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MELT EVAPORATION METHOD: A SOLID DISPERSION STRATEGY TO ENHANCE SOLUBILITY AND DISSOLUTION OF LAFUTIDINE

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ABSTRACT

Lafutidine is a novel potent H_2-receptor antagonist and very widely used during gastric ulcers, duodenal ulcers and stomach ulcers. Lafutidine is yellowish white crystalline powder practically insoluble in water. Due to very poor solubility, its bioavailability rate is limited by dissolution. In this study, an attempt has been made to enhance the solubility and dissolution of Lafutidine by melt evaporation, which is a solid dispersion technique by using polyethylene glycol. Various ratio of drug: carrier was prepared and further evaluated for its saturation solubility, drug content and rate of dissolution. Spectral characteristics were carried out by UV spectroscopy and FTIR. Among all the formulations, dispersion with PEG 6000 shown highest saturation solubility of 133.07 µg/ml and drug content as 99.67 %.

KEY WORDS: Lafutidine, Bioavailability, solubility, Dissolution, Solid dispersion, Melt evaporation, PEG.

INTRODUCTION

Solid dispersion is frequently used to improve the dissolution rate of poorly water-soluble compounds. By adsorbing drug molecules onto the surface of adsorbents with large surface areas, the total surface area of the drug is increased, and the drug may even be transformed from crystalline form to amorphous form. By adsorbing a surfactant onto the crystal surface of poorly water-soluble drugs, dissolution rate can also be enhanced. This technique also used to improve the bioavailability of poorly soluble compounds for enhancing the dissolution profiles of these compounds.[1]

Melting method

First proposed by Sekiguchi and Obi which involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

Advantages

- Simplicity and economic.
- Ensured supersaturation of solute due to sudden quenching of melt.

Disadvantages

- Decomposition of drug or carrier at high temperature.
- Evaporation of volatile drug or volatile carrier during the fusion process at high temperature.

Melting –solvent method (Melt-evaporation)

For this, drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of carriers usually polyethylene glycol, obtainable below 70^{o}C without removing the liquid solvent.

Advantages

1. The method possesses the advantages of both the melting and solvent methods.
2. Accommodation of 5-10 % of liquid without compromised on solidification.
3. Limited to drugs with a low therapeutic dose e.g. below 50 mg.

Disadvantages

1. Non-miscibility of selected solvent or dissolved drug with the melt of the polyethylene glycol.
2. Change in polymorphic form of the drug precipitated in the solid dispersion due to liquid solvent. [2-11]

The following illustration gives scope of pharmaceutical applications of solid dispersions (Fig. 1) and the Table 1. enlists various carriers used for solid dispersion.

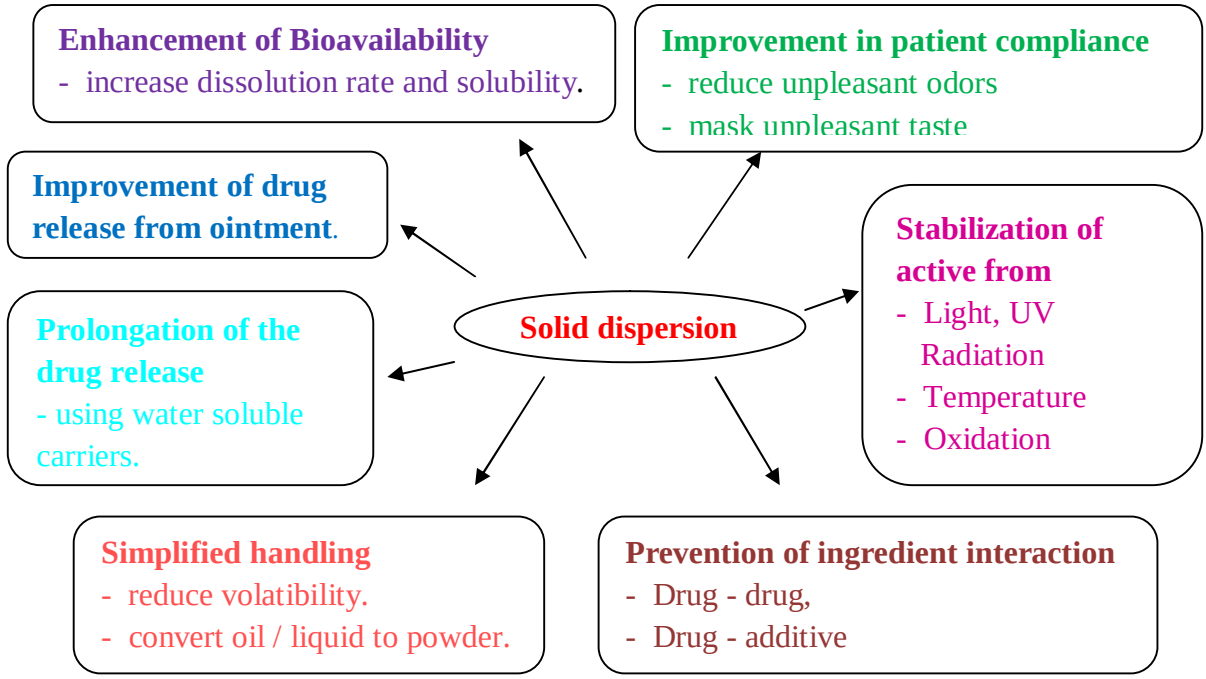


Fig. 1: Scope of pharmaceutical applications of solid dispersions.

