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Dissolution Rate Enhancement of Lansoprazole Tablet in Hydrophilic Carrier Solid Dispersions by Solvent Evaporation Methods

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Abstract

Solid dispersion technique has been developed for improving solubility of water-insoluble drugs, aiming to achieve a better oral bioavailability. The objectives of present investigation is to improve the solubility and rate of dissolution of poorly aqueous soluble drug lansoprazole by preparing solid dispersion with hydrophilic carrier Poly Ethylene Glycol 6000, hydroxy propyl methyl cellulose, Polyvinyl pyrrolidone by using solvent evaporation method and selecting the best solid dispersion. The drug and excipient compatibility study of selected solid dispersion was performed by FTIR and DSC. This study showed no interaction in drug and carrier. The designed granulation method was employed to prepare solid dispersion tablets and the formulation was optimized through investigating the dissolution behaviours. The results indicated PEG and Polyvinyl pyrrolidone in combination of solid dispersion showed the best effect both on physical characterizations and dissolution studies. Furthermore, all type of solid dispersions significantly improved the dissolution rates when compared to pure drug and its corresponding physical mixture (PM). All the evaluations were performed and complies with the pharmacopoeial standards. The formulation F7 showed 98.88% of cumulative drug release within 8 min with zero order release pattern. The solid dispersion tablets prepared in simplified tableting method exhibited better operability, stability and dissolution behaviour than the tablets prepared in traditional ways, which brought more opportunities to solid dispersion technique for industrial production

Keywords: *Solid dispersion, Solubility enhancement, Solvent evaporation, Lansoprazole.*

1. Introduction

Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances. Therapeutic efficiency of a drug is dependent on the bioavailability and eventually upon the solubility and absorption of drug molecules. The solubility is an important parameter to achieve the required concentration of drug in the systemic circulation and hence to attain the biological activity of the drug in the body [1].

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. They consist of the drug dispersed molecularly in a highly water-soluble carrier. By judicious selection of the carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude. Discontinuous solid solutions are those in which the solubility of each of the component in the other is limited. Depending on the location of the solvate molecules in the solvent, solid solutions can be substitutional crystalline, interstitial crystalline or amorphous solid solutions [2].

In case of a peptic ulcer is a rupture of the stomach's inner lining, the first section of the small intestine, and occasionally the lower oesophagus. A gastric ulcer occurs in the stomach, while a

duodenal ulcer occurs in the first part of the intestine. The most typical symptom of a duodenal ulcer is waking up with upper abdomen pain in the middle of the night, which improves with food. Eating might increase the pain associated with peptic ulcer disease. A searing or dull aching is frequently described as agony. Belching, vomiting, weight loss, and a loss of appetite are some of the other symptoms [3, 4].

A third of people over the age of 65 exhibits no symptoms. Bleeding, perforation and stomach blockage are all possible complications. In 15% of cases, there is bleeding. The majority of the time, the analysis is based on common signs and symptoms. The most common symptom of a peptic ulcer is abdominal pain. In other cases, doctors may treat ulcers without performing specific tests, instead of focusing on whether or whether the signs and symptoms improve, showing that their main analysis was correct [5,6].

2. Materials And Methods

Materials

Lansoprazole was obtained as a gift sample from Cipla Pvt. Ltd., Daund, Pune, India; Polyvinyl pyrrolidone, PEG 6000, Hydroxy Propyl Methyl Cellulose, Methanol, Microcrystalline cellulose, magnesium (Mg) sterate, Talcum powder and Mannitol were purchased from Research Lab Fine Chem. Ind, Mumbai (400 002), India. All further chemicals and reagents used were of analytical grade.

Pre-formulation Study

Melting Point

Melting point determination is an important parameter which comes under preformulating study. It gives the information regarding the purity of a compound. Lansoprazole, Polyvinyl pyrrolidone, PEG 6000, Hydroxy Propyl Methyl Cellulose, MCC, mannitol and Mg stearate were determined by capillary method. The substance whose melting point was determined was dried and introduced into a small dry capillary tube, which was then sealed at one end so as to form a compact column. The capillary was then tied to a thermometer and introduced in the thiele's tube. Heating was then started at the rate of increase in temperature of 3°C per minute. Heating was continued until the substance was melted. At this stage, the thermometer reading was noted [17].

