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FORMULATION AND EVALUTION OF LANSOPRAZOLE ORODISPERSABLE TABLETS

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ABSTRACT: Lansoprazole a proton pump inhibitor used in the short term treatment of gastric and duodenal ulcer, reflux esophagitis, structuring and erosive esophagitis. In the present investigation an attempt has been made to enhance the solubility and dissolution rate of lansprozole by formulating it as solid dispersions with KollidonVA64, Soluplus and poly ethylene glycol 6000 by solvent evaporation method. The solid dispersions were further compressed as tablets by using superdisintegrants such as croscarmellose sodium (CCS) & crospovidone (CP). 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 Soluplus showed rapid drug release than kollidon & PEG 6000 containing Solid dispersions and pure drug alone. The release was found to follow the first order kinetics. Solid dispersions prepared by the solvent evaporation method were further formulated into tablets with superdisintegrants such as croscarmellose sodium, crospovidone. The dissolution rate of such tablet formulations were found to release the drug at a faster rate than the tablets prepared with plain drug.

INTRODUCTION: Now a day's, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms [1].

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For the last few decades, researchers have been developing intraoral delivery systems (IDS) that can produce desirable drug exposure for optimum therapeutic effect. As a result, as evident from the abundance of scientific and patent literature over the last twenty years, nontraditional oral dosage forms (e.g., buccal, sublingual, etc.) have been or are being developed with emphasis on pre gastric absorption by the various tissues of the oral cavity with the intention to avoid first-pass and gut-wall metabolism, to enhance bioavailability, or improve convenience of dosing. The target sites for local drug delivery in the oral cavity include the following: buccal, sublingual, periodontal, periodontal pocket, peribuccal, perilingual, tongue (i.e., lingual), and gum (i.e., gingival) [2].

ODTs are being named as orodispersible, rapid-dissolving, mouth-dissolving, rapid-disintegrating tablets. There are some definitions that made by pharmacopeias and agency as follows:

Orodispersible tablets have been placed in the mouth where they 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 [3, 4]. 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 [5, 6]. 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* [9, 10]. 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 [11]. 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.

In present investigation an attempt has been made to enhance the solubility of lansoprazole by formulating it as solid dispersions and to enhance the dissolution rate by formulating it as orodispersible tablets employing superdisintegrants.

MATERIALS AND METHODS: Lansoprazole A Gift sample from Apotex pharma Ltd, Bangalore. Cros carmellose sodium and Crospovidone, KollidonVA64, Soluplus and PEG 6000 were commercially produced from Yarrow chem, Ltd., Mumbai. Magnesium stearate and mannitol were commercially produced from S.D Fine Chem, Ltd., Mumbai.

Saturated solubility studies: Saturated solubility studies of Lansoprazole were performed in different dissolution media. Excess amount of Lansoprazole was weighed and transferred into different conical flasks containing 10ml of different dissolution media i.e., Water, 6.8pH, 7.2 pH Phosphate buffer, 1.2 pH 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.

Preparation of Solid Dispersions: Solid dispersions were prepared by using PEG 6000, Soluplus and KollidonVA64 as a polymers by solvent evaporation method.

Solvent Evaporation Method: In this method Specified quantity of Lansoprazole and PEG 6000, KollidonVA64 & Soluplus 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 pH 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 pH 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 pH 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 **Fig. 5.** 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 analysis.

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 CCS and CP 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 **Fig. 6-7**.

Accelerated stability studies: The formulations, which showed good *in vitro* performance, were subjected to accelerated stability studies. The solid dispersion F6 and F8 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.

RESULTS AND DISCUSSION: Saturated solubility studies revealed that Lansoprazole show maximum solubility in 6.8 pH 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 hydrophilic carrier such as PEG 6000 and KollidonVA64 & Soluplus by solvent Evaporation method 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 172 ± 31-79 ± 2 µm. The drug content estimated in all solid dispersions was highly uniform in the range of 99.95 ± 0.3-97.10 ± 0.9% indicated the uniformity.