Table 1: Materials used as carrier for solid dispersion

Sr. No.	Category	Carriers	Example
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose	Rofecoxib with sorbitol and mannitol
2	Acids	Citric acid, succinic acid	Felodipine, Rofecoxib with citric acid
3	Polymeric materials	Polyvinyl pyrrolidone (PVP), Polyethylene glycol (PEG), Hydroxypropyl methyl cellulose (HPMC), Methyl cellulose (MC), Hydroxy ethyl cellulose, Cyclodextrin, Hydroxy propyl cellulose, Pectin, Galactomannan	Temazepam , Felodipine, Etoricoxib Rofecoxib with PEG 4000 & 6000 and Troglitazone and Rofecoxib from PVP K30
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), EudragitL100, Eudragit E100, Eudragit RL, Eudragit RS	Indomethacin with Eudragit E100
5	Surfactants	Polyoxyethylene stearate, Poloxamer 188, deoxycholic acid, Tweens, Spans	Felodipin and Rofecoxib with Poloxamer 188
6	Miscellaneous	Pentaerythritol, pentaerythrityl tetra acetate, urea, urethane, hydroxy alkyl xanthins	Rofecoxib with urea

MATERIALS AND METHODS

Lafutidine was received as gift sample from Ajanta Pharma Mumbai. Polyethylene glycol 4000, 6000 and 8000 was purchased from Merck laboratory Mumbai. All other chemicals used are of analytical grade.

Determination of solubility of lafutidine in different solvent

The required quantities of Lafutidine were dissolved separately in 1 ml of each water, methanol, ethanol and glacial acetic acid contained in separate glass test tubes. The solutions were shaken vigorously and observed visually for clarity. The result was shown in table 1 as follows.

Table 1: Solubility of Lafutidine in solvent.

Sr. No.	Solvents	Solubility
1.	Distilled water	Very slightly soluble
2.	Ethanol	Sparingly soluble
3.	Methanol	Soluble
4.	Glacial acetic acid	freely soluble

A. Preparation of solid dispersions with various water soluble carriers

Solid dispersions of Lafutidine were prepared by Melt evaporation method as follow:

Melt evaporation method (MEM)

Required quantities of Lafutidine and each of water soluble-carriers for solid dispersions viz. PEG 4000, PEG-6000, PEG 8000 were weighed accurately. The polymers were melted at 55-60^0 C in 50 ml beaker. The molten mass was cooled up to 40-45^{0}C with constant stirring. The methanolic solution of drug was added into molten mass in small portions with constant stirring. Subsequently, methanol was evaporated in vacuum evaporator and resulting solid dispersions were stored in desiccators for 24 hr to congeal. Finally, dispersions were triturated in a mortar and passed through sieve no. 44. The resulting solid dispersions were stored in tightly closed containers until further use.

Table 2: Composition of solid dispersions prepared by MEM.

Sr. No.	Solid dispersion systems	Ratio of Drug: Carrier
1.	Lafutidine : PEG-4000	1:1
2.	Lafutidine : PEG-4000	1:5
3.	Lafutidine : PEG-4000	1:9
4.	Lafutidine : PEG-6000	1:1
5.	Lafutidine : PEG-6000	1:5
6.	Lafutidine : PEG-6000	1:9
7.	Lafutidine : PEG-8000	1:1
8.	Lafutidine : PEG-8000	1:5
9.	Lafutidine : PEG-8000	1:9

B. II. Evaluation of solid dispersions of Lafutidine

The prepared solid dispersion was evaluated for Appearance, Saturation solubility, Contents of Lafutidine, Spectral characteristics such as UV spectroscopy and IR spectroscopy, Release of Lafutidine (*in vitro*).

1. Appearance

Appearance and colour were assessed visually and the odour was characterized by subjective perception.

2. Saturation solubility

Saturation solubility of solid dispersions of Lafutidine was estimated in phosphate buffer (pH 6.8) contained in glass vials (triplicate). For this, 5 ml phosphate buffer (pH 6.8) was added into each of the vial and to it excess amounts of solid dispersions (SDs) were added. These vials were shaken continuously for 24 hr on a lab shaker incubator ($37^0C \pm 2^0C$) and the resulting solutions were filtered through Whatman filter paper (No. 41). Appropriate dilutions of filtrates were made; UV absorbances were recorded at the experimental λmax value of Lafutidine. From the absorbance-concentration data, saturation solubility values were calculated. The saturation solubility for various solid dispersion systems shown in table 3 as follows.

Table 3: Saturation solubility of solid dispersion systems prepared by MEM.

