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Research Article

FORMULATION AND EVALUTION OF SOLID DISPERSION OF LANSOPRAZOLE

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ABSTRACT

Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The solid dispersions based on the concept that the drug is dispersed in an inert water-soluble carrier at solid state. Several water-soluble carriers such as methyl cellulose, urea, lactose, citric acid, polyvinyl pyrrolidone and polyethylene glycols 4000 and 6000 are used as carriers for solid dispersion. Thus, the solid dispersion technique can be successfully used for the improvement of dissolution of Lasoprazole. Various solvents, carrier materials, diluents, disintegrating agents, lubricants have been used for the preparation of solid dispersion of Lasoprazole. Lansoprazole by solid dispersion method using Mannitol, polyethylene glycol (PEG) 4000 and Polyethylene glycol 6000, ß-cyclodextrin as carrier in 1:1,1:2,1:3,1:4 and 1:5 ratios. Solid dispersion of Lansoprazole was prepared by solvent evaporation method. In vitro release profiles of solid dispersions in phosphate buffer pH 6.8 were comparatively evaluated and also studied against pure Lansoprazole. Faster dissolution was exhibited by LPZ -Mannitol Solid dispersion containing 1:5 ratio. The prepared Solid dispersions were subjected for Assay, saturation solubility studies in distilled water and phosphate buffer pH 6.8.

KEY WORDS: Solid Dispersion, Bioavailability, Solubility, In Vitro Dissolution Study.

INTRODUCTION

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [1]. Improvement in the dissolution rate of the poorly soluble drugs after oral administration is one of the most crucial challenges in modern pharmaceutics. Many methods are available to improve these characteristics including salt formation, micronization and addition of Solvent or surface-active agents. In this study polyethylene glycol was selected and solid dispersion was prepared by the method of solvent evaporation [2]. Lansoprazole is a potent anti-inflammatory and antacid agent indicated for acute and chronic treatment of peptic ulcer. Lansoprazole suffered from low and variable bioavailability which was attributed to its low water solubility. Several ways have been used to improve the oral bioavailability of poorly soluble drugs as an example solid dispersion technique with water soluble carriers. The increase in dissolution rate of poorly water soluble drugs from SDs can be attributed to one or combination of different factors Among the popular carriers used in the formulation of SD are polyethylene glycols (PEGs). They are widely used because of their

hydrophilicity, low melting point, and low toxicity. The development of a pharmaceutical formulation is usually a trial and error technique including a careful control of the variables one at a time in a series of logical steps. This is generally a time-consuming method in which the effect of each experimental variable will be investigated separately, while keeping all others constant [3]. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs 2-4 there are practical limitation of these techniques. In 1961, Sekiguchi and Obi 5 developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water soluble drugs can be overcome. This method, which was later, termed solid dispersion which involved the formation of eutectic mixture of drugs with water-soluble carriers by the melting of their physical mixtures [4]. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method [5, 6]. The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960 [7]. Among the various approaches to improve solubility, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous [8]. Solid dispersion means a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous in nature. Most commonly used carriers for the preparation of SDs are different grade of polyethylene glycols (PEGs) and polyvinylpyrrolidone (PVPs), Gelucire 44/14, Labrasol, sugars, and urea [9-11]. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [12]. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi [8]. This technique has been used by many researchers/scientists for a wide variety of poorly aqueous soluble drugs to enhance the solubility of the drugs and hence bioavailability [8]. Literature reviews on solid dispersion of past four decades suggests that there is an increasing interest in using this approach [14]. Despite an active research interest, the number of marketed products arising from this approach is really disappointing. Only few commercial products were marketed during the last four decades [15, 16]. Several marketed and late stage drugs are designed for improved solubility by solid dispersion [15-17]. The goal of paper is to highlight the historical background of solid dispersion technology, various preparation techniques with emphasis given to their advantages and disadvantages, commonly used carrier in the preparation of solid dispersions and the recent advances in the field of solid dispersion technology.