The dissolution studies of Lansoprazole solid dispersions prepared were performed in 6.8 pH 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 **Fig. 6-7**. The kinetics of drug release from all the formulation follows first order kinetics. It was observed that as the concentration of PEG 6000 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 Soluplus with drug to carrier ratio of 1:2 were found to undergo rapid dissolution rates than the other dispersions. The Solid dispersions KOD2, PEG2 and SOL2 were further characterized by FTIR analysis to understand the drug excipient compatibility before formulating them as orodispersible tablets. The results of analysis showed that all the peaks observed in the IR spectrum of pure drug Lansoprazole were also found in the IR spectras of solid dispersions which confirmed the compatibility of drug and excipients.

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± 3.0 to 200 ± 10 mg, hardness was found to be 3.5 ± 0.4 kg/cm^2, friability values were in the range 0.1-0.8% and drug content values were in the range of 29.98 ± 0.2 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 PH 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 CP tablets with the croscarmellose sodium 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 CCS > CP in the tablet formulations for superdisintegrants. Among the various tablet formulations F6 & F10 shows rapid drug release (up to 99%) when compared to marketed formulation (86.76%). 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**.

The formulations, which showed good *in vitro* performance, were subjected to accelerated stability studies. The formulation F6 & F10 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 F6 & F10 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 **Fig. 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.

TABLE 1: SATURATED SOLUBILITY STUDIES OF LANSOPRAZOLE

S. No	Medium	Solubility (mg/10ml)
1	Distilled Water	0.25
2	6.8 pH phosphate buffer	0.79
3	7.2 pH phosphate buffer	0.44
4	0.1N HCl	0.65

TABLE 2: COMPOSITIONS OF VARIOUS OF SOLID DISPERSION OF LANSPORAZOLE 1:1 AND 1:2 RATIO

Ingredients(mg)	PEG 6000		KollidonVA64		Soluplus	
	P1	P2	K1	K2	S1	S2
Lansoprazole(mg)	30	30	30	30	30	30
Carrier(mg)	30	60	30	60	30	60

TABLE 3: DISSOLUTION PARAMETERS OF LANSPORAZOLE 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	12	60.5	0.382	0..929	0.80	0.010
2	KOD1	18	43.33	0.493	0.781	0.93	0.015
3	KOD2	14	53.33	0.493	1.006	1.08	0.027
4	PEG1	9	56.66	0.482	0.643	0.93	0.027
5	PEG2	5	66.66	0.507	0.697	1.0	0.021
6	SOL1	4	58.75	0.7	1.243	0.92	0.021
7	SOL2	5	68.98	0.6	1.446	0.99	0.029

TABLE 4: COMPOSITIONS OF VARIOUS LANSOPRAZOLE ORODISPERSIBLE TABLETS

Ingredients (Mg/tab)	Formulations											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lansoprazole SD (kollidon) (Equivalent to 30 mg)	90	90	90	90	-	-	-	-	-	-	-	-
Lansoprazole SD (PEG) (Equivalent to 30 mg)	-	-	-	-	90	90	90	90	-	-	-	-
Lansoprazole SD (Soluplus) (Equivalent to 30 mg)	-	-	-	-	-	-	-	-	90	90	90	90
Croscarmellose sodium(CCS)(mg)	20	30	-	-	20	30	-	-	20	30	-	-
Crospovidone(mg)	-	-	20	30	-	-	20	30	-	-	20	30
MCC(mg)	60	50	60	50	60	50	60	50	60	50	60	50
Mannitol	28	28	28	28	28	28	28	28	28	28	28	28
Magnesium state (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 4: 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	F1	10	60.5	0.382	0..929	0.80	0.010
2	F2	8	43.33	0.493	0.781	0.93	0.015
3	F3	11	53.33	0.493	1.006	1.08	0.027
4	F4	10	56.66	0.482	0.643	0.93	0.027
5	F5	7	36.66	0.507	0.697	1.00	0.021
6	F6	5	28.75	0.702	1.243	0.92	0.021
7	F7	8	32.98	0.612	1.446	0.99	0.029
8	F8	6	25.5	0.382	0..929	0.80	0.010
9	F9	7	33.33	0.493	0.781	0.93	0.015
10	F10	5	25.33	0.493	1.006	1.08	0.027
11	F11	6	30.66	0.482	0.643	0.93	0.027
12	F12	6	31.66	0.507	0.697	1.00	0.021