Solubility

A qualitative determination of the solubility was made by adding solvent in small in cremental amount to a test tube containing a fixed quantity of solute or vice versa affects each addition the system is vigorously shaken and observed visually. Add Lansoprazole in Solvent. Take a Dilution[A] 1mg drug add into 1 ml of particular solvent (Primary Solution), B] 1ml sample from Primary Solution add into 10 ml dissolution medium (0.1 N HCl) and Observe solution. Record Absorbance of Observe solution by UV Spectroscopy with a particular wavelength. Plot the graph & formed the bar graph of all observation. [16]

Quantification of Lansoprazole by UV Spectroscopy

Stock solution (100µg/mL) of TM was prepared in phosphate buffer (pH 7.4) and acetate buffer (pH 1.2), which was then analyzed in the range 200–400 nm, using a UV double-beam spectrophotometer (Schimadzu-1800 UV) for the determination of λ max. From this stock solution, standard solutions in the range 2–10 µg/mL were prepared, and the absorbance of each standard solution was determined spectrophotometrically at the λ max. obtained. Using absorbance–concentration data, a calibration curve was constructed [18, 19].

FTIR Studies of Lansoprazole

The FTIR spectra of TM were recorded using a Fourier Transform Infrared spectrophotometer (BRUKER 10074425) with diffuse reflectance principle. The spectrum was scanned over a frequency range 4000–400 cm-1. The peaks obtained in the spectra were compared with corresponding functional groups in the structures of TM [20]

Drug Excipients Compatibility studies

Interaction of drug i.e., Lansoprazole with the excipients, which was present in the formulations is monitored with the help of FTIR (BRUKER 10074425). The FTIR spectrums of the Lansoprazole and

physical mixture of Lansoprazole: Polyvinyl pyrrolidone: PEG 6000: Hydroxy Propyl Methyl Cellulose:MCC:Mannitol:Mg stearate, in 1:1 proportion, respectively were compared for any possible drug–excipients inter1action [21].

Preparation of Solid Dispersion [7-15]-

Lansoprazole solid dispersion was prepared by using hydrophilic carriers like polyethylene glycol (PEG 6000) Polyvinyl pyrrolidone and Hydroxy propyl methyl cellulose in proportions viz .1:1 (drug: carrier) (30mg:30mg), 1:2 (30mg: 60mg) and 1:1:1 (drug: carrier: carrier) (30mg: 30mg: 30mg) was prepared by a solvent evaporation method. Lansoprazole and carriers were dissolved in methanol and mixed with magnetic stirring. The solvent was evaporated at reduced pressure at 40^0C in a rotatory evaporation apparatus. Subsequently solid dispersion was stored under vacuum over silica gel for 12hrs at room temperature. After drying, the solid dispersion was passed through a 250µm sieve. Sample was stored in a desiccator and used for further investigation.

Table 1: Composition of Solid Dispersion.

Ingredient(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lansoprazole	30	30	30	30	30	30	30	30	30
PEG6000	30	-	-	60	-	-	30	30	-
PVP	-	30	-	-	60	-	30	-	30
HPMC	-	-	30	-	-	60	-	30	30

Evaluation of Formulations –

Evaluation of solid dispersion-

Solid dispersions were evaluated and characterized by the following methods [22– 25]

Drug Content Determination of lansoprazole in Solid Dispersion-

Solid Dispersions equivalent to 10 mg of lansoprazole was accurately weighed and transfer to 100 ml volumetric flask. The solution was diluted up to the mark with methanol. Suitably diluted solution was measured spectrophotometrically at 280 nm.

Fourier Transform Infrared (FTIR) spectroscopy-

FT-IR spectroscopy was carried out on an FTIR Spectrophotometer (Alpha, Bruker, Germany). The spectrum was reported. The spectra obtained for drug, polymer, physical mixture and optimized solid dispersion were compared.

Differential Scanning Calorimetry (DSC)-

The thermal behavior of the samples was studied by Differential Scanning calorimeter (DSC-PYRIS-1, perkinelmer). DSC scan was carried out in an atmosphere of dry nitrogen within the measuring range of -2 mW to 20 mW. The samples were heated at a rate of 10°C min^{-1} from room temperature to the melting point using reference of an empty aluminium pan.

