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Formulation and evaluation of lansoprazole orodispersable tablets using novel excipients

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ABSTRACT

In the present work an attempt has been made to increase the solubility and dissolution rate of lansprozole by formulating it as solid dispersions by lipid carriers such as compritol 888 ATO Phospholipon 90 H and Lipoid S100 by using Fusion method, Kneading method and solvent evaporation method. Further the solid dispersions were compressed as orodispersible tablets by using croscarmelloe sodium (CCS) & sodium starch glycolate (SSG) as superdisintegrants. Rapid release of lansoprazole from solid dispersions was observed which was influenced by the proportion of carrier concentration. Among the solid dispersions prepared the dispersion formulated using Phospholipon 90 H showed rapid drug release than compritol 888 ATO & Lipoid S100 containing Solid dispersions and pure drug alone. The release was found to follow the first order kinetics. Solid dispersions prepared by the various methods were further formulated into tablets with superdisintegrants such as sodium starch glycolate (SSG) & crospovidone (CP) The dissolution rate of such tablet formulations were found to release the drug at a faster rate than the tablets prepared with plain drug. Characterization was carried out by pure drug (Lansprozol) and optizimed formulation L6 by FTIR and DSC Studies. The Studies shows that there was no drug and polymer interaction.

Key words: Solid dispersions Oro dispersible tablets, Lansoprazole, compritol 888 ATO Phospholipon 90 H and Lipoid S100.

INTRODUCTION

Lansoprazole is a proton pump inhibitor (PPI) which inactivates the final step in the gastric acid secretion pathway in gastric parietal cells in a dose-dependent manner. Bioavailability is 85% after the first dose – the highest among PPIs and acid inhibition is swift, resulting in rapid relief of symptoms. Lansoprazole also exhibits antibacterial activity against Helicobacter pylori in vitro [1,2] Seventeen years of clinical experience worldwide have shown lansoprazole to be an effective and well-tolerated treatment option in the management of acid-related disorders, including gastric and duodenal ulcers and gastroesophageal reflux disease, and the treatment or prevention of gastroduodenal lesions induced by NSAIDs [3].Lansoprazole is also effective in combination with different regimens for H. pylori eradication and is included in the first-line PPI-based options for this purpose. Lansoprazole comes under the BCS II classification drug which has poor aqueous solubility & bioavailability.

Solid dispersion (SD), in which compounds are dispersed into water-soluble carriers, are generally used to improve the solubility and the bioavailability of poorly soluble drugs [4, 5]. There is a demand for developing new

technologies has been increasing annually. For most therapeutic agents are used to produce systemic effects, the oral route still represents the most desirable route of drug administration, owing to its several advantages and high patient compliance compared to many other routes. Drug dissolution and absorption as well as onset of action and drug bioavailability may be significantly greater than conventional dosage forms [6, 7].

Among various solid dispersions, lipid based carriers have been used in higher success rate in increasing the bioavailability of Class II drugs. Few most novel carriers are compritol 888 ATO Phospholipon 90 H and Lipoid S100. They should enhancing and improving the dissolution rate of poorly soluble drugs at a low carrier concentration [8-12].

Now a day's ODTs are being named as orodispersible, rapid-dissolving, mouth-dissolving, rapid-disintegrating tablets. There are some definitions that made by various pharmacopeias. Orodispersible tablets are placed in the mouth where they dissolve or disperse fast before being swallowed and they are uncoated tablets. Orodispersible tablets disintegrate within 180 seconds when the disintegration tests have been conducted up to the test for disintegration of tablets [8, 9]. Orally disintegrating tablets are intended to disintegrate fast in the mouth to provide dispersion before being swallowed where the active ingredient is intended for gastrointestinal delivery and/or absorption [13-15].

In present investigation has been made to increase the solubility and of lansoprazole by formulating it as solid dispersions using various concentration of lipid carriers and to enhance the dissolution rate by formulating it as orodispersible tablets of lansprozol by employing superdisintegrants Sodium starch glycolate (SSG) and Crospovidone(CP).

MATERIALS AND METHODS

Lansoprazole A Gift sample procurred from Apotex pharma Ltd, Bangalore. Cros carmellose sodium and Sodiumstarch glycolate were commercially procured from Yarrow chem, Ltd., Mumbai. compritol 888 ATO Phospholipon 90 H and Lipoid S100 a gift samples from gattefosse. Magnesium stearate and mannitol were commercially produced from S.D Fine Chem, Ltd., Mumbai.