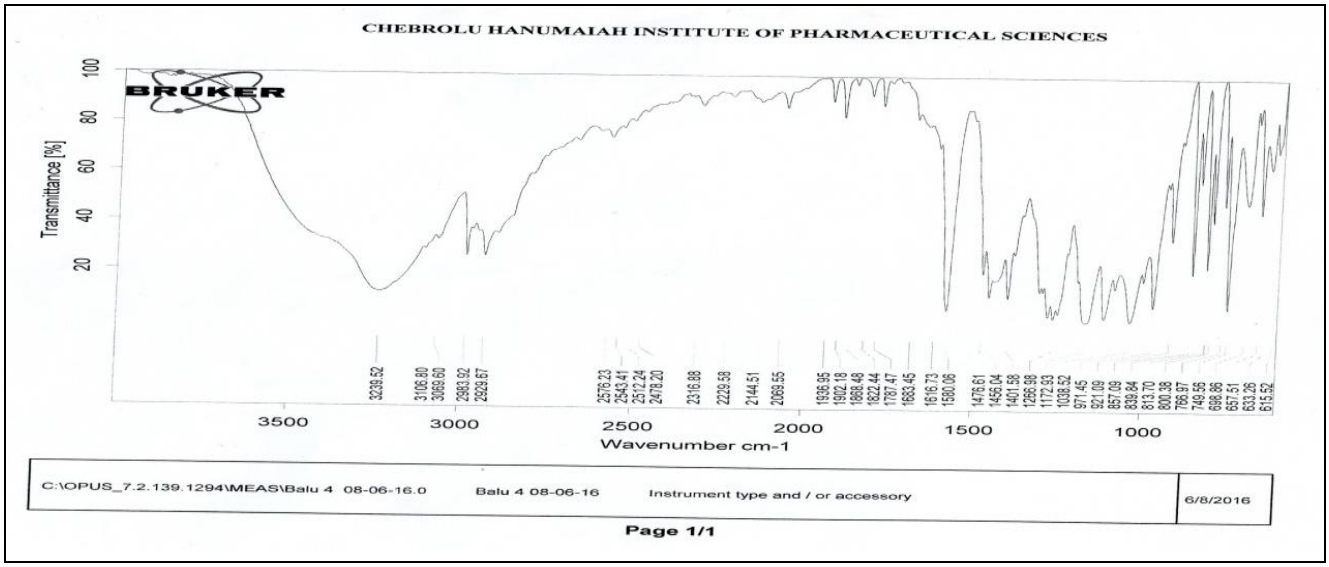

FIG. 1: FT IR SPECTRA OF LANSOPRAZOLE PURE DRUG

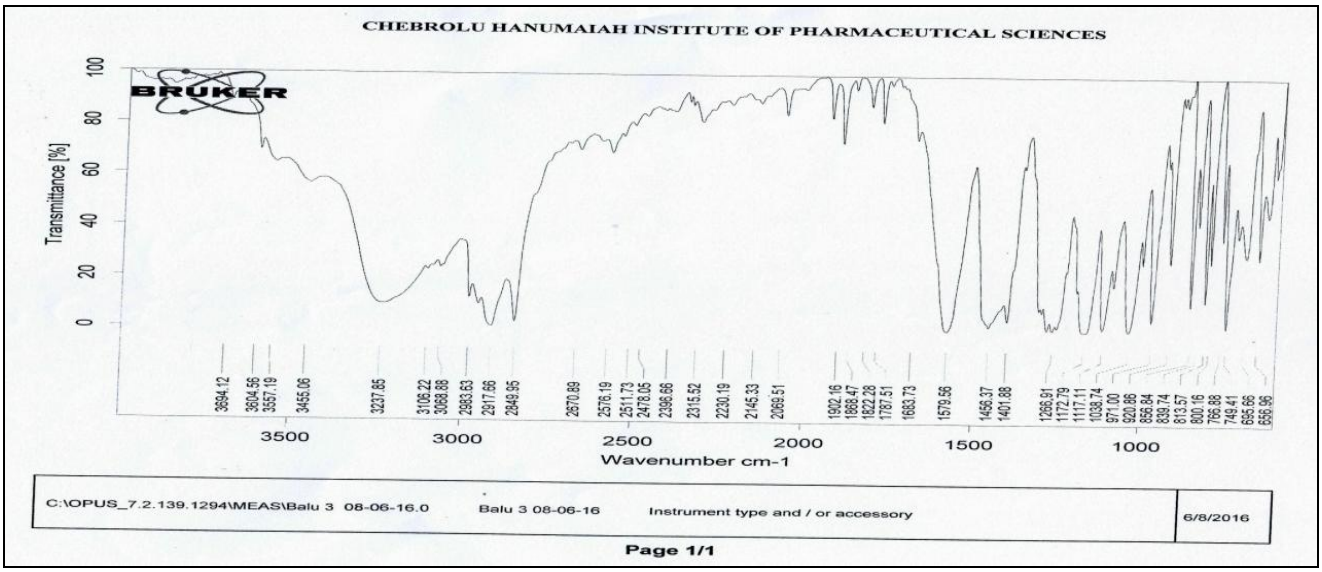

FIG. 2: FTIR SPECTRA OF SOLID DISPERSION PEG2

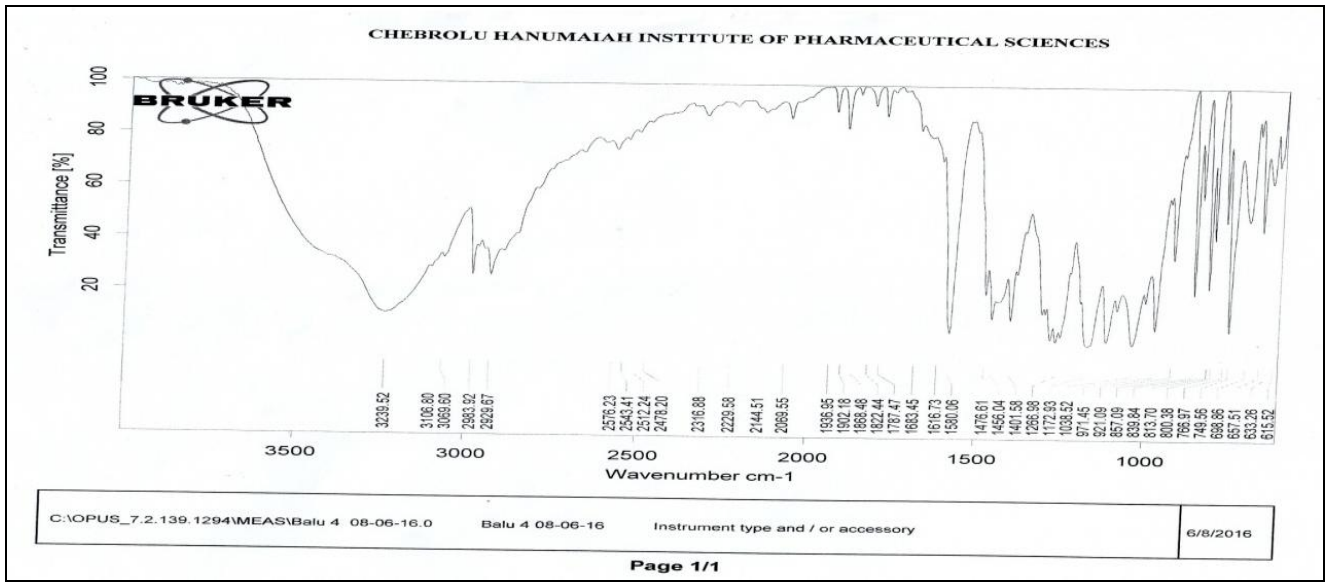

FIG. 3: FTIR SPECTRA OF SOLID DISPERSION SOL2