Lansoprazole

Lansoprazole belongs to a group of drugs called proton pump inhibitors. It decreases the amount of acid produced in the stomach. Lansoprazole is used to treat and prevent stomach and intestinal ulcers, erosive esophagitis (damage to the esophagus from stomach acid), and other conditions involving excessive stomach acid such as Zollinger-Ellison syndrome. Over the counter lansoprazole (Prevacid OTC) is used to treat frequent heartburn that happens 2 or more days per week. Lansoprazole is not for immediate relief of heartburn symptoms.

Peptic Ulcer[17]

A peptic ulcer is the most common ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. It is defined as mucosal erosions equal to or greater than 0.5 cm. As many as 70–90% of such ulcers are associated with Helicobacter pylori a spiral- shaped bacterium that lives in the acidic environment of the stomach; however, only 40% of those cases go to a doctor. Ulcers can also be caused or worsened by drugs such as aspirin, ibuprofen, and other NSAIDs

Role of Lansoprazole In Peptic Ulcer[18]

Proton pumps are found on cells that line the stomach and are used by these cells to produce stomach acid. Lansoprazole works by inhibiting the action of the proton pumps, and thus reduces the production

of stomach acid. Lansoprazole stops excess acid flowing back into the esophagus and can be used to relieve heartburn symptoms associated with acid reflux. It also allows the esophagus to heal in reflux esophagitis.Lansoprazole can also be used to prevent and treat peptic ulcers that can occur as a side effect of non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac. NSAIDs relieve pain and inflammation by reducing the production of substances called prostaglandins. Unfortunately, prostaglandins are also produced in the stomach and help to protect the stomach lining from acid, so NSAIDs can allow the acid to irritate the stomach. Lansoprazole is used to treat peptic ulcers that occur due to this irritation.

MATERIALS AND METHODS

Lansoprazole (Triveni chemicals), Beta cyclodextrin (Research lab fine chem industries), Mannitol, Talc, Magnesium, stearate and MCC (Rajesh chemicals), Methanol (Priya chemicals), PEG 4000 (Merck ltd.), PEG 6000 (Central drug house pvt ltd) and Colorcoat EC4W (Corel pharma chem.)

Preparation of physical mixtures:

Five physical mixtures (PMs) of different proportions of Lansoprazole with beta cyclodextrin, Mannitol , PEG 4000, PEG 6000 were prepared in the ratios of 1:1 ,1:2 ,1:3 ,1:4,1:5 w/w. The required amounts of Lansoprazole and beta cyclodextrin, Mannitol, PEG 4000, PEG 6000 were weighed and mixed thoroughly by light trituration for 3 min in a glass mortar. The mixture was sieved and the powder fraction corresponding to mesh size less than 60 was collected for further investigation.

Preparation of Solid Dispersion

Solvent Evaporation Method

Polymers used include: beta cyclodextrin, Mannitol, PEG 4000, PEG 6000. Drug and carriers were dissolved in common solvent methanol 30 ml. Then solvent was evaporated under room temperature. The experiment was carried out in dark because drug is light sensitive. The resultant mixtures were powdered in mortar, sieved through 60 mesh sieve and stored in cap vial at room temperature until evaluation. Characterization of solid dispersion

Angle of repose:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The prepared granules were allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the granules from the funnel mouth forms a pile of granules at the surface this is continued until the pile touches the stem tip of the funnel. A rough circle is drawn around the pile base and the radius of the granule cone was measured. Angle of repose was then calculated with the use of the following formula:

$$\tan\theta = h / r$$

Where, θ = angle of repose

h= height of the pile

r = average radius of the powder cone

Bulk Density:

Bulk density of the sample was determined by pouring gently 10g of sample through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density will be calculated as follows:

$$\text{Bulk Density (g/ml)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

Tapped Density:

10 grams of sample was being poured gently through a glass funnel into a 50ml graduated cylinder. The cylinder will be tapped from height of 2 inches until a constant volume will be obtained. Volume occupied by the sample after tapping will be recorded and tapped density will be calculated as follows:

$$\text{Tapped Density (grams/ml)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