Saturated solubility studies of Lansprozol

Saturated solubility studies were conducted on Lansoprazole by using different dissolution media. Excess amount of Lansoprazole was weighed and transferred into different conical flasks containing 10ml of different dissolution media i.e., Water, 6.8p^H, 7.2 p^H Phosphate buffer, 1.2 P^H and were closed appropriately. All conical flasks were placed in the REMI incubator shaker. The shaker was allowed to operate at 50 rpm at 37°C ± 1°C for 24 h [12**]**.Then the conical flasks were removed from the incubator shaker and the samples were filtered by using Whatman filter paper. The clear solution obtained by filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 284 nm by using corresponding dissolution media as blank solutions. The Saturated solubility studies of Lansprozol were given in the table 1.

Methods of preparation

Solid dispersions were prepared by using compritol 888 ATO Phospholipon 90 H and Lipoid S100 as a lipid based carriers by various methods.

Solid dispersions by Kneading Method In this method, polymer was triturated in a mortar with water to get slurry like consistency. Later drug was incorporated into it by continuous trituration and it was carried out for about 1hr. Slurry was then air dried at 25^{0}C for 48 hrs. The product was pulverized and passed through sieve number 100. The compositions various solid dispersions were shown in table -2.

Solid dispersions by Fusion Method Specified quantity of Carriers was taken in a china dish and it was heated at 50 ºC on a mantle until molten solution was formed. To the molten solution add specified quantity of lansprozol and triturated vigorously at room temperature. Grind the mass if necessary and screen through sieve No. 100. Then the mixture was collected, packed and was hermetically sealed and was stored at an ambient condition. The compositions various solid dispersions were shown in table -2.

Solid dispersions by Solvent Evaporation Method In this method Specified quantity of lansprozol and carriers were taken in a china dish and to that few ml of methanol was added and slightly heated until both drug and polymer

dissolves. Then it is subsequently allowed to evaporate. The obtained mixture was dried, passed through the sieve no. 80, packed in a wide mouthed amber colored glass container and was hermetically sealed and stored 10. Various compositions of solid dispersions are given in Table 2.

Evaluation of solid dispersions

Solid dispersions prepared by using solvent evaporation methods were evaluated for particle size, flow properties and the drug content. Particle size was determined by sieve analysis and flow properties of solid dispersions were determined by angle of repose and Carr's index.

Estimation of Lansoprazole in solid dispersions

Solid dispersions of Lansoprazole from a batch were taken at random and were transferred into a 100 ml volumetric flask and 70 ml of methanol was added to it. It was shaken occasionally for about 15 mins and the volume was made up to 100 ml by adding 6.8 P^H phosphate buffer. About 10 ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using Whatmann filter. Then the filtrate was subsequently diluted with 6.8 P^H phosphate buffer and the absorbance was measured at 284 nm.

Dissolution rate studies on Lansoprazole

The dissolution test for the solid dispersions was carried out in United States Pharmacopoeia (USP) Apparatus Type II (paddle) [USPNF, 2007] with 900 ml of 6.8 P^H phosphate buffer as the dissolution medium. The samples were drawn at 5, 10, 15, 20, 30, and 45mins Fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions and constant volume throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium and the amount of drug dissolved was estimated by ELICO SL210 double beam spectrophotometer at 284 nm and subsequently analyzed for the cumulative percentage of drug released. The dissolution studies on each formulation were conducted in triplicate. The dissolution profiles of solid dispersions were shown in Figure 4**.** The *in vitro* dissolution parameters of various solid dispersions were given in Table 3**.**

Characterization of solid dispersions

Among the various solid dispersions prepared using Soluplus showed rapid drug release was further evaluated for the drug excipient compatibility by FTIR and DSC Studies.

Fourier transforms infrared spectroscopy study

The FTIR spectra of pure drug Lansprozol and optimized formulations L6 were obtained by using brucker FTIR spectrophotometer to study the interaction between drug and carrier in solid dispersions. The samples were prepared in KBr discs (2mg sample in 200mg KBr) and the sampling range was 400 - 4000 cm-1 and the resolution was 4cm-. The FTIR spectra were shown in Figure 1-2.