Sr. No.	Solid dispersion system	Ratio	Saturation solubility (µg/ml) for MEM
1.	Lafutidine	Plain	25.28
1.	Lafutidine : PEG 4000	1:1	56.35
2.	Lafutidine : PEG 4000	1:5	112.57
3.	Lafutidine : PEG 4000	1:9	108.92
4.	Lafutidine : PEG 6000	1:1	83.30
5.	Lafutidine : PEG 6000	1:5	109.14
6.	Lafutidine : PEG 6000	1:9	**133.07**
7.	Lafutidine : PEG 8000	1:1	57.21
8.	Lafutidine : PEG 8000	1:5	69.92
9.	Lafutidine : PEG 8000	1:9	107.42

*All values are Mean ± S.D. (n=3)

3. Contents of Lafutidine

The percentage content of Lafutidine, in each of the solid dispersions was estimated by dissolving quantities of solid dispersions equivalent to 10 mg of Lafutidine in sufficient quantities of phosphate buffer (pH 6.8) and final volume of 100 ml was made up. Stock solutions were further diluted with phosphate buffer (pH6.8) to get final concentration of 20 µg/ml. The absorbances were recorded at the experimental λmax value of Lafutidine. The contents were estimated using previously prepared calibration curve of Lafutidine in phosphate buffer (pH6.8), given in table 4 as follows.

Table 4: Drug content of solid dispersion systems prepared by MEM.

Sr. No.	Solid dispersion system	Ratio	% Drug content (MEM)
1.	Lafutidine : PEG 4000	1:1	97.78
2.	Lafutidine : PEG 4000	1:5	95.34
3.	Lafutidine : PEG 4000	1:9	98. 23
4.	Lafutidine : PEG 6000	1:1	98.46
5.	Lafutidine : PEG 6000	1:5	98.38
6.	Lafutidine : PEG 6000	1:9	99.67
7.	Lafutidine : PEG 8000	1:1	96.65
8.	Lafutidine : PEG 8000	1:5	95.87
9.	Lafutidine : PEG 8000	1:9	97.84

*All values are Mean ± S.D. (n=3)

4. Spectral characteristics

a. UV spectroscopy

For this, stock solutions of solid dispersions (100µg/ml) were prepared by dissolving quantities equivalent to 10 mg of Lafutidine in required quantities of phosphate buffer (pH 6.8). These stock solutions were diluted with buffer to give solutions of 20µg/ml concentration. The solutions were scanned in the range of 400 to 200 nm and λmax values were reported.

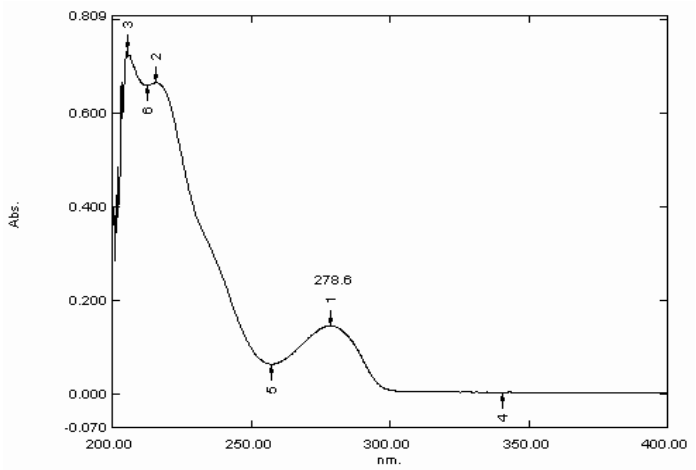


Fig. 2: UV absorption spectrum of Lafutidine: PEG 4000 solid dispersion system (1:1) prepared by melt evaporation method.

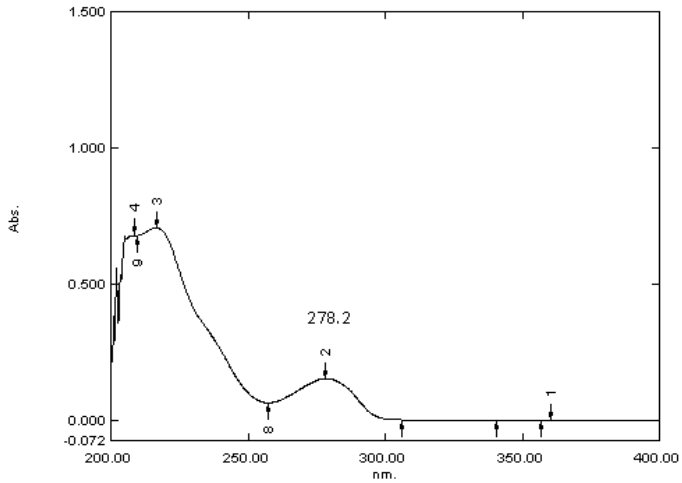


Fig. 3: UV absorption spectrum of Lafutidine: PEG 4000 solid dispersion system (1:5) prepared by melt evaporation method.

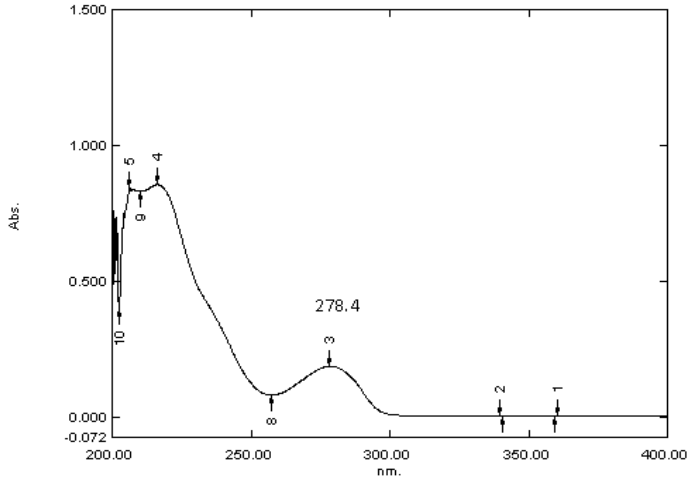


Fig. 4: UV absorption spectrum of Lafutidine: PEG 4000 solid dispersion system (1:9) prepared by melt evaporation method.