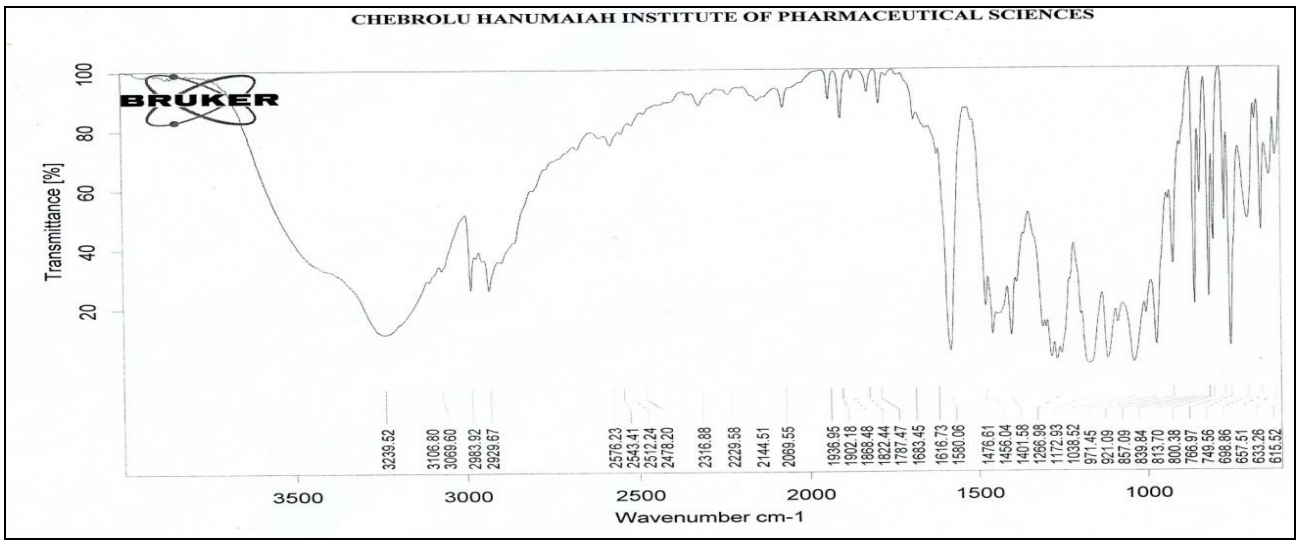

FIG. 4: FTIR SPECTRA OF SOLID DISPERSION KOD2

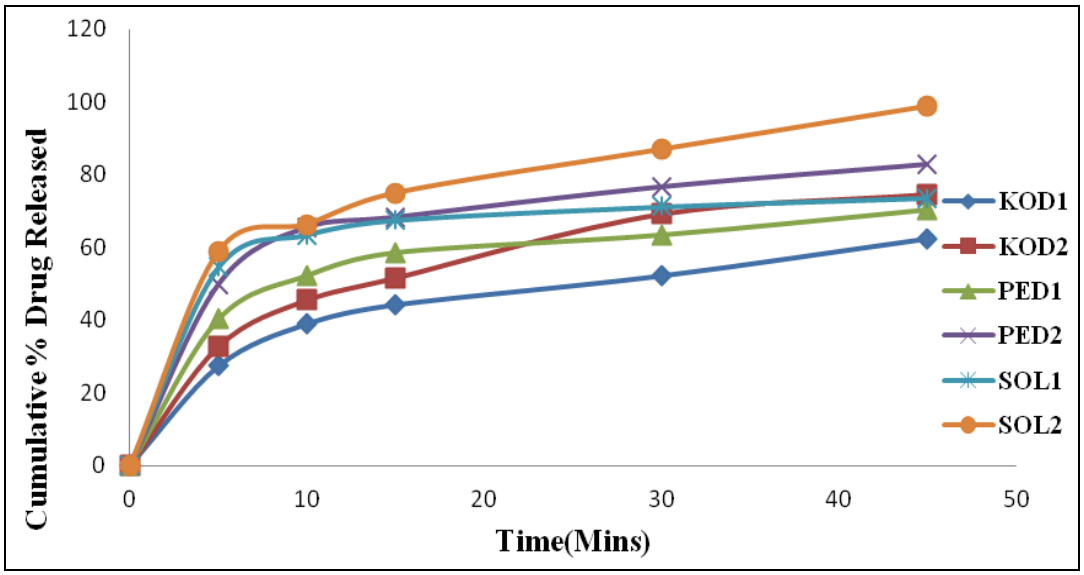

FIG. 5: DRUG RELEASE PROFILES OF LANSOPRAZOLE SOLID DISPERSIONS

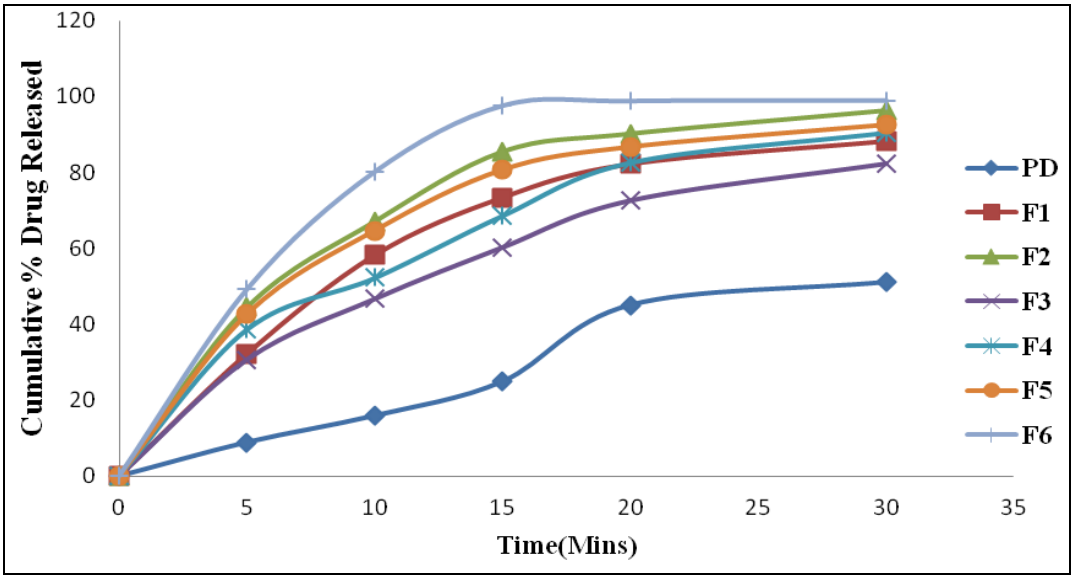

FIG. 6: DRUG RELEASE PROFILES OF LANSOPRAZOLE ORODISPERSIBLE TABLETS