Differential Scanning Calorimetry:

Differential Scanning Calorimetry measurements were performed on Lansprozol and on optimized formulation L6 using differential scanning calorimeter (METTLER TOLEDO with eSTAR software). The samples were placed in a sealed aluminium crucible and evaluated with a heating rate of 20 º C/min at a temperature range of 25-250ºC. The thermograms were recorded and were shown in the figure 3-4.

Preparation of Lansoprazole orodispersible tablets from solid dispersions

Among the solid dispersions prepared and based on the dissolution studies performed, one optimized dispersion was selected for the preparation of tablets. The selected solid dispersion was blended with super disintegrants such as Croscarmellose sodium(CCS) and Sodium Starch Glycolate (SSG) magnesium stearate and talc as lubricant and glidant. The powder blend was directly compressed into tablets by using lostatin mini press (ELITE). The compositions of various tablet formulation were given in the Table 4.

Evaluation of physical parameters for Lansoprazole Orodispersible tablets

The compressed tablets were further evaluated for their physical parameters such as weight uniformity, hardness, friability and drug content.

Dissolution studies on Lansoprazole Orodispersible tablets

Dissolution rate studies of Lansoprazole tablets were performed in USP Apparatus Type II (paddle) As per the

procedure described earlier. Based upon the data obtained from the dissolution studies various parameters such as T_{50}, $DE_{30\%}$, zero order, first order release rate constants were estimated. The dissolution parameters such as T_{50}, and $DE_{30\%}$, were measured directly from the dissolution profile curves as shown in Figure 5-6.

Accelerated stability studies

The formulations, which showed good *in vitro* performance, were subjected to accelerated stability studies. The solid dispersion P2 and optimized formulation L6 was subjected to accelerated stability studies. These studies were conducted using stability testing chamber at a temperature and relative humidity (RH) of 25 + 2°C, 60 + 5% RH for 6 months and at 40 + 2°C, 75 + 5% RH for 3 months. The tablets were evaluated after storage for physical parameters and drug release studies. the dissolution profile of accelerated stability studies as shown in Figure 7.

RESULTS AND DISCUSSION

Saturated solubility studies revealed that Lansoprazole show maximum solubility in 6.8 P^H Phosphate buffer medium than the other dissolution medium used. The drug concentration was measured at an absorption maximum of 284 nm using ultraviolet spectrophotometer (ELICO SL120) for all dissolution medium. The absorbance values and their corresponding solubilities were shown in Table 1.

The solid dispersions were prepared with a lipid based carriers such as compritol 888 ATO Phospholipon 90 H and Lipoid S100 by various methods as per the compositions shown in the Table 2. All dispersions were prepared under similar conditions to avoid batch to batch variation. The dispersions were found to be uniform in their characteristics. The particle size range for the prepared solid dispersions were in the size range of 174 ± 31-79 ± 2 µm. The drug content estimated in all solid dispersions was highly uniform in the range of 98.77 ± 0.3-98.09 ± 0.9% indicated the uniformity.

The dissolution studies of Lansoprazole solid dispersions prepared were performed in 6.8 P^H Phosphate buffer by using the paddle method. The dissolution study of solid dispersions were found to be rapid than its pure drug. The T_{50}, and $DE_{30\%}$ values of all the formulation indicated there rapid drug dissolution than the pure drug of Lansoprazole. The drug release profiles of the prepared solid dispersions were shown in the Figure 3. The kinetics of drug release from all the formulation follows first order kinetics. It was observed that as the concentration of Phospholipon 90 H increases in solid dispersions prepared by solvent evaporation method the rate of dissolution of drug was also increased. Solid dispersions prepared by solvent evaporation method using Phospholipon 90 H with drug to carrier ratio of 1:2 were found to undergo rapid dissolution rates than the other dispersions. The Solid dispersions P2 and optimized formulation were subjected to characterize by FTIR and DSC Studies analysis to understand the drug excipient compatibility before formulating them as orodispersible tablets.

