol 15000 and Soluplus were purchased from Yarrow Chem, Mumbai. All other chemicals of analytical grade were used.

Preparation of calibration curve of lansoprazole

The stock solution of lansoprazole was prepared by as per pharmacopoeial standards. To obtain a concentration of 100 µg/ml, lansoprazole 10 mg drug was accurately weighed and dissolved in 100 ml of pure methanol. From stock solution with proper dilution with distilled water, 10 µg/ml to 50 µg/ml solution were prepared, scanned them in UV range 200-400 nm using spectrophotometer. The absorption maxima of was found to be 284 nm. The standard curve of calibration was plotted and assessment of values of slope, coefficient of correlation and intercept was done [9].

Saturaed Solubility study of lansoprazole

Solubility of lansoprazole in distilled water, phosphate buffer pH 7.2, phosphate buffer pH 6.8 and 0.1N hydrochloric acid solution was determined as per the standard procedure, after suitable dilution absorbance was measured at 284 nm by respective a blank solution [10, 11].

Preparation of solid dispersion of lansoprazole

Three different carriers were used in preparation of lansoprazole solid dispersion; among these polyethylene glycols 6000 (PEG 6000) and polyethylene glycols 15000 (PEG 15000) are hydrophilic while Soluplus is one amphiphilic carrier. The drug: carrier ratios and method of preparations as mentioned in table 2 were used for preparation of SDs. The method for SDs with different kinds of ways mentioned in table 2 were carried as per reported procedure [1].

Solvent evaporation methodas

Lansoprazole and carrier were to methanol and the dissolved material is then transferred to china dish, then heated to formed dried mixture after solvent evaporation. Then these resultant mixtures were powdered in mortar, passed through the sieve no. 80 and stored in a well-closed amber colored container [12].

Solvent melting method

Lansoprazole was added in methanol, Carrier was added in china dish, which heated not exceeding 80 °C. Lansoprazole solution was added in molten carriers, and mixed for 15 min. Then mass was cooled at-70 °C for 24 h using a deep freezer [13].

Microwave oven method

Lansoprazole and carrier were mixed well in mortar, 1 ml of water is added to the mixture to form a slurry, which is then transferred in

petri plate with cover of teflon then kept in microwave and operated at power of 560W for different timings as 2, 3, 4, 5 min. Then after removal, plate was kept at room temperature for solidification [14].

All SDs mass was powdered using mortar, passed through sieve no. 80 and then mass was stored in a light-resistant glass container

Saturated solubility determination of lansoprazole in solid dispersion formulation

Solubility of lansoprazole in SDs were carried out in distilled water, phosphate buffer pH 7.2, phosphate buffer pH 6.8 and 0.1N hydrochloric acid solution, as per the standard procedure, after suitable dilution absorbance measured at 284 nm by respective a blank solution [1, 10].

Characterization of lansoprazole solid dispersion

The formed SDs were studied for compatibility using FTIR and DSC analysis as per regular procedure. The FTIR spectra was scanned in the range of 4000-400 cm-1 [15]. For DSC thermogram scanning rate 10 °C/min was maintained to heat the sample from 30 °C to 350 °C [16]. For Lansoprazole also similar characterization was done.

RESULTS AND DISCUSSION

Calibration curve of lansoprazole

Lansoprazole do not showed linearity in acidic media for calibration curve, therefore, it was prepared in methanol at 284 nm and it exhibited good linearity. The linear regression equation and correlation coefficient was depicted in fig. 1.