Determination of Saturation Solubility

The shake flask method was used to determine saturation solubility of prepared solid dispersions in distilled water and phosphate buffer pH 6.8. Excess quantities of solid dispersions were added in 10 ml distilled water and phosphate buffer pH 6.8 which is then incubated in orbital shaker at 37˚C and at 100 rpm for 24 hrs. Solutions were filtered through Whatman filter paper. Absorbance of resulting solutions was measured on UV spectrophotometer at 285 nm and 271.5 nm in distilled water and phosphate buffer pH 6.8. Saturation solubility was then calculated by putting measured absorbance value in calibration curve equation for distilled water and phosphate buffer pH 6.8. Assay

Preparation of Standard Solution:

Lansoprazole 10 mg was weighed accurately and transferred to 10 ml volumetric flask. It was dissolved in methanol and volume was made to 10 ml with phosphate buffer pH 6.8. From this stock solution (1000 µg/ml). 1 ml solution was removed and diluted to 10 ml with to get the solution of 100 µg/ml. 1 ml from this solution was taken and further diluted to 10 ml with phosphate buffer pH 6.8. to obtain the solution of final concentration 10 µg/ml. Absorbance of resulting solutions were measured on UV spectrophotometer at 271.5 nm.

Preparation of Sample Solution:

Solid dispersion equivalent to 10 mg Lansoprazole was weighed accurately and transferred to 10 ml volumetric flask. It was dissolved in methanol and volume was made to 10 ml with phosphate buffer pH 6.8. From this stock solution (1000 µg/ml). 1 ml solution was removed and diluted to 10 ml with to get the solution of 100 µg/ml. 1 ml from this solution was taken and further diluted to 10 ml with phosphate buffer pH 6.8. to obtain the solution of final concentration 10 µg/ml. Absorbance of resulting solutions was measured on UV spectrophotometer at 271.5 nm.

In vitro Dissolution studies of solid dispersion:

In vitro dissolution studies were performed for solid dispersion using US Pharmacopoeia Dissolution Apparatus II (paddle type). An accurately weighed sample of solid dispersions (equivalent to 30 mg Lansoprazole) was placed into 900 ml of phosphate buffer (pH 6.8), maintained at a temperature of 37ºC ± 0.5ºC and stirred at a speed of 75 rpm. At 15 min time intervals, a 10-ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37ºC. The collected samples were filtered and analyzed at λ_{max} 271.5 nm using a UV visible spectrophotometer against phosphate buffer (pH 6.8) taken as blank.

RESULT AND DISCUSSION

Evaluation of powder blend

Table 1: Data for evaluation of powder blend

Sr. No.	Evaluation tests	Results	
		SD	PM
1	Bulk Density (g/ml^3)	0.544	0.472
2	Tapped density (g/ml^3)	0.720	0.659
3	Angle of Repose (^{0})	45.52	40.41

Determination of Saturation Solubility

Table 2: solubility of physical mixtures in water

Sr. No	Polymer	Ratio	Saturation Solubility [mg/ml]	% Increase in solubility	In times
1	Beta cyclodextrin	1:1	0.0413	124.45	2.24

		1:2	0.0233	26.63	1.26
		1:3	0.0336	82.60	1.82
		1:4	0.0281	52.74	1.52
		1:5	0.0473	157.6	2.57
2	Mannitol	1:1	0.0261	41.84	1.41
		1:2	0.0312	41.02	1.69
		1:3	0.0336	82.60	1.82
		1:4	0.0274	48.91	1.48
		1:5	0.0366	98.91	1.98
3	PEG 4000	1:1	0.0271	47.28	1.47
		1:2	0.0268	45.65	1.45
		1:3	0.0185	0.54	1.08
		1:4	0.0244	32.60	1.32
		1:5	0.0274	48.91	1.48
4	PEG 6000	1:1	0.0253	37.5	1.37
		1:2	0.0200	8.69	1.08
		1:3	0.0197	7.06	1.07
		1:4	0.0187	1.63	1.01
		1:5	0.0226	22.82	1.22

