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DESIGN AND EVALUATION OF ORODISPERSABLE TABLETS OF ESOMEPRAZOLE

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Abstract:

The present research work is mainly focused on design and evaluation of orodispersable tablets of esomeprazole, which are used for the treatment of gastro esophageal reflux disease. An attempt was made to increase the solubility and dissolution rate of esomeprazole by formulating it as solid dispersions by physical method, kneading method and solvent evaporation method. Later the optimized solid dispersions were further formulated into orodispersable tablets using superdisintegrants such as Crosmellose sodium & crospovidone by direct compression technique. Characterization studies were carried out by pure drug (Esomeprazole) superdisintegrants (Croscarmellose sodium & Crospovidone) and optimized formulation E6 by FTIR and DSC Studies. The Studies were shown that there was no drug and excipient interaction. Based on the study, it may be concluded that esomeprazole tablets prepared by using optimized solid dispersions (ES2) 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.

Key words: *Solid dispersions Oro dispersible tablets, Esomeprazole, Soluplus, Croscarmellose sodium and crospovidone.*

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INTRODUCTION:

Orodispersible tablet are unit solid dosage forms like conventional tablets along with super disintegrants, which facilitates the tablets for rapid disintegration in the mouth in presence of saliva without any problem of swallowing [1, 2] esomeprazole is a antiulcer drug in which gastric acid secretion pathway is inactivated and it is final step in gastric parietal cells in a dose-dependent manner and its bioavailability is 85%. It also showed antibacterial activity against Helicobacter pylori in vitro studies [3, 4] in worldwide that proton pump inhibitors are used effectively for the treatment of gastric and duodenal ulcers and GERD [5]. In 2015, they are 6 protom pump inhibitors are approved by the USFDA. This class of drugs indicates the primary choice for treatment of esophagitis, nonerosive reflux disease peptic ulcer disease and prevention of NSAIDS associated ulcers, Zollinger-Ellison syndrome and dyspepsia [5-9]. Esomeprazole belonging to BCS II drug which has slight solubility in aqueous medium & bioavailability. Solid dispersions are the methods which are used for dispersing the active ingredients into aqueous-soluble carriers, which are prominently used to enhance the dissolution, bioavailability solubility and bioavailability of BCS class II drugs [10]. In the present research work has been made to enhance the dissolution rate and solubility of esomeprazole by developing it as solid dispersions using various ratios of carriers and to increase the rate of dissolution by formulating it as esomeprazole orodispersible tablets by direct compression technique using croscarmellose sodium and crospovidone as superdisintegrants.

MATERIALS AND METHODS:

Esomeprazole and Soluplus were procured as a gift samples from Aurbindo pharma Ltd, Hyderaded. Croscarmellose sodium and Crospovidone were procured commercially from Qualigens Fine Chemicals., Mumbai. Magnesium stearate and talc were obtained commercially from yarrow Chem, Ltd., Mumbai.

Esomeprazole saturated solubility studies

Solubility studies of esomeprazole were conducted in various dissolution media. 10mg of the drug was weighed the transferred into different conical flasks containing 10ml of various dissolution media i.e., Water, 0.1NHCl 6.8pH and 7.2pH Phosphate buffer and were closed appropriately. All the conical flasks were placed in a REMI incubator shaker at 50 rpm, 37º C ± 1º C for 24 hrs. The conical flasks were removed from the incubator shaker and samples were filtered using Whatman filter paper. The clear solution obtained by filtration and was suitably diluted with appropriate dissolution media and the absorbance values were noted at 296 nm by using corresponding dissolution media as blank solutions [9]. The solubilities of esomeprazole in various dissolution media were given in table 1.

Table: 1 Saturation Solubility Studies of Esomeprazole in Different Dissolution Media

S. No	Dissolution Medium	Amount of Esomeprazole Soluble (µg/ml)
1	Distilled Water	284.36
2	6.8 pH phosphate buffer	667.35
3	7.2 pH phosphate buffer	436.22
4	0.1N HCl	323.14

Methods of preparation

Methods such as physical mixing, kneading method and Solvent evaporation methods were employed for the preparation of esomeprazole solid dispersions using soluplus as a carrier. The compositions of various Solid dispersions were given in table 2.

Physical Mixing

Weighed quantity of drug and soluplus were taken and passed through sieve no. 80 and collected and transferred into a clean dry glass mortar to this add drug and carrier and were triturated for 5 min and again passed through sieve no. 80 collected and packed in a suitable glass container and was sealed hermetically and stored at an ambient condition.