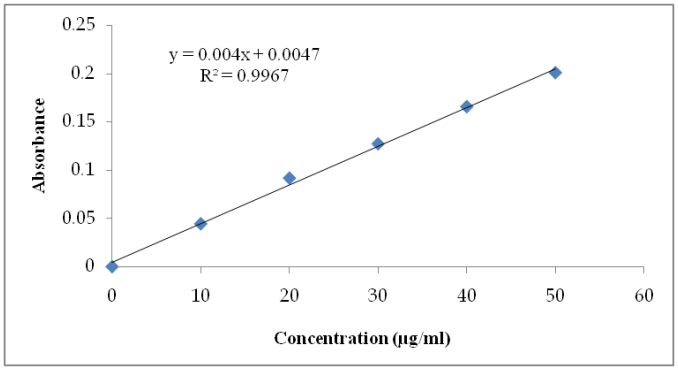

Fig. 1: Calibration curve of drug-lansoprazole

Solubility study of lansoprazole

Lansoprazole had exhibited less solubility to neutral and alkafigfline media pH 7.2 as compared to acidic solution as shown in table 1. The data indicates pH-dependent solubility and stability of lansoprazole. It was shown a stability issue in acidic media and less stability in solution form to the solid form. This solubility data primarily showed sublingual route will be most suitable, as saliva has a pH 6.2 to 7.6.

Table 1: Solubility data of lansoprazole in different dissolution medium.

S. No.	Medium	Solubility (mg/ml)*
1	Distilled water	0.022±0.14
2	Phosphate buffer pH 6.8	0.072±0.11
3	Phosphate buffer pH 7.2	0.042±0.12
4	0.1N HCL	0.063±0.10

Data given in mean±SD, n=3.

Development of lansoprazole solid dispersions

Solubility enhancement by adopting solid dispersion is already established method by many researchers. Less solubility of drugs shows problem in dissolution. Here attempt is made to select suitable carrier and ratio for preparing SDs. The all SDs looked as uniform fine powder form and having white buff color. Compositions with different methods, and solubility data of SDs are shown in table 2.

It was observed that the molecular weight of the PEG has a greater influence on solubility. Greater the molecular weight of the PEG, greater the solubility. The PEG 15000 showed the enhanced solubility as compared to the PEG 6000 as PEG 15000 is more hydrophilic as compared to PEG 6000. The lansoprazole SDs prepared with Soluplus by method of solvent melting with composition 1:3 showed enhanced solubility as 1.74 mg/ml when compared to the solubility of all other SDs prepared by different methods and pure drug in phosphate buffer pH 6.8. Soluplus is graft polymer, amphiphilic nature may be imparting micellar solubilization of the drug. Micelles have polyethylene glycol head groups and vinyl caprolactam/vinyl acetate as lipophilic tail. Increase in the concentration of carrier increases the solubility therefore, 1:3 ratio showed highest solubility with all carriers irrespective of method of preparations.

Characterization of lansoprazole solid dispersion

The FTIR spectra of lansoprazole showed the functional groups peaks as per reported peaks [1] and DSC thermogram of lansoprazole exhibited at 180.55 °C endothermic peak; this specifies the crystalline nature of lansoprazole and peak at 181.94 °C is exothermic, confirms the decomposition of lansoprazole [16]. The FTIR spectra and DSC thermogram represented in fig. 2 and fig. 3 respectively.

The FTIR spectra of lansoprazole-PEG 6000, lansoprazole-PEG15000 and lansoprazole-Soluplus SDs did not show sharp peak indicates the amorphous state of drug within the SDs or miscibility of drug with the carrier matrix due to hydrogen bonding.

The thermogram (DSC) of all lansoprazole SDs were primarily designated amorphization of the lansoprazole. Two endothermic peaks were presented by SDs of PEG 6000 and 15000. First peak was at 55.43 °C present the melting point of PEG 6000 and 15000, while the second broad peak at 163.66 °C and exothermic peak was disappeared, explains drug has completely miscible within a molten carrier along with no degradation during SDs formulation. The thermogram (DSC) of SDs prepared with soluplus exhibited presence of two endothermic peak similar to above, one at 59.74 °C

and other at 163.66 °C, confirms amorphous nature with no degradation. The SDs matrix are formed with molecular dispersion. The threat that exists here is spontaneous crystallization may be occurred when molecular mobility exceeds the threshold of nucleation especially due to heating effect. The FTIR spectra of SDs are indicated in fig. 2 and DSC thermogram of SDs are shown in fig. 3.