Table 3: solubility of solid dispersion in water

Sr No	Polymer	Ratio	Saturation Solubility [mg/ml]	% Increase in solubility	In times
1	Beta cyclodextrin	1:1	0.0863	369.02	4.69
		1:2	0.0431	134.23	2.34
		1:3	0.0895	386.41	4.86
		1:4	0.0642	248.91	3.48
		1:5	0.0910	394.56	4.94
2	Mannitol	1:1	0.0187	1.63	1.01
		1:2	0.0342	85.86	1.85
		1:3	0.0363	97.28	1.97
		1:4	0.0321	74.45	1.74
		1:5	0.0422	129.34	2.29
3	PEG 4000	1:1	0.0321	74.45	1.74
		1:2	0.0318	72.82	1.72
		1:3	0.0235	27.71	1.27
		1:4	0.0294	59.78	1.59
		1:5	0.0324	76.08	1.76
4	PEG 6000	1:1	0.0303	64.67	1.64

		1:2	0.0250	35.86	1.35
		1:3	0.0247	34.23	1.34
		1:4	0.0217	17.93	1.17
		1:5	0.0276	50.0	1.50

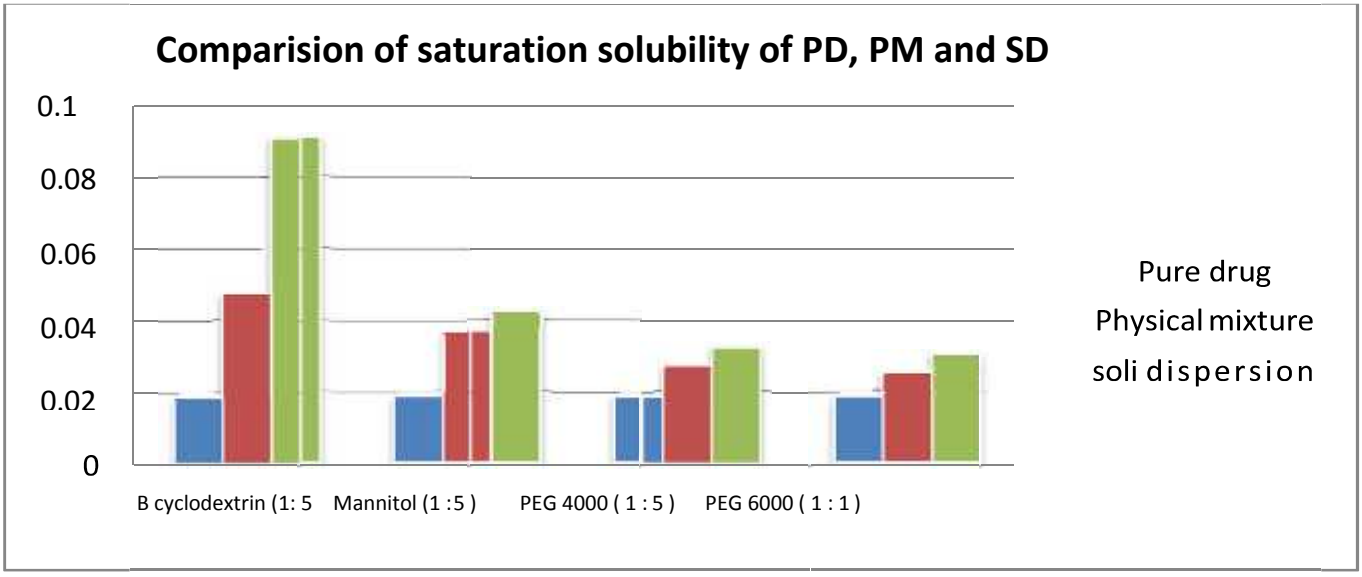

Table 4: solubility of physical mixture in phosphate buffer

Sr. No	Polymer	Ratio	Saturation Solubility [mg/ml]	% Increase in solubility	In times
1	Beta cyclodextrin	1:1	0.0464	25.40	1.25
		1:2	0.0726	96.21	1.96
		1:3	0.0538	45.40	1.45
		1:4	0.0433	17.02	1.17
		1:5	0.0737	99.18	1.99
2	Mannitol	1:1	0.0713	92.70	1.92
		1:2	0.0396	7.02	1.07
		1:3	0.0693	87.29	1.87
		1:4	0.0389	5.13	1.05
		1:5	0.0740	99.18	1.99
3	PEG 4000	1:1	0.0405	9.45	1.09