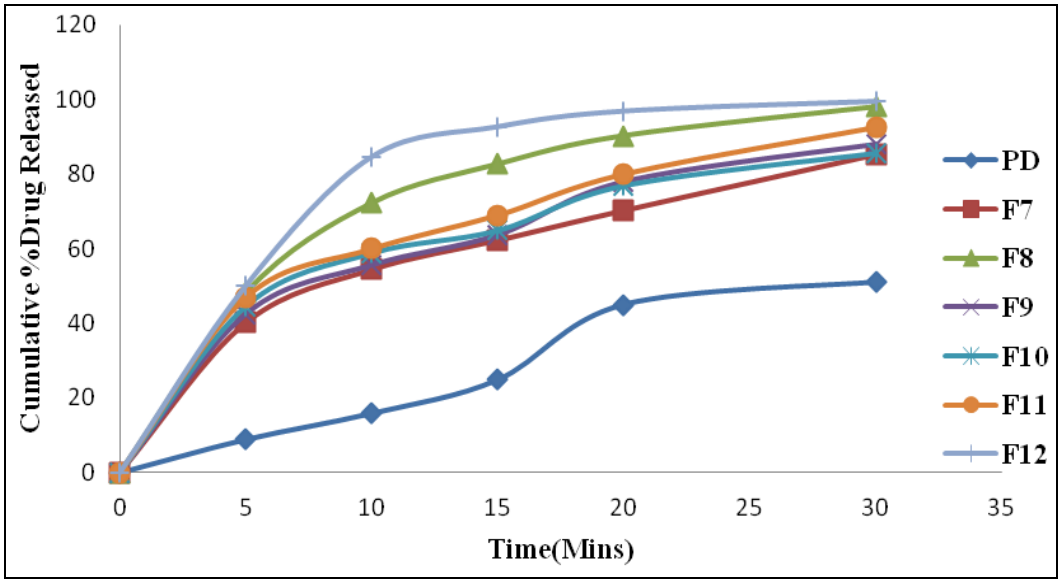

FIG. 7: DRUG RELEASE PROFILES OF LANSOPRAZOLE ORODISPERSIBLE TABLETS

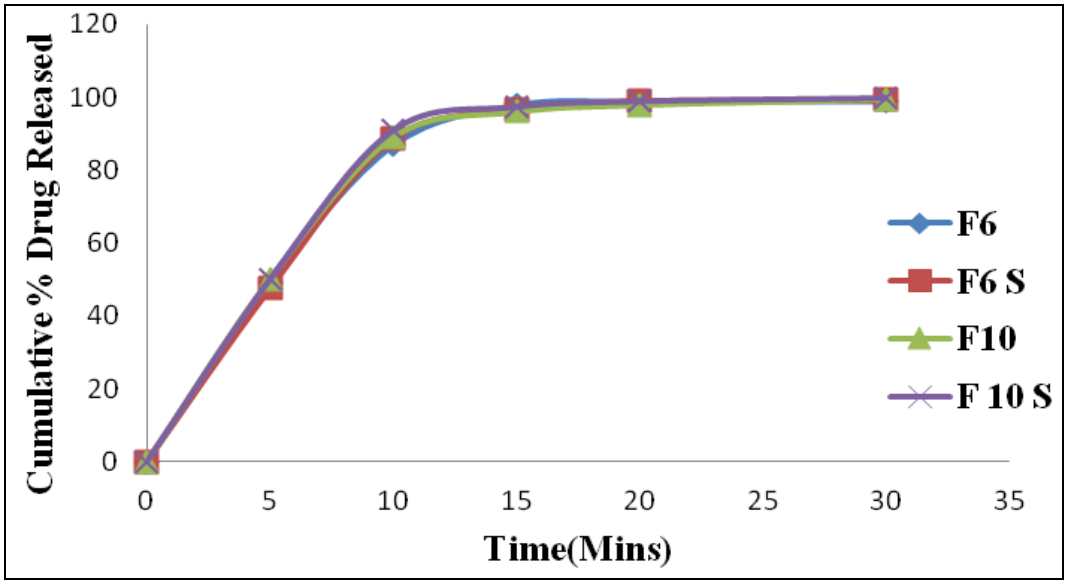

FIG. 8: DISSOLUTION PROFILES OF OPTIMIZED LANSOPRAZOLE FORMULATIONS BEFORE AND AFTER STABILITY STUDIES

CONCLUSION: The present study has shown that it is possible to increase the dissolution rate of poorly soluble drug Lansoprazole by preparing it as solid dispersions with carriers like PEG 6000, KollidonVA64 & Soluplus. Among the various methods employed for the preparation of solid dispersions. Dispersions prepared by solvent evaporation method with soluplus 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 Soluplus & croscarmellose sodium 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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