Table 2: Lansoprazole SDs and their solubility study

S. No.	Method	Composition	Ratio (Drug: carrier)	Solubility (mg/ml)
1	Solvent Evaporation Method	Lansoprazole+ PEG 6000	1:01	0.23
			1:02	0.35
			1:03	0.45
		Lansoprazole+ PEG 15000	1:01	0.24
			1:02	0.37
			1:03	0.51
		Lansoprazole+ soluplus	1:01	0.43
			1:02	0.82
			1:03	1.63
2	Solvent Melting Method	Lansoprazole+ PEG 6000	1:01	0.26
			1:02	0.38
			1:03	0.48
		Lansoprazole+ PEG 15000	1:01	0.27
			1:02	0.39
			1:03	0.53
		Lansoprazole+ soluplus	1:01	0.45
			1:02	0.93
			1:03	1.74
3	Microwave Oven Method	Lansoprazole+ PEG 6000	1:01	0.22
			1:02	0.34
			1:03	0.44
		Lansoprazole+ PEG 15000	1:01	0.24
			1:02	0.36
			1:03	0.49
		Lansoprazole+ soluplus	1:01	0.4
			1:02	0.77
			1:03	1.62

Data given in mean±SD, n=3.

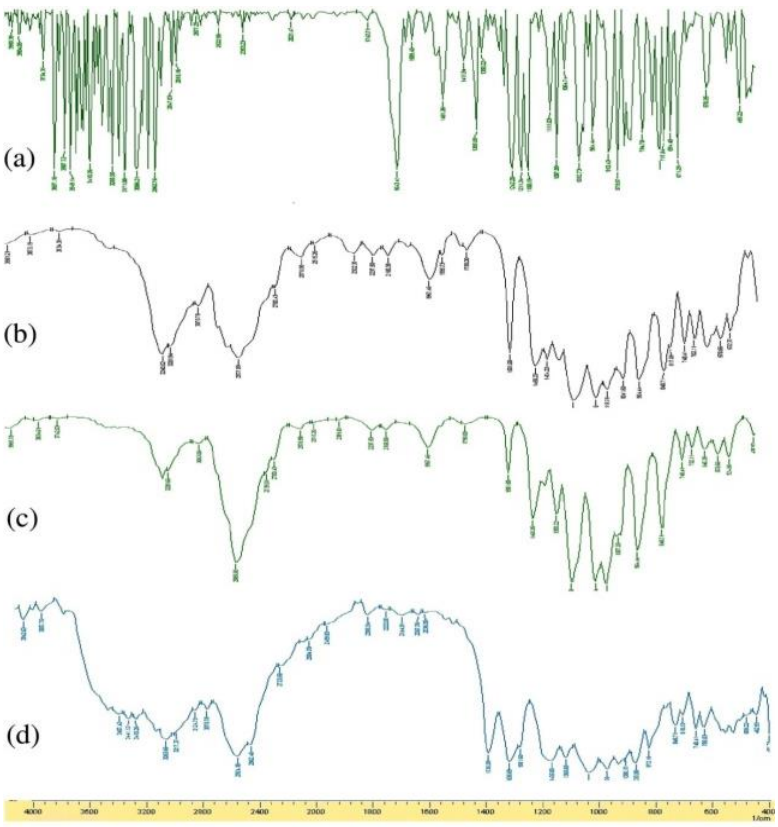

Fig. 2: FTIR spectra of (a) pure lansoprazole, (b) lansoprazole PEG 6000 solid dispersion, (c) lansoprazole PEG 15000 solid dispersion, (d) lansoprazole soluplus solid dispersion