		1:2	0.0378	2.16	1.02
		1:3	0.0371	0.27	1.00
		1:4	0.0384	3.78	1.03
		1:5	0.0508	37.29	1.37
4	PEG 6000	1:1	0.0453	22.43	1.22
		1:2	0.0405	9.45	1.09
		1:3	0.0376	1.62	1.01
		1:4	0.0392	5.94	1.05
		1:5	0.0386	4.32	1.04

Table 5: solubility of solid dispersion in phosphate buffer

Sr. No	Polymer	Ratio	Saturation Solubility [mg/ml]	% Increase in solublility	In times
1	Beta cyclodextrin	1:1	0.0514	38.9	1.38
		1:2	0.0776	109.7	2.09
		1:3	0.0588	58.9	1.58
		1:4	0.0483	30.5	1.30
		1:5	0.0787	112.7	2.12
2	Mannitol	1:1	0.0773	108.9	2.08
		1:2	0.0456	23.2	1.23
		1:3	0.0753	103.5	2.03
		1:4	0.0449	21.3	1.21
		1:5	0.0797	115.4	2.15
3	PEG 4000	1:1	0.0425	14.8	1.14
		1:2	0.0388	4.86	1.04
		1:3	0.0376	1.62	1.01
		1:4	0.0394	6.48	1.06
		1:5	0.0528	42.7	1.42
4	PEG 6000	1:1	0.0463	25.1	1.25

		1:2	0.0415	12.1	1.12
		1:3	0.0381	2.97	1.02
		1:4	0.0402	8.64	1.08
		1:5	0.0396	7.02	1.07

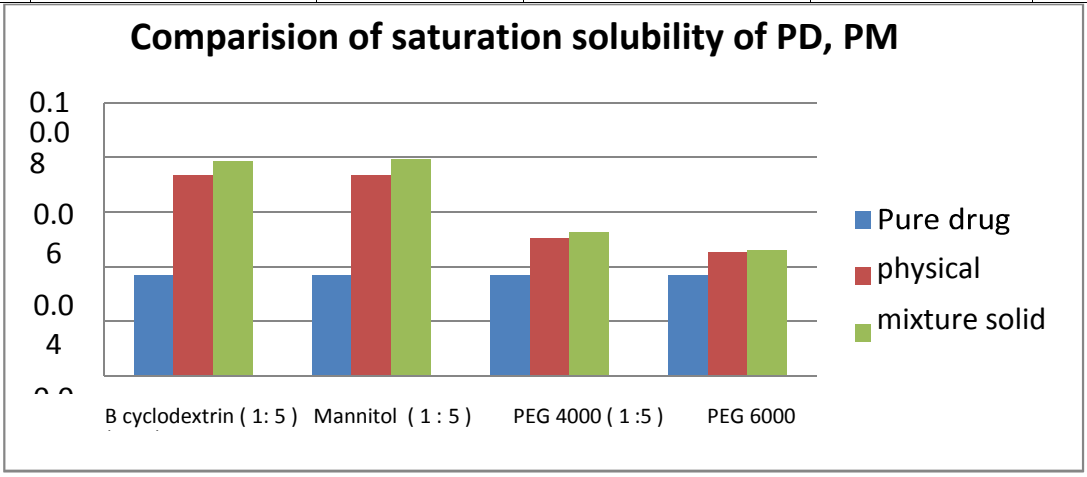

Fig. 2: Comparison of saturation solubilty of PD, PM and SD

SDs prepared by solvent evaporation method for 1:5 ratio of beta cyclodextrin and Mannitol showed maximum increase in Saturation solubility as compared to other ratios. However, Mannitol shows highest increase in solubility in phosphate buffer (pH 6.8).