The compositions of various tablets prepared were shown in Table 4. All the solid dispersions were compressed under identical conditions to avoid processing variables. The physical parameters such as weight uniformity, hardness, friability, drug content, were evaluated for all the tablets prepared. The physical parameters evaluated were highly uniformed and all tablets were found to be within the I.P. specified limits. The weight uniformity values were in the range of 198± 4.0 to 200 ± 10 mg, hardness was found to be 3.6 ± 0.4 kg/cm^2, friability values were in the range 0.1-0.8% and drug content values were in the range of 29.88 ± 0.4 mg/tablet for the Lansoprazole orodispersible tablet formulations. The dissolution studies on Lansoprazole marketed tablet and all the tablet formulations were performed by using 6.8 P^H Phosphate buffer using paddle method. The dissolution rate of the tablet formulations were found to be rapid when compared to marketed tablet of Lansoprazole (Lan 30, Intas Pharmaceuticals). Among the tablets prepared with the superdisintegrants such as CCS and SSG tablets with the Sodium starch glycolate as superdisintegrants in the concentration of 15 % tend to exhibit rapid dissolution than all the formulations. The rate of rapid drug release is in the order of SSG > CCS in the tablet formulations for superdisintegrants. Among the various tablet formulations L6 shows rapid drug release (up to 98.7%) when compared to marketed formulation (84.77%) This can be attributed improved wettability and dispersibility as well as increased amorphous fraction of drug. It was also found that as the concentration of superdisintegrants increases, the tablets undergo rapid dissolution and drug release. This may be due to rapid intake of water by superdisintegrants, which leads to faster dissolution of the tablets and showed the improved dissolution profiles of poorly soluble Lansoprazole. The in vitro dissolution parameters were given in the table 5.

Table 1: Saturated Solubility Studies of Lansoprazole

S. No	Medium	Solubility (mg/10ml)
1	Distilled Water	0.89
2	6.8 p^H phosphate buffer	3.79
3	7.2 p^H phosphate buffer	2.44
4	0.1N HCl	1.65

Table 2: Compositions of various of Solid dispersion of Lansporazole 1:1 and 1:2 ratios

Ingredients(mg)	Compritol 888 ATO		Phospholipon 90 H		Lipoid S 100	
	C1	C2	P1	P2	L1	L2
Lansoprazole(mg)	30	30	30	30	30	30
Carrier(mg)	30	60	30	60	30	60

Table 3: Dissolution parameters of Lansprazole solid dispersions

S.No	Tablet formulations	T_{50} (min)	DE 30%	Zero order		First order	
				R^2	K (mg/min)	R^2	K (min^{-1})
1	PD	11	62.33	0.375	0..918	0.88	0.010
2	C1	16	44.66	0.493	0.781	0.93	0.015
3	C2	14	52.88	0.483	1.005	1.08	0.027
4	P1	8	56.66	0.472	0.643	0.83	0.027
5	P2	5	68.66	0.517	0.697	1.0	0.022
6	L1	4	58.75	0.7	1.243	0.92	0.011
7	L2	7	67.98	0.6	1.426	0.98	0.019

Table 4: Compositions of various Lansoprazole orodispersible tablets

Ingredients (Mg/tab)	Formulations											
	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12
Lansoprazole SD (Compritol) (Equivalent to 30 mg)	90	90	90	90	-	-	-	-	-	-	-	-
Lansoprazole SD (Phospholipon 90 H) (Equivalent to 30 mg)	-	-	-	-	90	90	90	90	-	-	-	-
Lansoprazole SD (Lipoid S 100) (Equivalent to 30 mg)	-	-	-	-	-	-	-	-	90	90	90	90
Sodium Starch Glycolate (SSG)(mg)	20	30	-	-	20	30	-	-	20	30	-	-
Croscarmellose sodium(CCS)(mg)	-	-	20	30	-	-	20	30	-	-	20	30
MCC(mg)	60	50	60	50	60	50	60	50	60	50	60	50
Mannitol	26	26	26	26	26	26	26	26	26	26	26	26
Stevia powder (mg)	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium sterate(mg)	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight of Tablets (mg)	200	200	200	200	200	200	200	200	200	200	200	200

Table 5: Dissolution Parameters of Lansoprazole Orodispersible Tablets

S.No	Tablet formulations	T_{50} (min)	DE 30%	Zero order		First order	
				R^2	K (mg/min)	R^2	K (min^{-1})
1	L1	10	60.5	0.382	0..929	0.80	0.010
2	L2	8	43.33	0.493	0.781	0.93	0.015
3	L3	9	53.33	0.493	1.006	1.08	0.027
4	L4	10	56.66	0.482	0.643	0.93	0.027
5	L5	6	36.66	0.507	0.697	1.00	0.021
6	L6	5	28.75	0.702	1.243	0.92	0.021
7	L7	8	32.98	0.612	1.446	0.99	0.029
8	L8	6	25.5	0.382	0..929	0.80	0.010
9	L9	7	33.33	0.493	0.781	0.93	0.015
10	L10	7	34.77	0.483	0.706	0.98	0.024
11	L11	6	30.66	0.482	0.643	0.93	0.027
12	L12	7	31.66	0.507	0.697	1.00	0.021