Kneading Method

Accurate quantity of drug and soluplus were taken in two different mortars and triturate separately them to get fine powder. soluplus was added to mortar containing drug and mixed thoroughly with required amount of water for 2 minutes with high pressure. The mixtures were passed to sieve no 60 and collected, stored in a amber colored container and sealed [11]

Solvent Evaporation

Required quantity drug and soluplus was taken in a china dish and to this add few ml of methanol and evaporated under vacuum using rota evaporator. The obtained mixture was triturated in a glass mortar and passed through sieve no.100 and screened. Then the resulting mixture was dried and passed through the sieve no.100, packed in a wide mouthed bottle and sealed [11].

Table: 2 Compositions of various Esomeprazole Solid Dispersions

Method	Solid dispersion Code	Composition	Ratio	Concentration
Physical Mixing Method	EP1	E+ Soluplus	1:1	40:40
	EP2	E+ Soluplus	1:2	40:80
Kneading Method	EK1	E+ Soluplus	1:1	40:40
	EK2	E+ Soluplus	1:2	40:80
Solvent Evaporation Method	ES1	E+ Soluplus	1:1	40:40
	ES2	E+ Soluplus	1:2	40:80

Evaluation of solid dispersions

Parameters such as angle of repose, carr's index, average particle size and drug content was evaluated and physical parameters are within the official limits. The obtained data was showed in table 3.

Table: 3 Physical Parameters of esomeprazole solid dispersions

S.NO	Solid Dispersion	Angle of Repose(°)	Carr's index (%)	Particle size(µm)	Drug content (mg)
1.	EPD	28.62	19.63	186±2	40.00±0.2
2.	EP1	24.22	16.45	173±2	39.43±0.3
3.	EP2	23.17	15.78	172±4	39.54±0.3
4.	EK1	22.45	14.55	174±4	39.22±0.2
5.	EK2	23.80	12.78	175±6	39.68±0.3
6.	ES1	21.32	16.67	173±4	39.78±0.2
7.	ES2	20.66	14.88	174±2	39.89±0.2

Estimation of esomeprazole solid dispersions

Esomeprazole solid dispersions were taken and transferred into 100ml volumetric flask to this few ml of methanol was added shaken occasionally for about 30 minutes and the remaining volume was made by adding 6.8 pH Phosphate buffer to the up to 100ml volumetric flask. From the above flask take 10ml solution was taken and centrifuged. The supernatant solution obtained was collected and filtered. Then the filtrate diluted with 6.8 pH Phosphate buffer and the absorbance was noted at 296 nm. This test was repeated six times (N=6) for all the formulations. The estimation of esomeprazole from all the formulations were showed in table 3

Dissolution studies on esomeprazole solid dispersions

Solids dispersions were subjected to dissolution studies using USP paddle Type II apparatus with 900ml of dissolution medium containing 6.8 pH phosphate buffer. The samples were drawn up to 45 minutes. Samples were taken and suitably diluted with 6.8 pH phosphate buffer and the amount of dissolved drug was determined by ELICO SL-210 double beam spectrophotometer at 296 nm and simultaneously determined for the % cumulative drug released. The dissolution studies for all the formulation were performed in triplicate. The dissolution profiles for all the solid dispersions were shown in figures 1. The release rate constants, T_{50}, T_{90}, and DE_{30}% were given in the table 4.