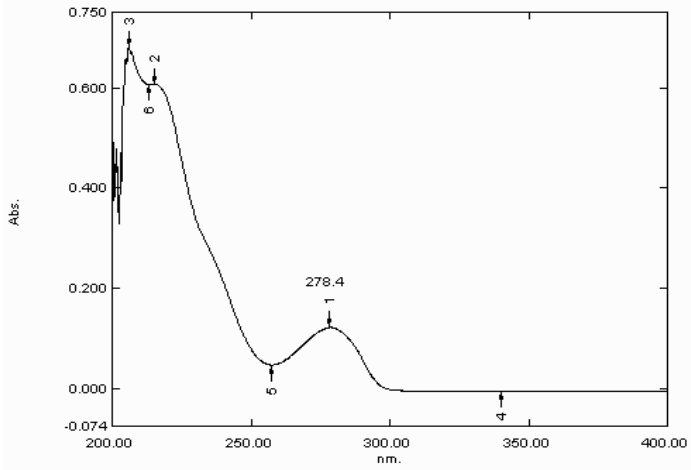


Fig. 5: UV absorption spectrum of Lafutidine: PEG 6000 solid dispersion system (1:1) melt evaporation method.

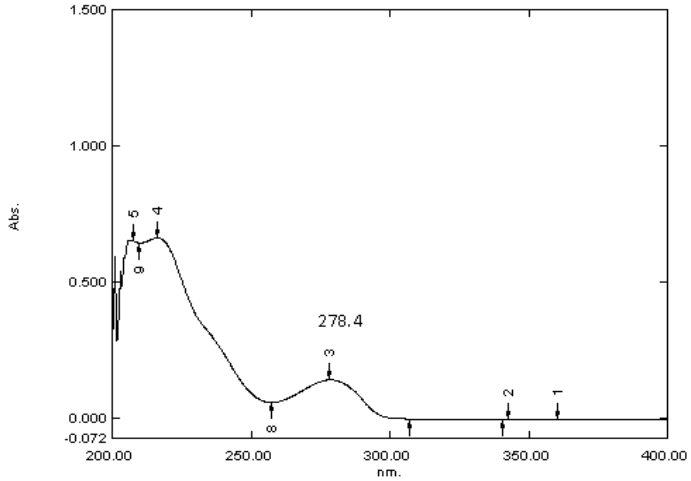


Fig. 6: UV absorption spectrum of Lafutidine: PEG 6000 solid dispersion system (1:5) melt evaporation method.

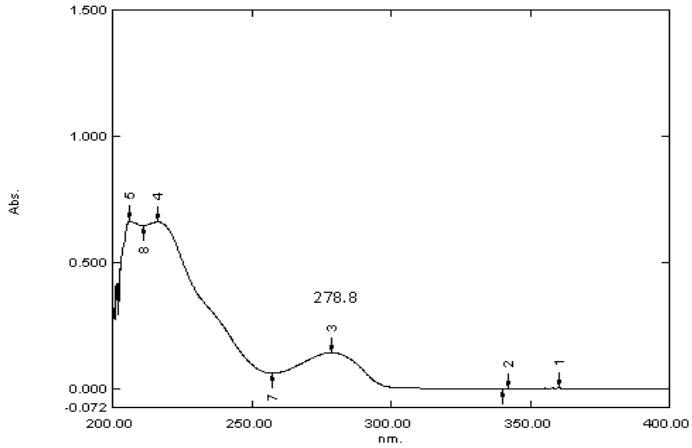


Fig. 7: UV absorption spectrum of Lafutidine: PEG 6000 solid dispersion system (1:9) prepare by melt evaporation method.

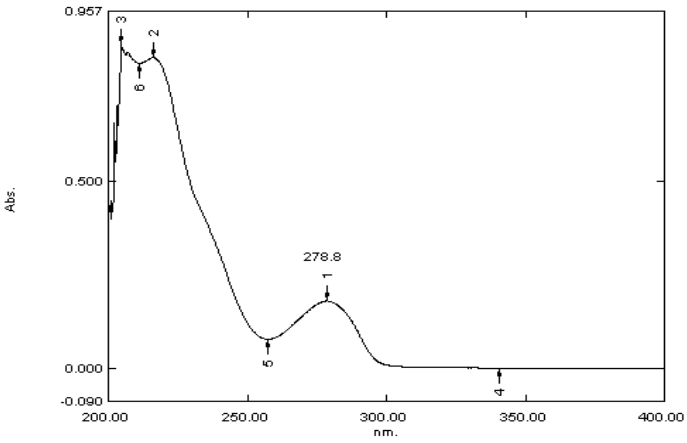


Fig. 8: UV absorption spectrum of Lafutidine: PEG 8000 solid dispersion system (1:1) prepared by melt evaporation method.