Evaluation of Solid Dispersion

Flow properties such as angle of repose, poured density, tapped density and compressibility Index of solid dispersions, which showed better release and solubility enhancement, were evaluated to determine the suitability for tablet formulation [25-27]-

The angle of Repose (θ)-

Angle of repose was determined by funnel method. The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose (θ) was then calculated by measuring the height (h) and radius (r) of the heap of granules formed.

$\tan \theta = h/r$

Where, θ= angle of repose is the height of the cone, R= radius of the base of the cone

Bulk Density -

Apparent bulk density was determined by pouring a weighed quantity of powder into a graduated cylinder and measuring the volume of packing.

Bulk Density = weight of the powder/volume of the packing

Tapped Density-
Tapped density was determined by tapping method. Weighed quantity of powder was placed in a graduated cylinder and tapped until no further change in volume of powder was noted and the volume of tapped packing was noted. Tapped Density= weight of the powder/tapped volume of the packing.

Compressibility Index-
The compressibility of the powder was calculated by determining the Carr's index and Hausner's ratio. Compressibility Index= Tapped Density-Bulk Density/Tapped Density X 100

Hausner 's ratio = Tapped Density/Bulk Density

Preparation of Tablets with Lansoprazole1Solid Dispersion [25-27]-
Direct Compression Method Solid dispersions were prepared by solvent evaporation method and were formulated into tablets by direct compression method. In the case of direct compression, mannitol a directly compressible vehicle was used as filler. Microcrystalline cellulose, talc, and magnesium stearate were incorporated, respectively as disintegrant and lubricants. All ingredients were blended thoroughly in a closed dry plastic container. The blend of powders was compressed in to tablet weight of 300mg by using 8mm flat punch [27]. Compositions of various formulations are shown in Table 2.

Table 2: Formulations Composition of Lansoprazole Tablets of 300mg.

Ingredient(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lansoprazole	30	30	30	30	30	30	30	30	30
PEG6000	30	-	-	60	-	-	30	30	-
PVP	-	30	-	-	60	-	30	-	30
HPMC	-	-	30	-	-	60	-	30	30
Microcrystalline Cellulose	89	89	89	89	89	89	89	89	89
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talcum Powder	70	70	70	70	70	70	70	70	70
Mannitol	73.5	73.5	73.5	43.5	43.5	43.5	43.5	43.5	43.5
Methanol	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Total	300	300	300	300	300	300	300	300	300

Evaluation of Tablets [27-30]-

Physicochemical Properties
Tablets were evaluated and characterized by the following methods [22– 25]

Thickness
Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. Thickness of tablets was measured by digital caliper.

Hardness
The hardness of the prepared tablets was estimated using Pfizer hardness tester. Three tablets from each formulation batch were selected and force was applied diametrically. It is expressed in kg/cm^2.

Friability
Roche friabilator was used for testing the friability of prepared fast dissolving tablets. It subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm for 4 min or 100 revolutions. Pre-weighed samples (Wi) of tablets were placed in the friabilator and were subjected to the 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed (Wf). The friability (F) is given by the formula:

F= Wi- Wf/ Wi X 100

Weight Variation Test
Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and were compared with average weight. The comparison variation was within the I.P limits, it passed the weight variation test.

Disintegration Time

The disintegration time of the tablets was determined as per Indian pharmacopoeia. The test was carried out using tablet disintegration apparatus. Distilled water was used as a disintegrating medium at 37±0.2°C. The time required to obtain complete disintegration of all the tablets was noted.

Drug Content-

Five tablets were weighed and powdered using glass mortar and pestle. An accurately weighed 150 mg of powder was taken in to 50 ml volumetric flask, dissolved in ethanol and the solution was filtered through what man filter paper no. 41. The filtrate was collected and suitably diluted with phosphate buffer of pH 1.2. The drug content was determined at 280nm by UV spectrophotometer

In-vitro Drug Release Study

The in vitro drug release study of sold dispersion tablets was carried out by using United States of Pharmacopoeia (USP) – type II dissolution apparatus (paddle type). Phosphate buffer (pH 1.2) 900 mL was used as dissolution medium and the release was achieved at 37° ± 0.5 C, by maintaining rotation speed of paddle 50 rpm. The Samples (10 mL) were withdrawn at predetermined time intervals and the volumes were replaced with the fresh dissolution medium. The samples were filtered through what-man filter paper and analyzed by UV spectrophotometer at 280 nm. The experiment for different formulations (F1–F9) was conducted in triplicate, and cumulative percentage drug release was calculated.