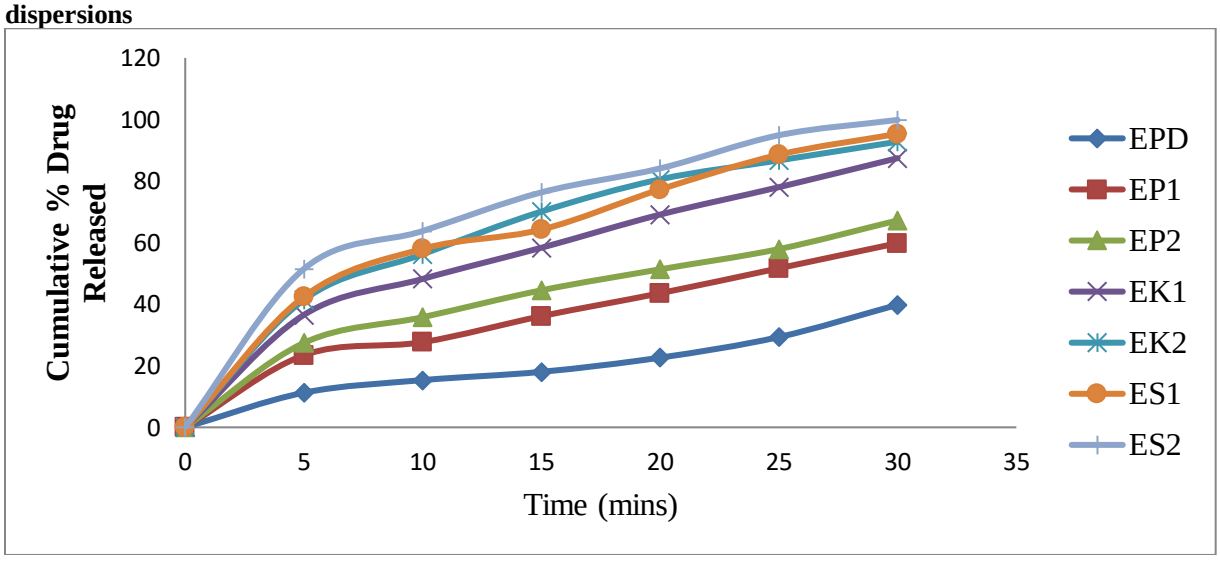

Figure 1: Drug Release Profiles of Esomeprazole Solid Dispersions

Table: 4 *Invitro* Dissolution Parameters of Esomeprazole Solid Dispersions

Formulation	T_{50} (Mins)	T_{90} (Mins)	DE_{20}%	K (Min^{-1})	R^2
EPD	> 30	> 30	23.8	0.0014	0.942
EP1	25	> 30	64.21	0.0016	0.959
EP2	20	25	65.48	0.0015	0.956
EF1	15	> 30	70.12	0.0202	0.971
EF2	10	28	71.80	0.0783	0.982
ES1	8	24.5	73.91	0.0409	0.989
ES2	6	22.5	75.46	0.0648	0.998

CHARACTERIZATION OF ORODISPERSIBLE TABLETS

FTIR and DSC studies can be performed on esomeprazole, Croscarmellose sodium, crospovidone and (E6) optimized formulations.

Fourier transforms infrared spectroscopy (FTIR)

The FTIR spectra of esomeprazole, Croscarmellose sodium, crospovidone and (E6) optimized formulations were obtained using Brucker FTIR spectrophotometer. The FTIR spectra were shown in Figures 2 to 5.