Assay

The drug content of prepared solid dispersions was found to be in the range of 99 to 102 % w/w. The drug content values are shown in Table. Satisfactory reproducibility of results was observed when assay was repeated.

Table 6: Assay of solid dispersion and physical mixture

Sr no	Polymer	Ratio	Assay*	
			PM	SD
1	Beta cyclodextrin	1:1	100.23 ± 0.02	101.64 ± 0.28
		1:2	100.01 ± 0.14	101.83 ± 0.12
		1:3	99.97± 0.23	100.03 ± 0.17
		1:4	98.88± 0.41	99.92 ± 0.12
		1:5	100.02 ± 0.34	102.01 ± 0.09
2	Mannitol	1:1	100.25± 0.39	101.12 ± 0.40
		1:2	98.5 ± 0.45	99.45 ± 0.23
		1:3	97.08 ± 0.56	99.76 ± 0.07
		1:4	97.25 ± 0.33	98.01 ± 0.18
		1:5	99.99 ± 0.21	101.99± 0.33
3	PEG 4000	1:1	85.52 ± 0.44	86.30 ± 0.49
		1:2	91.52 ± 0.28	92.20 ± 0.16
		1:3	95.54 ± 0.05	96.85 ± 0.33
		1:4	96.58 ± 0.33	98.23 ± 0.32
		1:5	96.74 ± 0.36	97.76 ±0.45
4	PEG 6000	1:1	80.78 ± 0.29	86.82 ±0.02

		1:2	84.22 ± 0.17	85.54 ±0.29
		1:3	81.25 ± 0.21	82.65 ±0.03
		1:4	84.48 ± 0.23	86.01 ±0.15
		1:5	82.3 ± 0.33	82.65 ±0.32

Dissolution studies

Dissolution studies were carried out to determine the drug release profile from formulations and its comparison with that of pure drug.

In vitro Dissolution studies in phosphate buffer pH 6.8

% Drug release for PD, PM and prepared SDs is shown in Table No. 7.

Table 7: Cumulative Percent drug release of physical mixture in phosphate buffer pH 6.8

Time	% drug release in phosphate buffer pH 6.8								
	Pure drug	Betacyclodextrin (1 :5)		Mannitol (1: 5)		PEG 4000 (1 :5)		PEG 6000 (1 : 1)	
		PM	SD	PM	SD	PM	SD	PM	SD
15	3.98	60.34	64.74	48.20	61.27	23.93	25.7	29.13	32.6
30	14.39	71.68	75.21	57.79	69.14	38.69	41.33	52.57	58.65
45	17.01	92.57	98.21	66.53	95.52	76.02	77.79	61.29	67.39
60	22.23	97.87	105	86.54	103.03	83.91	89.55	73.51	77.46

From dissolution studies, it was observed that, PD shown 22-23% drug dissolved within 60 min. which shows strong need to improve the dissolution. Solid dispersions prepared by solvent evaporation method for all the four polymers showed marked increase in the dissolution profile of drug release as compared to PD and PM. However, complexation with beta cyclodextrin and solid dispersion with Mannitol showed complete drug dissolution.

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CONCLUSION

Lansoprazole is a NSAIDs drug having low solubility and high permeability. To improve upon the dissolution properties, solid dispersions of Lansoprazole were prepared in different ratios with four carriers viz. Beta cyclodextrin, Mannitol, PEG 6000, PEG 4000 by solvent evaporation method. The prepared solid dispersions were evaluated by saturation solubility study, dissolution studies and drug content. From the findings of the study conducted, following conclusions can be drawn: Solid dispersions prepared with all the carriers improved the solubility as well as dissolution rate of Lansoprazole. Solid dispersion of Mannitol and complex of beta cyclodextrin was found to be more efficient in improving the drug solubility and dissolution rate. In-vitro drug release studies indicated complete drug release in 60 min.in as compared to pure drug having only 22-23%

drug release in 60 min. From all the observation, it was concluded that solid dispersion with Mannitol [1:5] by solvent evaporation method showed marked improvement in solubility and dissolution. Capsule formulation of solid dispersion also proved better dissolution over pure drug.

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