3. Results and Discussion

Characterization of Pure Drug

The melting point of Lansoprazole, polyethylene glycol (PEG 6000) Polyvinyl pyrrolidone, Hydroxy propyl methyl cellulose, MCC, mannitol and Mg stearate were found to be 166-168 °C, 58-63 °C, 150-152 °C, 226-227 °C, 263- 265 °C, 165-167 °C and 198-200 °C respectively. From these melting points we know the purity of above-mentioned compounds. The calibration curve was found to be linear in the concentration range of 2–10 µg/mL having coefficient of regression value R^2 =0.9998 and Slope y = 0.0505x + 0.0409. Calibration curve refers to UV Visible measurements. By using the above-mentioned slope equation, we can easily find out the value of x (concentration of drug) in the content uniformity and in the percentage of drug release study. The FTIR spectra of pure Lansoprazole (Fig. 1) showed the peaks at wave numbers (cm^{-1}), corresponding to the functional groups pre1sent in the structure of the Lansoprazole (Table 3). The FTIR spectrum of Lansoprazole exhibited characteristic signals. The presence of absorption bands corresponding to the functional groups present in the structure of Lansoprazole, and the absence of any well-defined unaccountable peak showed a confirmation of the purity of the drug sample.

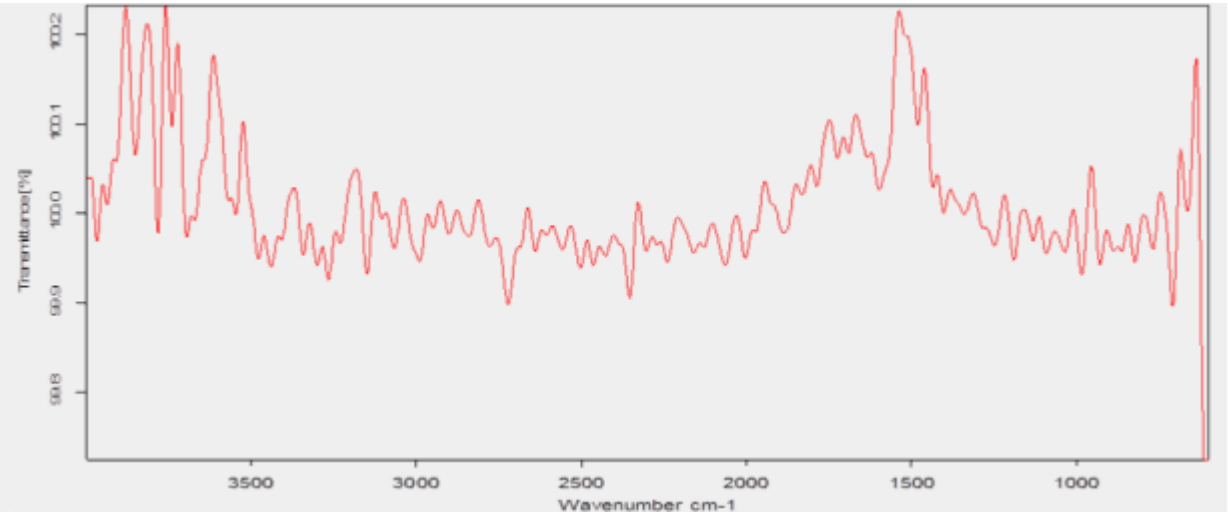

Fig.1 FTIR spectra of pure Lansoprazole

Table 3. Interpretation of FTIR spectrum of Lansoprazole.

Wavelength (cm^{-1})	Functional Groups
1015.21	S=O Stretching
1283.15	C-N Stretching
2761.96	C-H Stretching
3187.20	N-H Stretching

Drug-excipients Compatibility Studies

The stability of Lansoprazole in the presence of excipients used in the formulations was observed. The FTIR spectrum of the Lansoprazole (A) was compared with FTIR spectrum of the solid dispersion of Lansoprazole and excipients (B) which did not show any shifting of the functional group of TM (Fig. 2), therefore, there was no possible drug-excipients interaction.