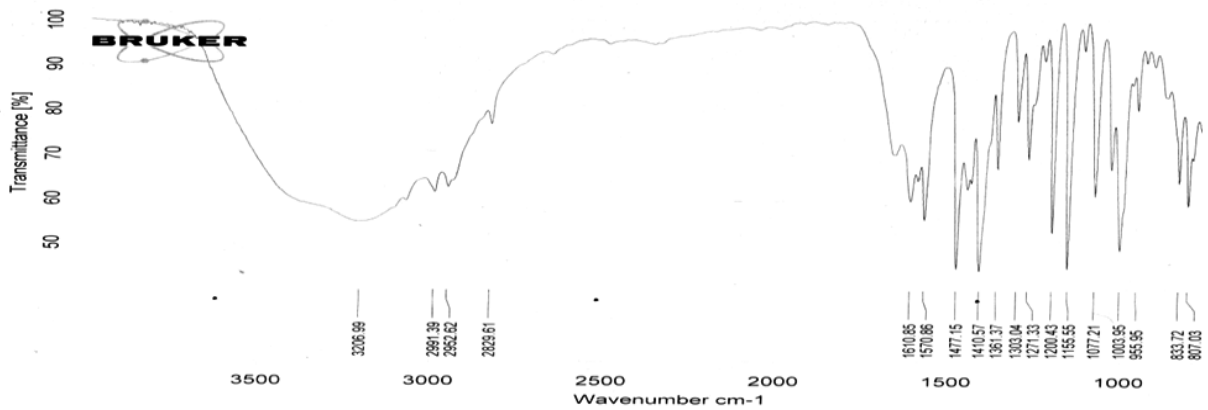

Figure 2: FTIR Spectra of Esomeprazole Pure drug

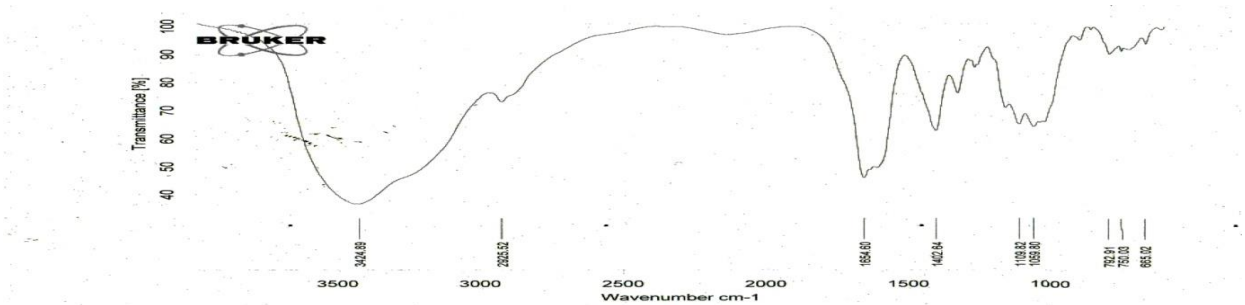

Figure 3: FTIR Spectra of Croscarmellose Sodium

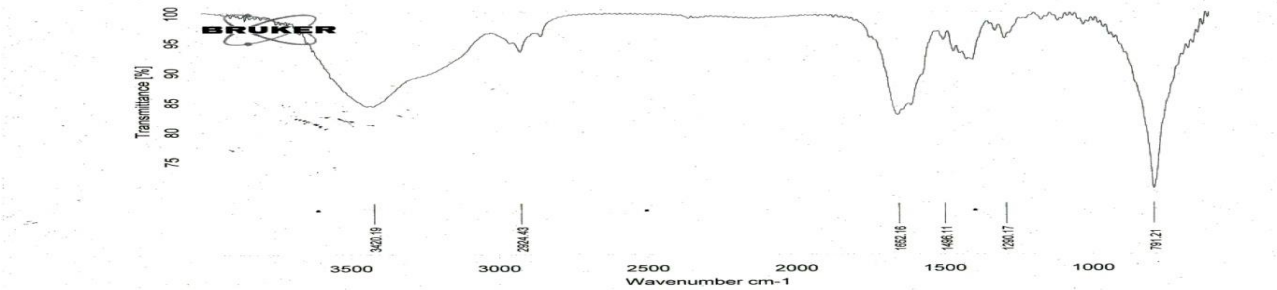

Figure 4: FTIR Spectra of Crospovidone

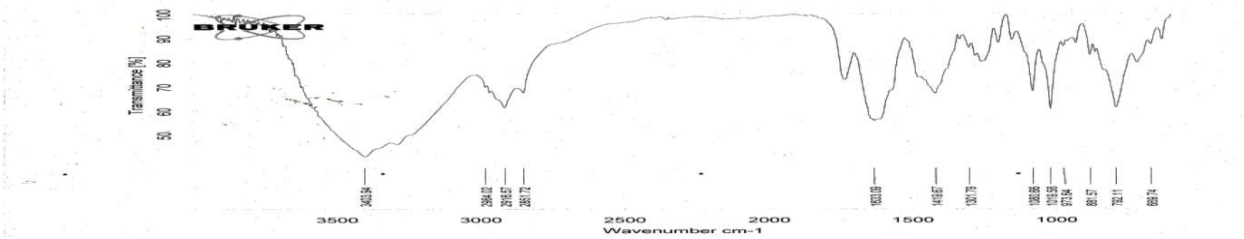

Figure:5 FTIR Spectrum of Optimized Formulation E6

Differential Scanning Calorimetry (DSC):

DSC Spectrum of esomeprazole, Croscarmellose sodium, crospovidone and (E6) optimized formulations using SHIMZDO & DSC-60. The DSC thermo grams were recorded and were shown in 6 to 9.