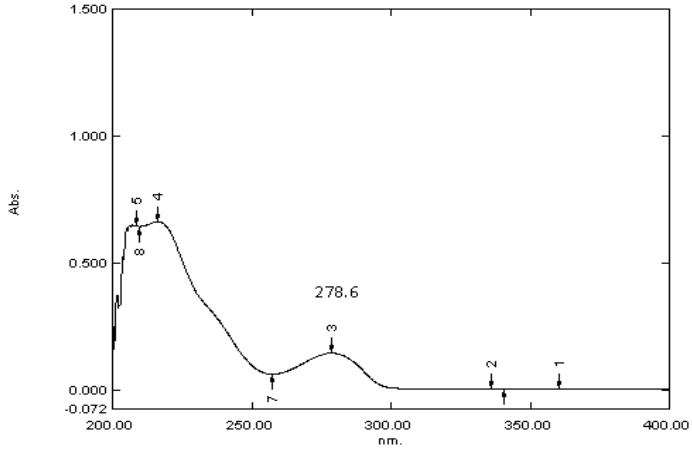


Fig. 9: UV absorption spectrum of Lafutidine: PEG 8000 solid dispersion system (1:5) prepared by melt evaporation method.

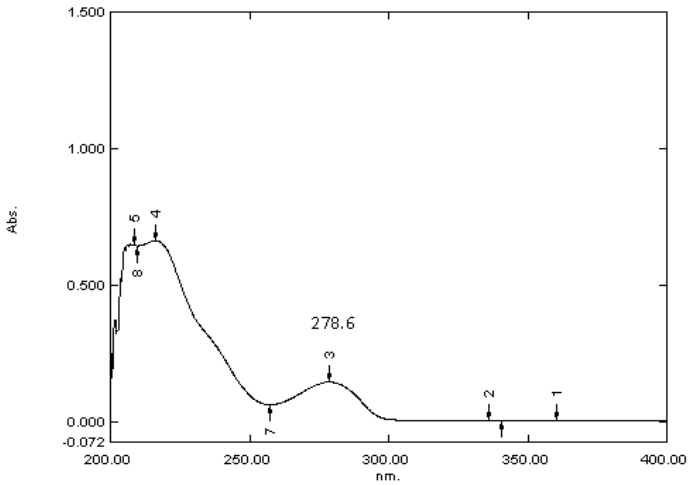


Fig. 10: UV absorption spectrum of Lafutidine: PEG 8000 solid dispersion system (1:9) prepared by melt evaporation method.

b. Fourier-Transform Infrared Spectroscopy

For this, solid dispersions were previously ground and mixed thoroughly with potassium bromide, at 1:100 (Sample: KBr) ratio. The discs were prepared by compressing the KBr dispersion powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 400 cm^{-1}. IR spectra of Lafitidine solid dispersions with PEG 4000, PEG 6000 and PEG 8000 are illustrated in Fig. no. 19 to 21.

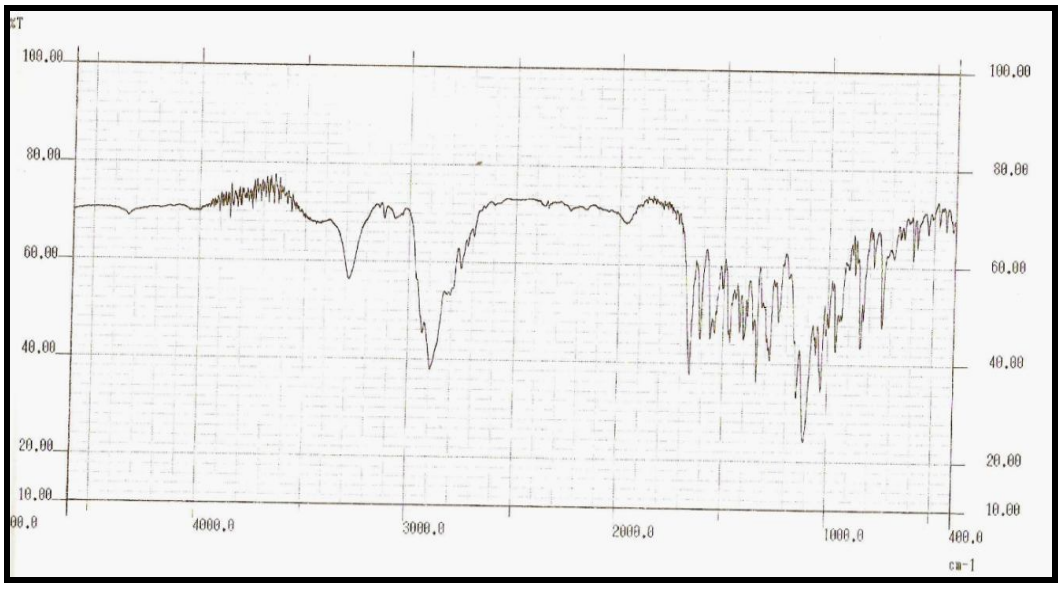


Fig. 11: IR spectrum of solid dispersions of Lafutidine and PEG 4000.