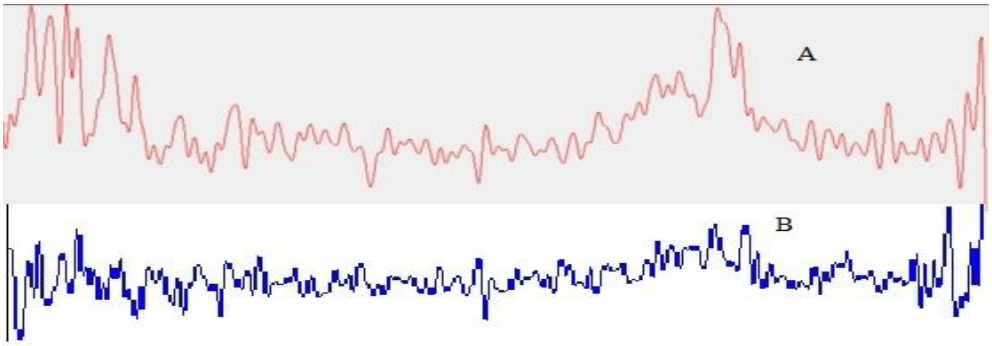

Fig. 2. Compatibility studies of Drug with Solid dispersion.

Solubility Study

The results of solubility and solubility enhancement are shown in fig. 3**.**

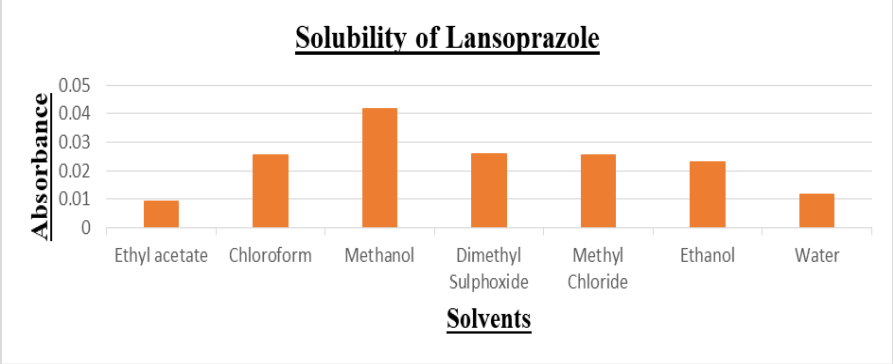

Fig. 3- Solubility Lansoprazole in different Solvents

As per the characterization study of solubility of Lansoprazole has the highest absorbance in methanol solvent, according to the solubility studies, thus we choose methanol as our organic solvent for formulations.

Differential Scanning Calorimetry (DSC)-

DSC thermograms of pure drug powder and that of solid dispersions prepared using PEG showed a sharp endotherm. DSC thermogram of pure Lansoprazole shows sharp peak at 122.44°C, corresponding to melting point which was obtained. It indicates that the drug Lansoprazole used was in pure crystalline state (Figures 4 and 5).

DSC of verapamil solid dispersions prepared with hydrophilic polymers shows decrease in enthalpy of fusion. The decrease in enthalpy of fusion of Verapamil in mixture form may be due to solubilizing effect of hydrophilic polymer during heating process. The DSC analysis provided additional evidence that solid dispersions were formed (Table 4)