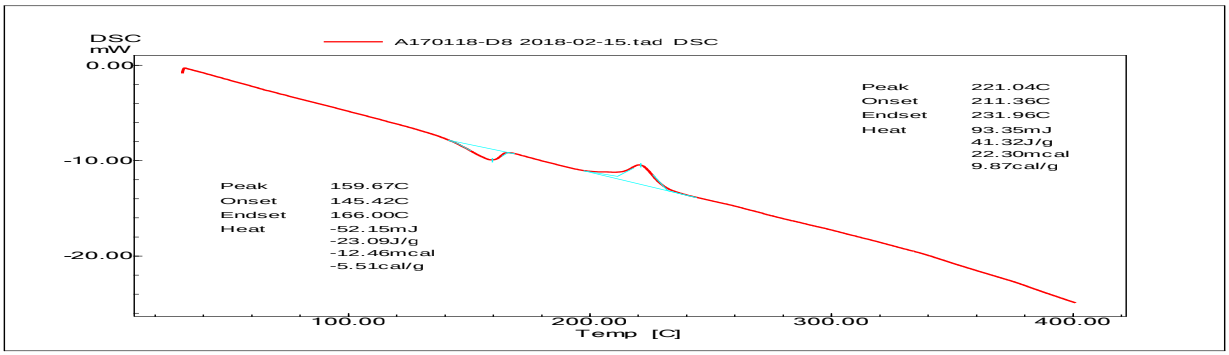

Figure 6: DSC Thermogram of Esomeprazole Pure drug

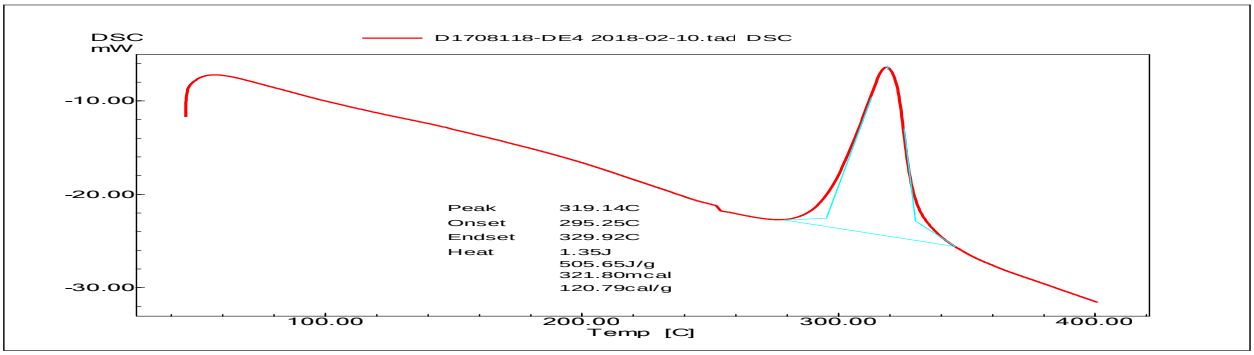

Figure 7: DSC Thermogram of Croscarmellose Sodium

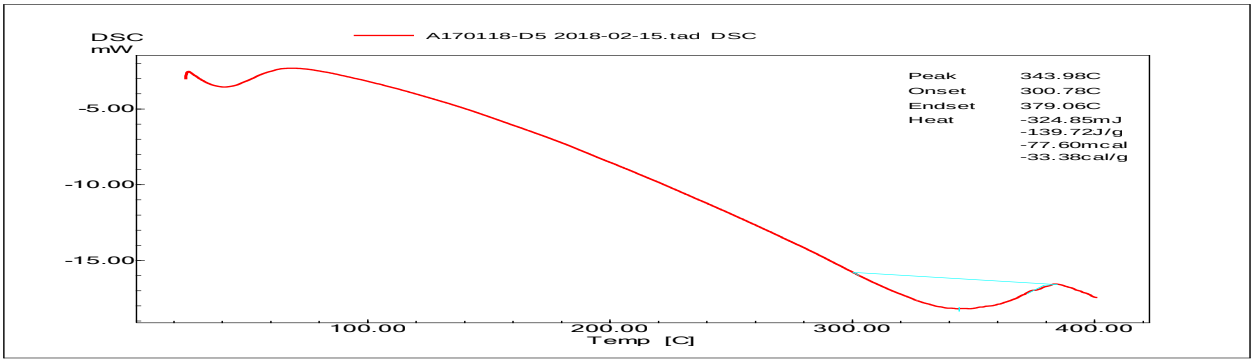

Figure8: DSC Thermogram of Crospovidone

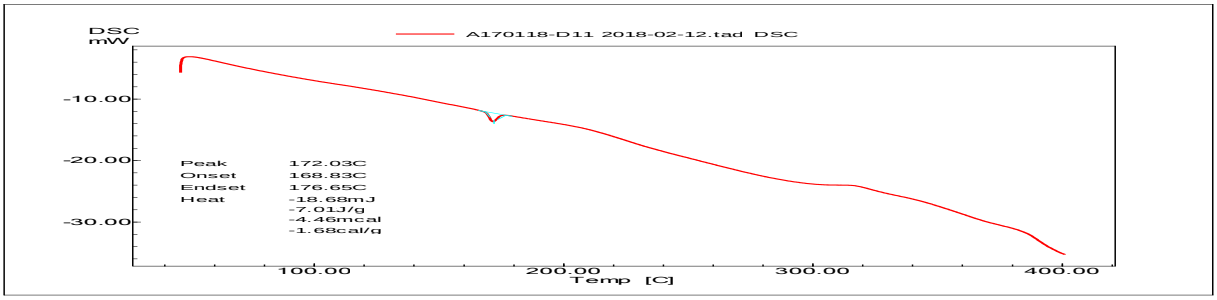

Figure 9: DSC Thermogram of Optimized Formulation

PREPARATION OF TABLETS WITH SOLID DISPERSIONS

The optimized solid dispersions (ES2) were selected and prepared in the form of orodispersible tablets of esomeprazole by direct compression technique. The tablets were prepared by taking optimized solid dispersion (ES2) along with crospovidone, croscarmellose sodium as superdisintegrants and microcrystalline cellulose as diluents and talc and magnesium stearate as glidant and lubricant. The drug and carrier proportions were maintained constant and superdisintegrants concentration was varied. The tablet weights of all the formulations were uniformly maintained by using microcrystalline cellulose. The compositions of tablet formulations were shown in the table 5. The weighed materials are individually passed through sieve No: 60 and mixed for 15 minutes by using double cone blender. Then the obtained the powder mixture was lubricated with talc and magnesium stearate and tablets were directly compressed as using ELITE 10 station mini press. The Compositions of various orodispersible tablets were given in table 5