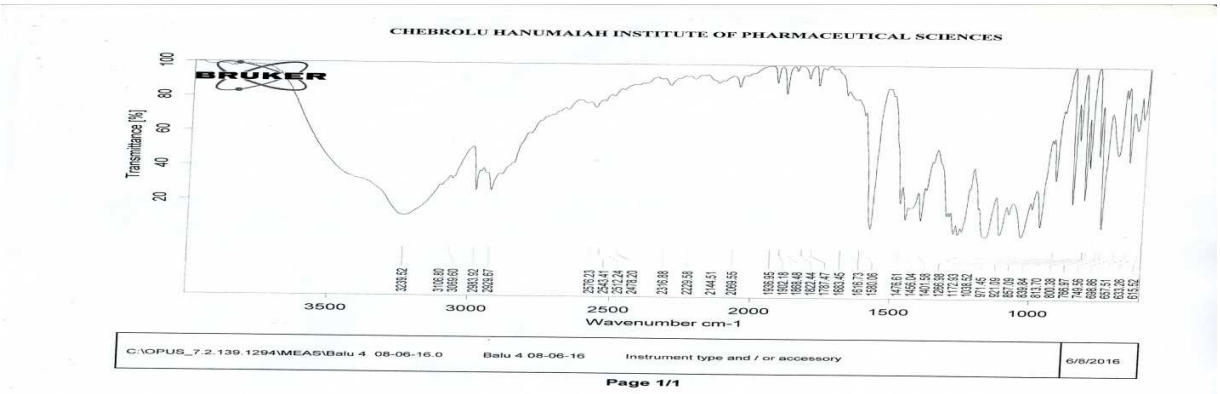

Figure 1: FT IR Spectra of Lansoprazole Pure drug

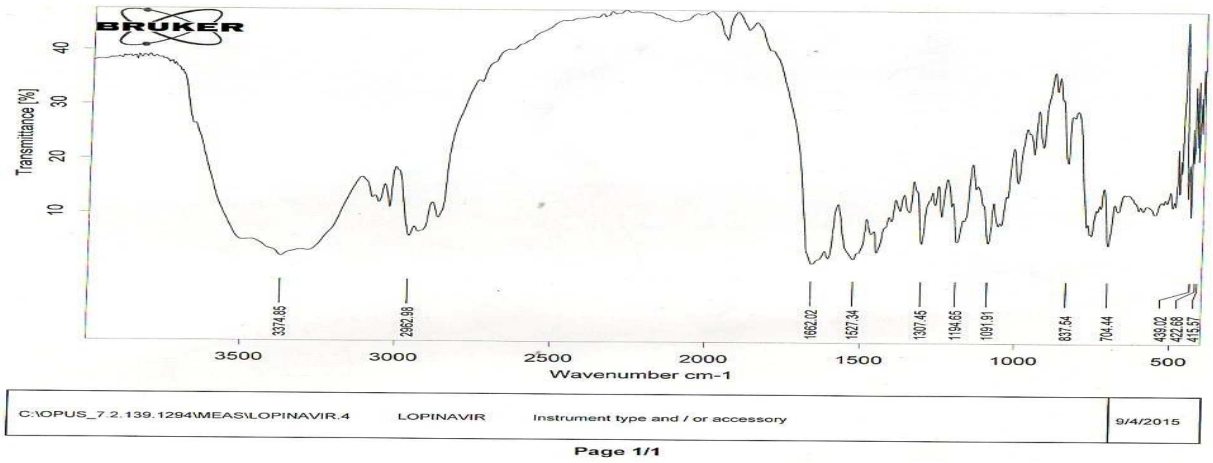

Figure 2: FT IR Spectra of Optimized Formulation L6

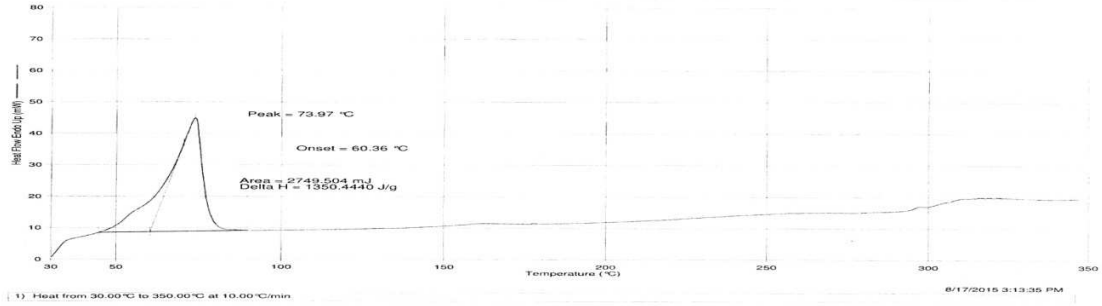

Figure 3: DSC Thermogram of Lansoprazole Pure drug

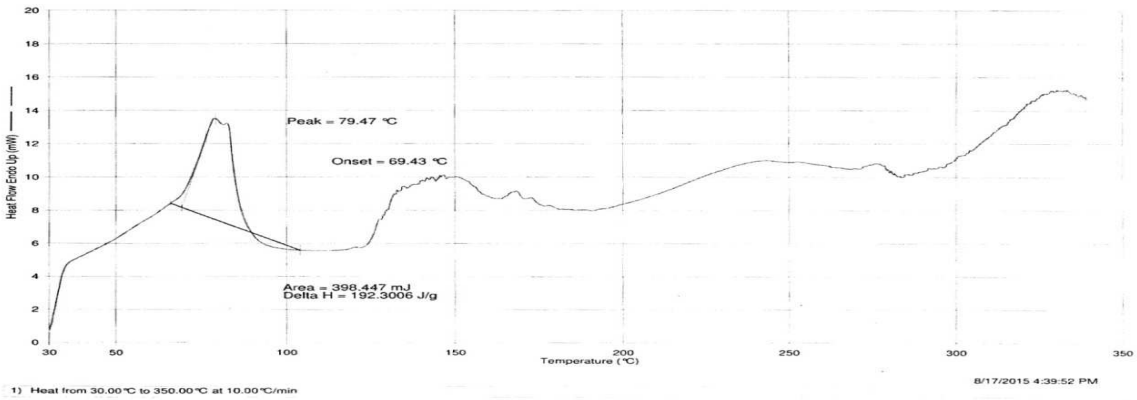

Figure 3: DSC Thermogram of Optimized Formulation L6

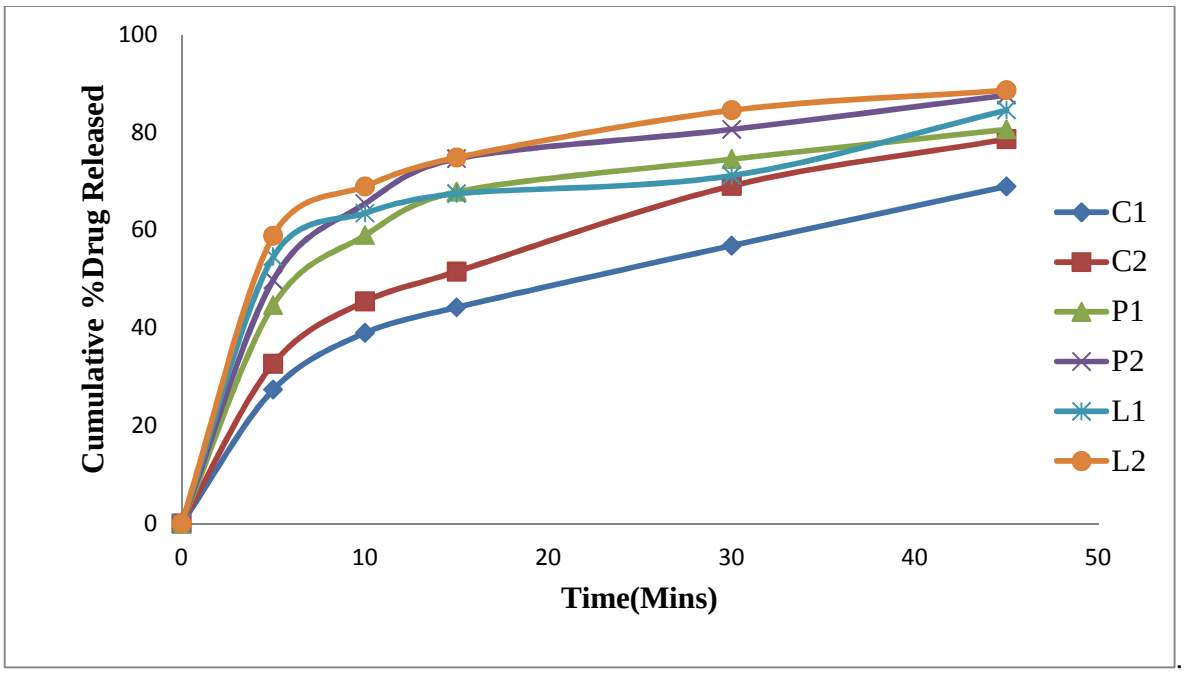

Figure 4: Drug Release Profiles of Lansoprazole solid dispersions

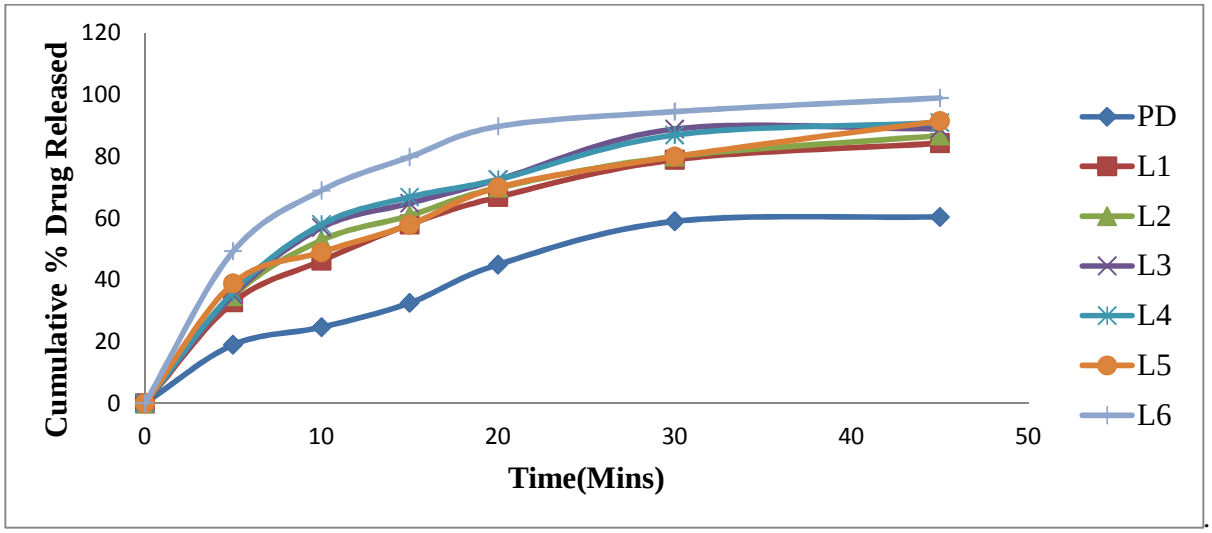

Figure5: Drug Release Profiles of Lansoprazole Orodispersible tablets

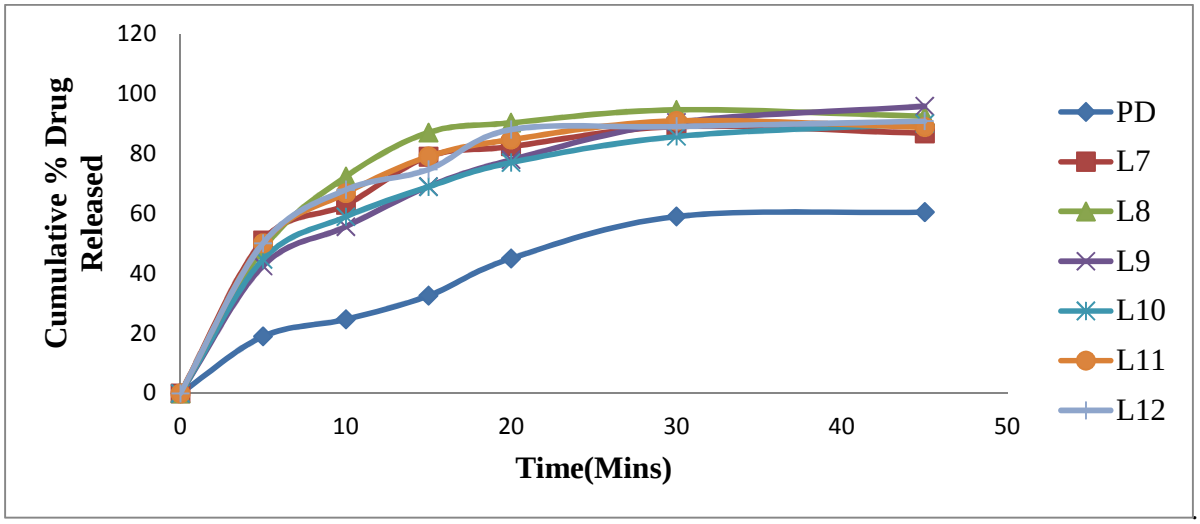

Figure 6: Drug Release Profiles of Lansoprazole Orodispersible tablets

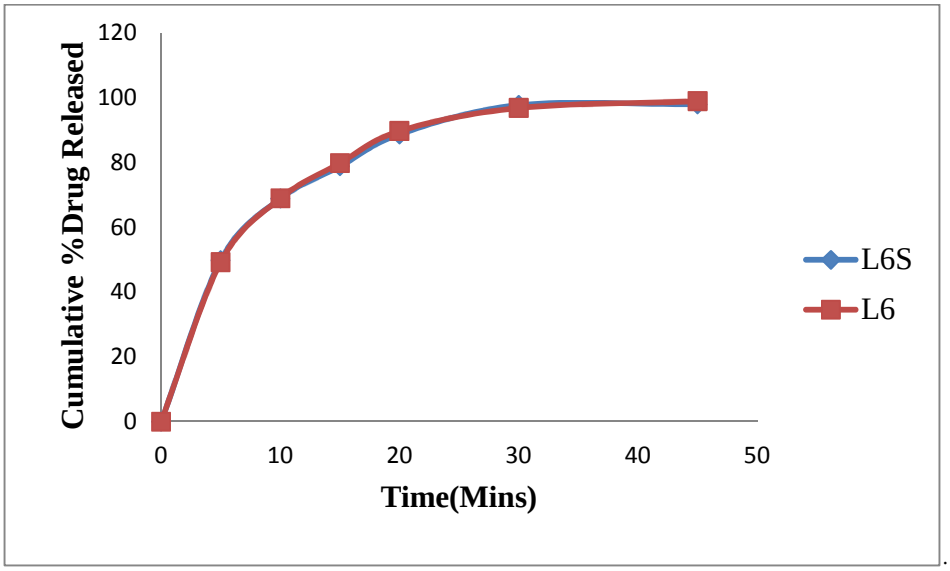