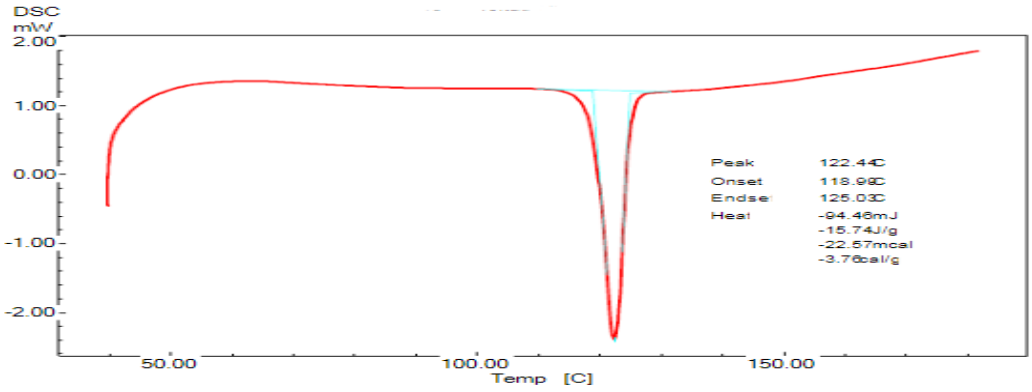

Fig. 4 - DSC thermogram of Lansoprazole

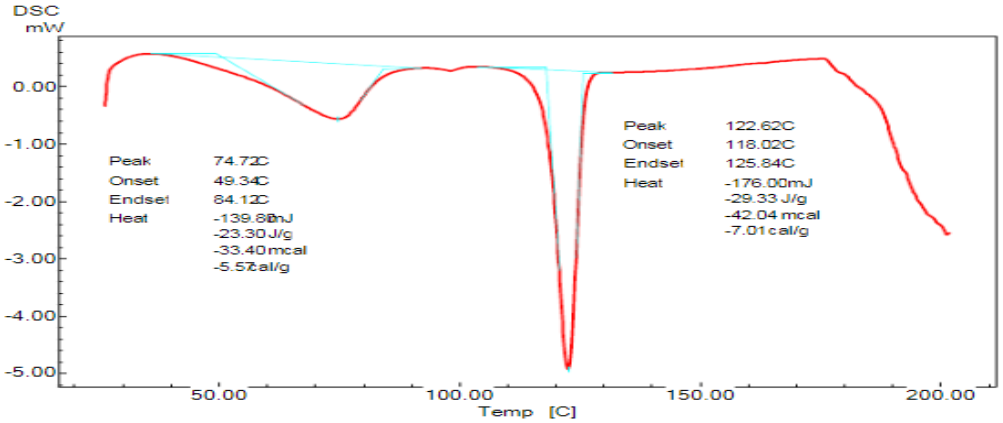

Fig. 5- DSC thermogram of Solid Dispersion formulation.

Table 4- DSC thermogram of Lansoprazole & Solid Dispersion

DSC thermogram	Onset temperature (°C)	Peak temperature (°C)
Lansoprazole	118.99°C	122.44°C
Solid Dispersion	118.02°C	122.62°C

Evaluation of Solid Dispersion Tablets Physicochemical Properties of Tablets

Physico-chemical parameters of all solid dispersion tablet formulations were found to be within acceptable limit. The tablets were uniform in size and shape, friable, and with acceptable hardness. There was no significant weight variation observed within average weight and individual weight. The % friability of the tablets was well within the acceptable range. The percentage friability ranged from 0.20 to 0.95%. The hardness of tablets ranged between 3.1±0.23 and 4.6±0.20 Kg/cm2.The thickness of the tablets was found to be 4.00–4.01 mm. Drug content of all batches was found to be within 85.86±0.49–99.90±0.0.49%.

Table 5 –Results of Quality Control test of Powder

Formulation Number	Bulk Density (mg/ml)	Tap Density (mg/ml)	Carr's Index (%)	Hausner's Ratio	Angle of repose Degree (º)
F1	0.291	0.300	3.0	1.030	27.94
F2	0.586	0.600	2.3	1.023	25.95
F3	0.577	0.590	2.2	1.022	25.93
F4	0.580	0.590	1.7	1.017	31.86
F5	0.591	0.600	1.5	1.015	28.51

F6	0.567	0.580	2.2	1.023	30.92
F7	0.570	0.583	2.2	1.023	25.86
F8	0.583	0.595	2.0	1.020	25.31
F9	0.586	0.602	2.7	1.027	40.82

Table 6 – Results of Quality Control test of Lansoprazole Solid Dispersion tablet