Table: 5 Compositions of various Esomeprazole orodispersible tablets

Ingredients (mg/tab)	Formulations							
	E1	E2	E3	E4	E5	E6	E7	E8
Drug + carrier equivalent to 40mg (1:2)	120	120	120	120	120	120	120	120
Crospovidone (CP)	5	10	15	20	-	-	-	-
Croscarmellose Sodium (CCS)	-	-	-	-	5	10	15	20
Microcrystalline cellulose (MCC)Avicel Ph-102	65	60	55	50	65	60	55	50
Aspartame(mg)	6	6	6	6	6	6	6	6
Strawberry Essence	qs	qs	qs	qs	qs	qs	qs	qs
Talc (mg)	2	2	2	2	2	2	2	2
Magnesium stearate(mg)	2	2	2	2	2	2	2	2
Total Weight of Tablets (mg)	200	200	200	200	200	200	200	200

Evaluation of physical parameters for esomeprazole orodispersable tablets

Physical parameters such as weight uniformity, hardness, friability and drug content were evaluated for compressed tablets. The results were shown in table 6

Table: 6 Physical parameters of esomeprazole orodispersible tablets

Formulation	Weight Uniformity (mg)	Hardness (kg/cm^2)	Friability (%)	Wetting Time (Sec)	Dispersion Time (Sec)	Drug Content (mg/Tablet)
E1	198± 4.0	3.5± 0.2	0.18	28.0±2.6	Passed	39.47±0.3
E2	199± 2.0	3.5± 0.4	0.19	26.8±3.6	Passed	38.74±0.4
E3	202± 2.0	3.5± 0.5	0.16	20.3±1.5	Passed	38.57±0.2
E4	199± 2.0	3.5± 0.4	0.20	34.5±2.5	Passed	38.47±0.2
E5	197± 2.0	3.5± 0.5	0.17	28.6±3.6	Passed	39.90±0.4
E6	201± 2.0	3.5± 0.4	0.20	34.5±2.5	Passed	39.97±0.3
E7	199± 2.0	3.5± 0.1	0.19	18.8±1.5	Passed	39.87±0.2
E8	198± 4.0	3.5± 0.3	0.18	26.8±3.6	Passed	39.57±0.1

Dissolution studies on esomeprazole orodispersible tablets

Dissolution studies for all the tablet formulation were conducted in an 8 stage dissolution apparatus with 900ml of 6.8 pH phosphate buffer as a medium and the paddles were operated at 50 rpm and the temperature is 37 ± 0.5 ^{0}c throughout the studies. Samples were taken at regular time intervals and replaced with equal volume to maintain the constant volume of dissolution medium throughout the studies. The drug content of the formulations was performed by UV spectrophotometer at 296 nm. The dissolution profiles of all tablet formulations were shown in figures10**.** The release rate constants, $T_{50,}$ T_{90}, and DE_{30}% were given in the table7.

Table: 7 *Invitro* dissolution parameters of Esomeprazole orodispersible tablets

Formulation	T_{50} (Mins)	T_{90} (Mins)	DE_{20}%	K (Min^{-1})	R^2
E1	22.5	> 30	64.50	0.0267	0.967
E2	15	> 30	64.4	0.0398	0.973
E3	8	29.5	65.6	0.0374	0.971
E4	9	29.5	70.5	0.0489	0.990
E5	13	> 30	67.8	0.0357	0.977
E6	4.5	13.5	74.0	0.3894	0.992
E7	7	24.5	73.5	0.3712	0.982
E8	9	28.5	71.5	0.0399	0.987