Figure 7: Dissolution profiles of optimized Lansoprazole formulations before and after stability studies

The formulations, which showed good *in vitro* performance, were subjected to accelerated stability studies. The formulation L6 was subjected to accelerated stability studies. These studies were conducted, using the stability testing chamber at temperature and relative humidity of 25 + 2°C, 60 + 5% RH for 6 months and 40 + 2°C, 75 + 5% RH for 3 months. The tablets were evaluated after storage for physical parameters and drug release studies. The accelerated stability studies for selected orodispersible tablets L6 were carried by investigations the effect of temperature of the physical properties of the tablets and on drug release of the tablets. The results of accelerated stability studies were shown in Figure 8. The results indicated that there were no visible and physical changes observed in the Lansoprazole orodispersible tablets after storage. It was also observed that there was no significant change in drug release from the tablet formulations. Thus, the drug release characteristics of Lansoprazole orodispersible tablets designed were found to be stable.

CONCLUSION

The aim of the present work has shown that it is possible to increase the dissolution rate of poorly soluble drug Lansoprazole by preparing it as solid dispersions with lipid based carriers like compritol 888 ATO Phospholipon 90 H and Lipoid S100. They are various technologies are employed for the preparation of solid dispersions. Dispersions prepared by solvent evaporation method with Phospholipon 90 H in the ratio of 1:2 for drug and carrier to exhibit rapid dissolution rate when compared with pure drug. Orodispersible tablets of Lansoprazole prepared using various superdisintegrants also shows the rapid dissolution and drug release when compared with marketed tablets. Based on the study, it may be concluded that Lansoprazole tablets prepared by using solid dispersions with Phospholipon 90 H & sodium starch glycolate as superdisintegrant was found to be ideal for rapid dispersion and for improving dissolution rate, which in turn increases the bioavailability.

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