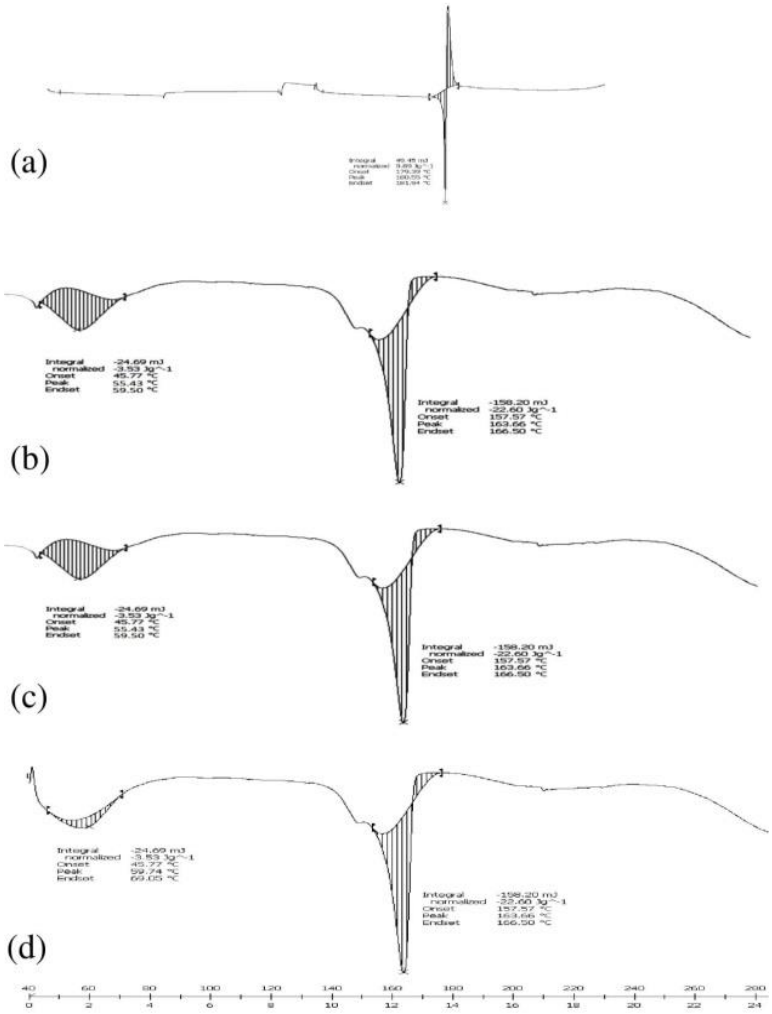

Fig. 3: DSC thermogram of (a) pure lansoprazole, (b) lansoprazole PEG 6000 solid dispersion, (c) lansoprazole PEG 15000 solid dispersion, (d) lansoprazole soluplus solid dispersion

CONCLUSION

The present research work has proved that for drugs like lansoprazole, having poor solubility, their solubility can be increased by preparing the solid dispersion with hydrophilic carriers like PEG 6000, PEG 15000 as well as amphiphilic carrier Soluplus. In case of a hydrophilic carrier, the molecular weight has a greater influence on the solubility. Greater the molecular weight, the greater the solubility. Concentration of carrier had shown a direct relationship with solubility, therefore, 1:3 ratio showed highest solubility compared to 1:1 and 1:2 ratios Method of preparation of solid dispersion also found to influenced the solubility. Solvent melting method has shown highest solubility in comparison to solvent evaporation and microwave oven method. In the present investigation, all prepared lansoprazole solid dispersion showed enhanced solubility among which solid dispersion of lansoprazole with 1:3 as drug: carrier ratio prepared with Soluplus by using solvent melting method had shown the highest solubility of the lansoprazole measured as 1.74 mg/ml. The represented studies indicated that carriers used were inhibited the crystallization, resulting in the formation of amorphous state of the drug in solid dispersion. The FTIR and DSC studies confirmed the amorphous state of drug in solid dispersion. Formulation of lansoprazole sublingual tablet in the form of solid dispersion with Soluplus will be the one of the alternatives to the conventional drug delivery system.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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