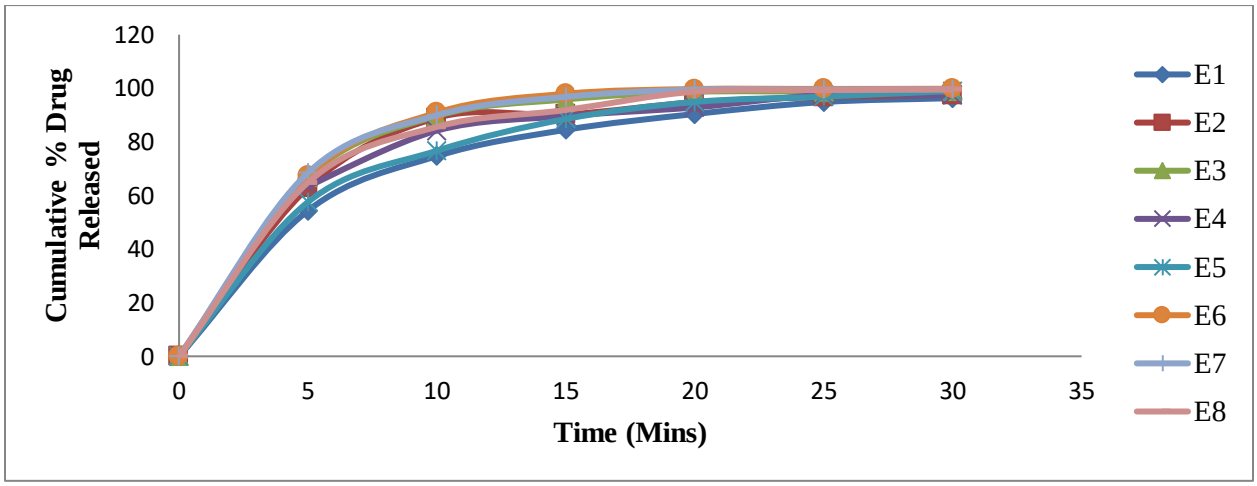

Figure 10: Dissolution Profiles of Essomeprazole Orodispersible Tablets

ACCELERATED STABILITY STUDIES

The tablet formulations which showed good in vivo performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of tablets and chemical stability of orodispersible tablets containing drugs. The tablet formulations such as E6 were subjected to accelerated stability studies. The above said formulations were kept in Petri dishes after preparation and stored in thermostated oven at a temperature and relative humidity of 25 ± 2^{0}c 60 ± 5% RH for 6 months and 40 ± 2^{0}c 75 ± 5% RH for 3 months. Then the samples of each type of formulations were evaluated for the earlier mentioned physical parameters. The dissolution profiles of optimized esomeprazole formulations before and after stability studies were shown in Figure 11.

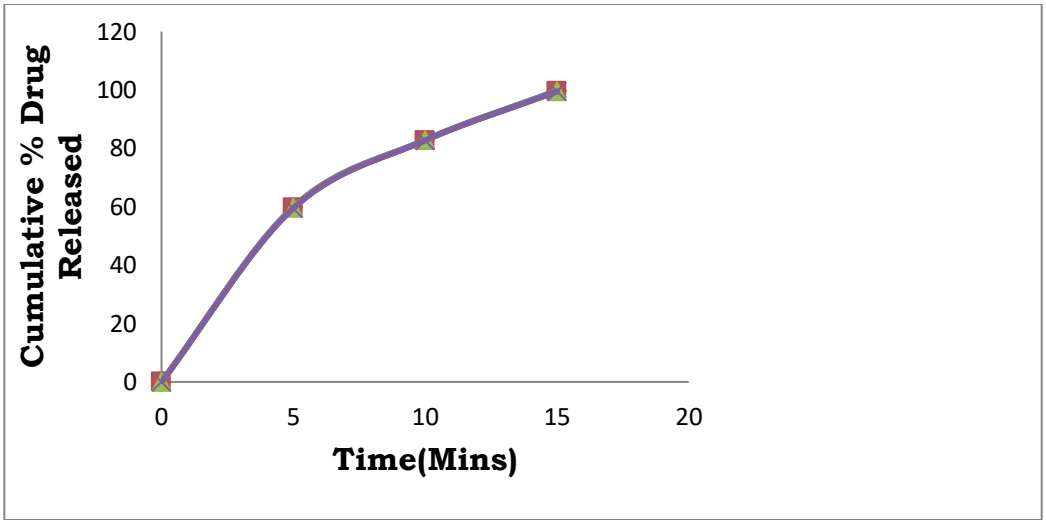

Figure 11: Dissolution profiles of optimized Esomeprazole formulations before and after stability studies

RESULTS AND DISCUSSION:

Esomeprazole solubility studies were conducted in Water, 0.1N HCl, 6.8pH and 7.2 pH Phosphate buffer as dissolution medium. The esomeprazole indicates maximum solubility in Phosphate buffer pH 6.8 and was selected as dissolution media in the present research work. The solubility values were shown in Table 1.

Physical mixing, kneading method and solvent evaporation methods were taken for the preparation of esomeprazole solid dispersions. These were prepared by changing the concentration of soluplus as a carrier. The various compositions of solid dispersions prepared by various methods were shown in table 2. All dispersions were quite stable and showed excellent characteristics.

The angle of repose, Carr's index, average particle size and drug content values obtained for various solid dispersions were in the range of 20.66° – 28.62º, 78 – 19.63%, 172±4to 186±2µm and.22±0.2 – 40.00± 0.2 mg.Thus all the solid dispersions were showed to be stable and suitable for preparation of tablets using direct compression technique. The obtained physical parameters were showed in table 3.