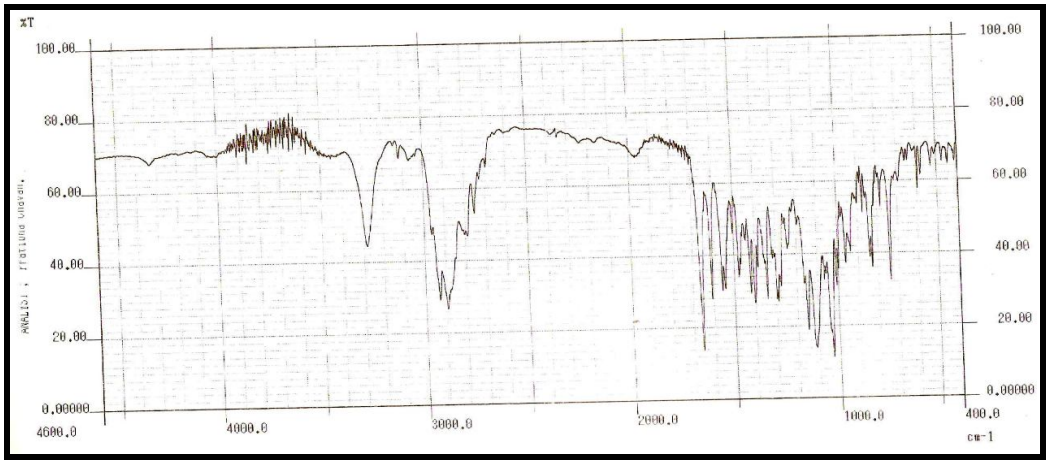


Fig. 12: IR spectrum of solid dispersions of Lafutidine and PEG 6000.

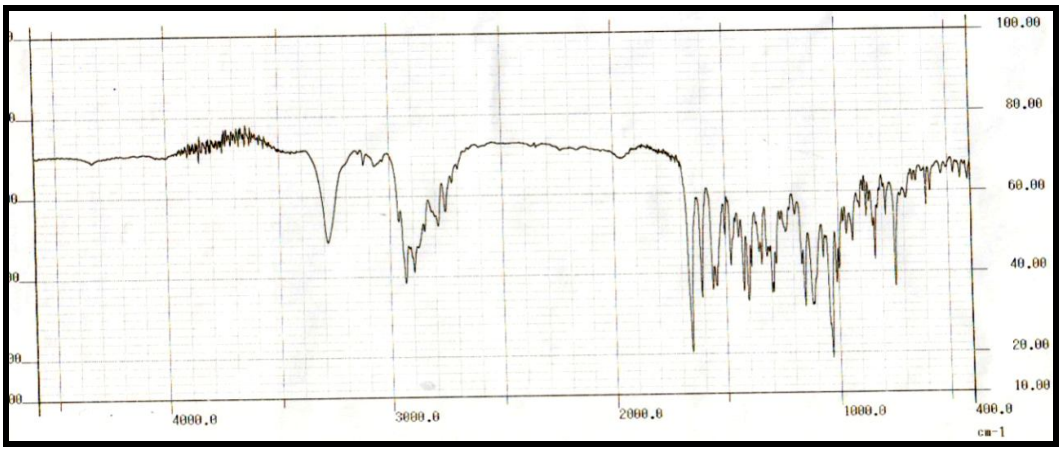


Fig. 13: IR spectrum of solid dispersions of Lafutidine and PEG 8000

5. Release (*in vitro*)

To carry out in-vitro drug released, the quantities of each solid dispersions equivalent to 10 mg of Lafutidine were used. The dissolution test was carried out using USP Dissolution Test Apparatus (Type II) at following test conditions. Lafutidine (10 mg) was used as control and was subjected to the similar test.

Test parameters

Dissolution medium: - 900 ml of phosphate buffer (pH 6.8).

Speed of paddle: - 100 rpm.

Temperature of dissolution medium: - 37.0 ± 0.5 ^{0}C.

Apparatus type: - USP XXII (paddle).