Batch code	Hardness (Kg/cm^2) (n=3)	Thickness (mm) (n=3)	Friability (%)	Disintegration Time (Min.)		Drug content (%)
				Acidic Media	Basic Media	
F1	3.55	4.00	0.95	20.62	30.39	92.83
F2	3.22	4.00	7.9	19.69	28.74	98.64
F3	3.82	4.00	0.25	21.57	30.38	95.45
F4	4.6	4.01	0.1	22.44	32.03	93.56
F5	4.3	4.00	0.9	22.19	30.38	94.63
F6	3.1	4.00	5.75	22.16	30.35	97.88
F7	3.91	4.01	0.2	22.17	30.19	99.90
F8	3.74	4.01	2.4	21.77	30.46	89.98
F9	3.82	4.01	0.65	22.01	30.44	85.86

In Vitro Drug Release/Dissolutions studes of Lansoprazole Solid Dispersion Formulations-

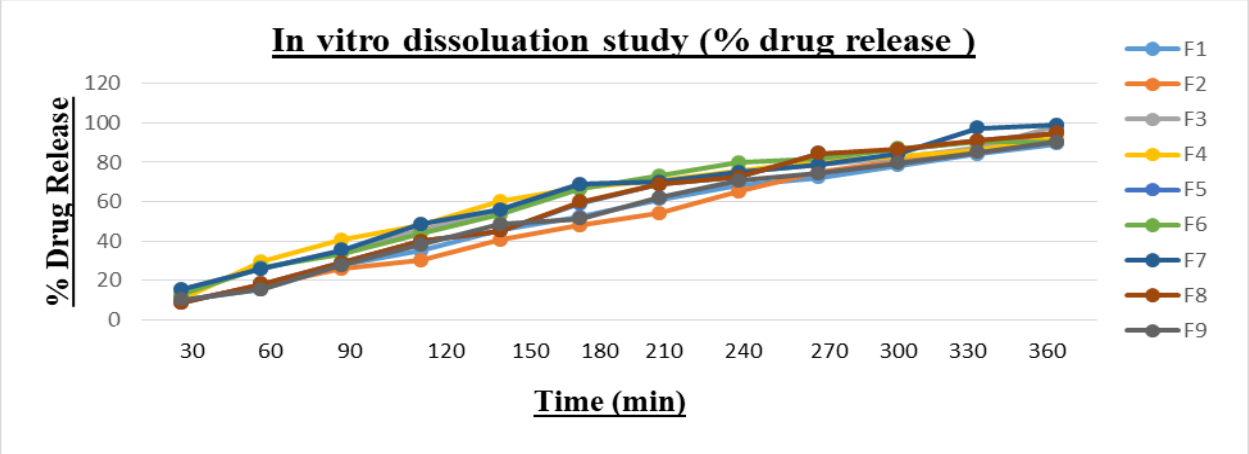

Fig 6– Dissolution Profile F1 to F9

According to Fig 6 & table 6 we see that the all formulation of solid dispersion tablet having adequate drug release capacity but as compare to each other the formulation number, F1 (89.2636%) having very low percentage drug release whereas the formulation number F7 (98.8854%), having High percentage drug release. So, we conclude that the formulation number F7 is the Optimize formulation according to this formulation.

4. Conclusion

From this study, the increase in dissolution rates of Lansoprazole solid dispersions can be observed. Solubility studies showed a solubilizing effect of carriers on Lansoprazole. FTIR and DSC studies of Lansoprazole solid dispersions indicated that the drug was entrapped within the carrier matrix and was present in amorphous form. In these systems drug carrier interaction was shown with the use of FTIR. The dissolution rates of physical mixtures were higher than those of pure drug, which was possibly caused by increased drug wettability. The pre-compression and post compression evaluations results are within the limit. Lansoprazole -HPMC/PVP/PEG6000 containing solid dispersions could be formulated into tablets by direct compression method. Formulation F7 showed faster drug release in comparison to other formulations. The increased dissolution rates in systems containing PEG and PVP were probably the result of decreased particle size, increased wettability and dispersibility of

Lansoprazole. The present study conclusively indicated that the use of various solid dispersion methods by using water soluble carriers improved the solubility of poorly water-soluble drug. It is clear from the data obtained that a higher polymer concentration gives faster drug release. Hence solid dispersion is one of most promising techniques used in enhancing the solubility of poorly water-soluble drug.

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Conflicts of interest-
The authors declare that they have no competing interests.

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