The prepared solid dispersions of esomeprazole were subjected to dissolution studies using USP Type II dissolution apparatus. These studies were performed in triplicate for all the solid dispersions. The rates of drug dissolution from solid dispersions were compared to esomeprazole pure drug. These results showed that all the solid dispersions were found to exhibit high solubility and dissolution rate than compared to the pure drug.

Solid dispersions of esomeprazole were prepared physical mixing, kneading method and solvent evaporation methods. Among these solid dispersions prepared by Solvent evaporation method were found to release the drug from 95.33±1.21% to 99.86±1.01% when compared to other methods and pure drug esomeprazole. The dissolution profiles of pure drug and prepared esomeprazole dispersions were shown in figure no 1.

The T_{50}, T_{90} DE $_{20}$% values are 6min, 22.5min and 75.46% for optimized ES2 solid dispersions respectively. The R^2 values attained for all the Solid dispersions of esomeprazole were in the range of 0.956 – 0.998. Among the various methods used, Solvent evaporation was showed complex formation between the drug and carrier. The order of rate of dissolution increased for various solid dispersions are solvent evaporation method >kneading Method > Physical Mixing Method. Based on the *invitro* studies ES2 solid dispersions prepared by solvent evaporation containing drug to carrier ratio of 1:2 was showed high dissolution rate, hence this optimized formulation ES2 was selected for preparation of ODTS by using various proportions superdisintegrants such as croscarmellose sodium and crospovidone were taken at 5, 10, 15, and 20% W/W of the tablet formulation and were prepared by direct compression technique. The compositions of esomeprazole tablet formulations were given in table 5.

Later the ODTS were evaluated for physical parameters such as weight uniformity, hardness, friability, wetting time, dispersion test and drug content for finding the stability of tablets. These studies shown that total formulations were in the IP

specified limits. The tablets hardness and weight uniformity of all batches were in the range of 3.5± 0.4kg/cm^2 and 197± 2.0 to 201± 2.0 mg. The friability loss and wetting time of different batches of tablets was given in the range of 0.16-0.20%. and 18.8±1.5-34.5±2.5sec. The dispersion test for various batches of tablets were passed by producing a uniform dispersion in water within few minutes and no solid mass was retained on sieve no: 22, when the dispersion was passed through it. The drug content for all the batches of tablets were in the range of 38.47 to 39.97±0. All the tablet formulations were stable and complied I.P limits. The results were given in table no 6.

The prepared esomeprazole orodispersible tablets were subjected to USP Type II dissolution apparatus containing 900 ml of Phosphate buffer pH 6.8 maintaining at a temperature 37 ± 0.5^0 C with a paddle speed at 50 rpm. These studies shown that all the tablet formulations prepared by using various superdisintegrants were found to exhibit high solubility and dissolution rate than compared to tablets prepared without superdisintegrants. The dissolution profiles of esomeprazole orodispersible tablets were shown in figure 10.

The T_{50}, T_{90} $DE_{20\%}$ values of E6 are 4.5min, 13.5min and 74.5%respectively. The R^2 valves obtained for all the esomeprazole orodispersible tablets were linear in the range of 0.971 – 0.992. orodispersible tablets of esomeprazole prepared with 5% concentration of Croscarmellose sodium were showed high dissolution rate when compared to other tablet formulation, due to the increased wettability, and faster release of drug.

Fourier transform infrared spectral studies were used to know the interactions between drug with the excipients in the ODTS. The IR Spectra of drug esomeprazole, CCS, CP and E6 optimized formulation were shown in figures 2 to 5. The FTIR interpretation shown that there were no interactions between drug and excipient used in the formulation. The figures were shown in 2 to 5.

The Differential scanning calorimetry studies were conducted by using DSC60, Schimadzu instrument. The thermograms of drug esomeprazole, CCS, CP and E6 optimized formulation were shown in figures 6 to 9.

The optimized formulation E6 containing esomeprazole were conducted to accelerated stability studies. The results of these studies were shown in figures no 11. The results indicated that there were no physical changes observed in the tablets after storage. Based on these stability studies it was concluded that E6 ODT tablet formulation were found to be stable.

CONCLUSION:

The present study has shown to increase the rate of dissolution of slightly soluble drug esomeprazole by preparing in the form of solid dispersions using Soluplus as carrier. Among various methods used, solid dispersions prepared by solvent evaporation method with drug and carrier ratio 1:2 were exhibit high rate of dissolution when compared with pure drug. esomeprazole ODTS prepared by using various superdisintegrants also shows the rapid drug release when compared with pure drug. Based on the study, it may be concluded that esomeprazole tablets prepared by using solid dispersions with soluplus & Croscarmellose sodium as superdisintegrant was found to be ideal for rapid dissolution and increases the bioavailability.

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