Sample volume: - 5ml

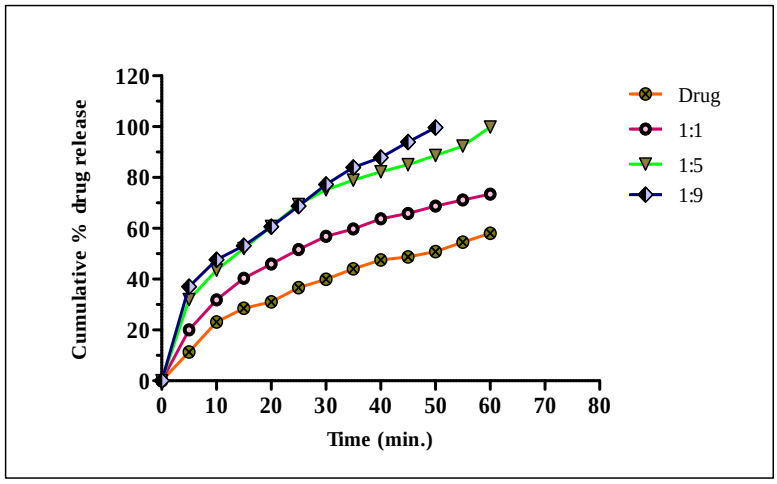
Sampling interval: - 5min

Duration of test: - 60 min

Procedure

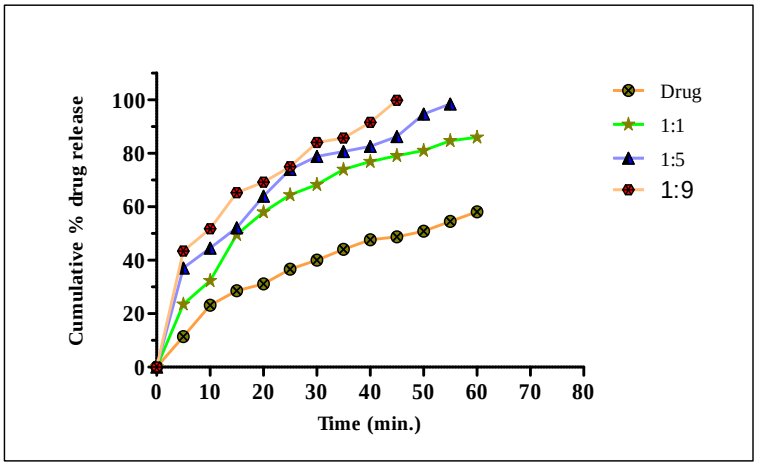
The quantity of solid dispersions equivalent to 10 mg of Lafutidine was placed in dissolution medium and apparatus was run maintaining above stated test conditions.

After every withdrawal, the equal volume of fresh dissolution medium was added to the bulk. Samples were filtered through Whatman filter paper (No.41) and the absorbances were recorded at the experimental λmax value of Lafutidine. Cumulative percentage of labeled amount of drug released at each time point was calculated. Values of t50 [Time required for 50% dissolution of stated amount of drug] and t90 [Time required for 90% dissolution of stated amount of drug] were also calculated.



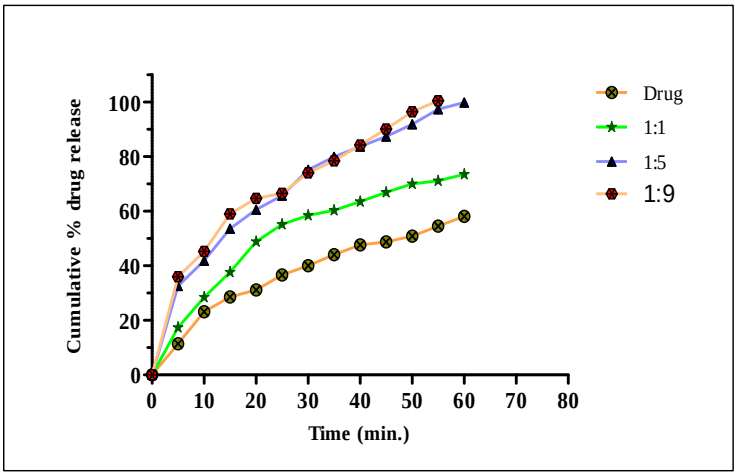
*All values are Mean ± S.D. (n=3)

Fig. 14: Dissolution profiles of Lafutidine from solid dispersions with PEG 4000 prepared by melt evaporation method.



*All values are Mean ± S.D. (n=3)

Fig 15: Dissolution profiles of Lafutidine from solid dispersions with PEG 6000 prepared by melt evaporation method.



*All values are Mean ± S.D. (n=3)

Fig. 16: Dissolution profiles of Lafutidine from solid dispersions with PEG 8000 prepared by melt evaporation method.

Table 5: The comparative dissolution data of Lafutidine from solid dispersions with PEG 4000, PEG 6000 and PEG 8000 prepared by MEM.

Sr. No.	Solid dispersion	Time					
		t_{50} (Min			t_{90} (Min)		
		1:1	1:5	1:9	1:1	1:5	1:9
1.	PEG 4000 (SE)	24.33	17.65	13.68	74.03	48.13	39.49
2.	PEG 4000 (ME)	24.18	14.42	14.19	73.54	53.61	43.11
3.	PEG 6000 (SE)	19.28	14.31	8.86	62.04	43.14	33.91
4.	PEG 6000 (ME)	15.12	14.39	9.67	62.84	47.53	39.33
5.	PEG 8000 (SE)	22.61	14.91	14.23	74.98	44.99	44.28
6.	PEG 8000 (ME)	22.65	14.01	12.72	73.53	49.00	44.97
7.	Drug	62.37			112.26		

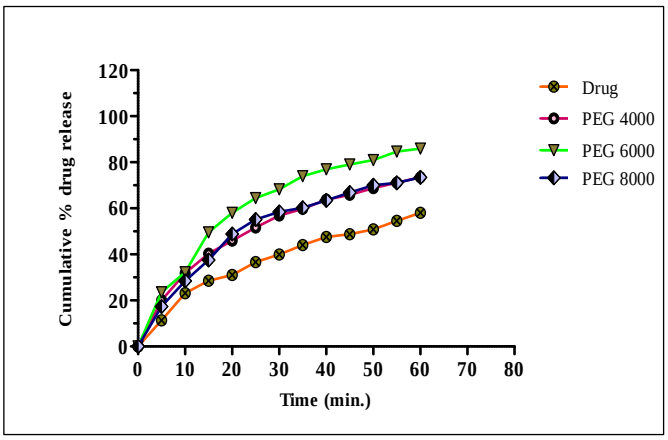
*All values are Mean ± S.D. (n=3)

Effect of type of polymer on dissolution rate of Lafutiidne from different sold dispersions.

Solid dispersions of Lafutidine prepared by both solvent evaporation and melt evaporation method exhibited improved dissolution profiles for drug in presence of carriers and the order was

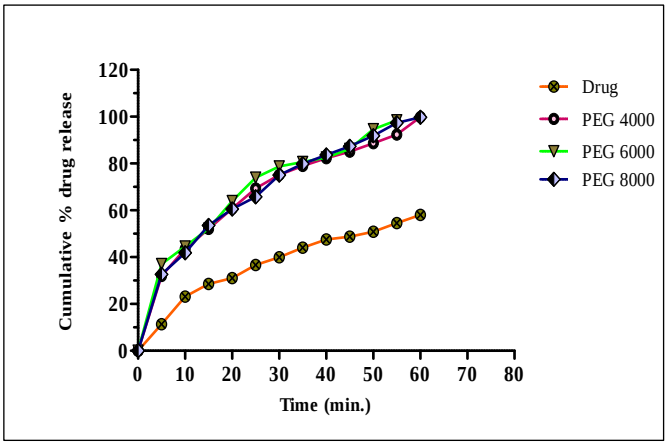
Lafutidine: PEG 6000 > Lafutidine: PEG 8000 > Lafutidine: PEG 4000

This trend was spotted at all the three proportions 1:1, 1:5, 1:9 of carriers employed. This may be due to inherent differences between the three polymers in terms of intrinsic rate of dissolution and hydration and possible decrease in crystallinity of the drug **(Fig. no. 28 to 33)**



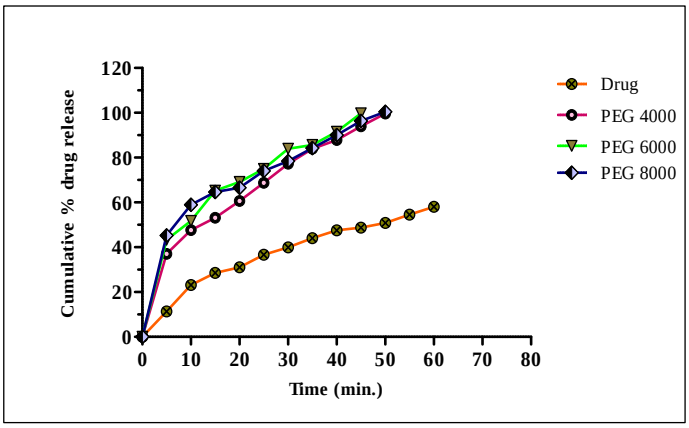
*All values are Mean ± S.D. (n=3)

Fig. 17: Effect of type of polymer on dissolution profiles of Lafutidine from solid dispersions (1:1) prepared by melt evaporation method.



*All values are Mean ± S.D. (n=3)

Fig. 18: Effect of type of polymer on dissolution profiles of Lafutidine from solid dispersions (1:5) prepared by melt evaporation method.



*All values are Mean ± S.D. (n=3)

Fig. 19: Effect of type of polymer on dissolution profiles of Lafutidine from solid dispersions (1:9) prepared by melt evaporation method.

RESULTS AND DISCUSSIONS

Significant increase in solubility of Lafutidine was noted for solid dispersion systems prepared by solvent evaporation method. A proportionate increase in the carrier weight fraction resulted in considerable change in the solubility of solid dispersions. Among all the solid dispersion systems, the one with the PEG 6000 (1:9) demonstrated highest saturation solubility.

Enhancement in the saturation solubility of Lafutidine solid dispersions was in the order, Lafutidine: PEG 6000 > Lafutidine: PEG 4000 > Lafutidine: PEG 8000.

The percentage contents of Lafutidine in all solid dispersions prepared by solvent evaporation method were greater than 95%. The high contents of Lafutidine in solid dispersions suggest that the drug has been uniformly dispersed within the soluble carriers. The UV spectra indicated λmax at 278±2 nm for all the solid dispersions. These values are almost identical with that of pure Lafutidine (278.3 nm). Hence, it may be concluded that there is no probable interaction between the drug and carriers used for preparation of solid dispersions.

All solid dispersions of Lafutidine prepared by solvent evaporation method presented better dissolution performance as compared to the pure drug in a given time course. Within first hour, 58.10 % of drug was dissolved, while all the solid dispersions of Lafutidine reported 70 to 100 % drug release within one or in less than 1 h. This may be attributed to improved wettability of the drug particles, significant reduction in drug particle size during the formation of the solid dispersions and the intrinsically higher rate of dissolution of the selected soluble carriers which could pull insoluble but finely mixed drug particles into the bulk of dissolution medium.

All the dispersions prepared exhibited a definite rise in both rate and the extent of drug dissolution with increasing proportions of carriers used. The possible reasons include facilitation of Lafutidine dissolution by higher amount of soluble carrier and decrease in the particle size of the drug within the dispersion.

CONCLUSION

The relative efficiency of different carriers used in solid dispersion to improve the dissolution profile of Lafutidine was in the order,

PEG 6000 > PEG 8000 > PEG 4000.

Dissolution rate of Lafutidine from solid dispersions increased with increased concentration of the carriers.

ACKNOWLEDGEMENT

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