IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2021 Vol.:22, Issue:2

Solubility Enhancement of Amlodipine Besylate by Using Solid Dispersion Techniques

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Nisha S. Mhaske*, Vishal J. Gaikwad, Supriya S. Shinde, Yogesh R. Thombare

Pravara Rural Education Society's College of Pharmacy (D.Pharm) Nashik (M.S), India.

Submitted: 19 August 2021
Accepted: 25 August 2021
Published: 30 September 2021

Keywords: Vasopastic angina, amlodipine besylate, solubility, dispersion, bioavailability

ABSTRACT

Amlodipine besylate is a long-acting calcium channel blocker used to treat chronic stable angina, vasospastic angina, and hypertension. It is a slightly water-soluble drug. Due to that, it's having poor bioavailability. The current study aimed to prepare solid dispersion of amlodipine besylate to enhance its solubility by using polymers like PEG 4000 and PEG 6000 which ultimately helps to increase the bioavailability of amlodipine besylate. Solid dispersion of amlodipine besylate was prepared by using a physical mixture and solvent evaporation method. Solubility of solid dispersion with PEG 4000 by solvent evaporation method in 1:1, 1:3, 1:5, 1:7, and 1:10 was found to be 121.2, 142.5, 325.95, 207.6, and 204.5 µg/ml respectively. Solubility of solid dispersion with PEG 6000 by solvent evaporation method in 1:1, 1:3, 1:5, 1:7, and 1:10 was found to be.137.36, 253.3, 264.3, 248.0, and 232.6 µg/ml respectively. Solubility of solid dispersion with PEG 4000 by physical mixture method in 1:1, 1:3, 1:5, 1:7, and 1:10 was found to be 40.76, 93.67, 147.43, 113.8, and 100.5 µg/ml respectively. Solubility of solid dispersion with PEG 6000 by physical mixture method in 1:1, 1:3, 1:5, 1:7, and 1:10 was found to be 130.09, 132.59, 141.51, 134.35, and 117.69 µg/ml respectively. According to their solubility study data 1:5 ratio almost increases solubility, therefore this was an optimized batch for use further investigation. The solubility of the drug was increased by the solvent evaporation method as compared to the physical mixture and pure drug. The bioavailability of solid dispersion formulation was also enhanced in comparison with Std. amlodipine besylate. Finally, it can be concluded that the solid dispersion technique is useful in improving the solubility and bioavailability of slightly water-soluble compounds such as amlodipine besylate.

INTRODUCTION:

Solid dispersions are defined by Chiou and Riegelmann; as "a dispersion of one or more active ingredients in an inert carrier or matrix at solid-state prepared by melting (fusion), solvent or melting-solvent method."

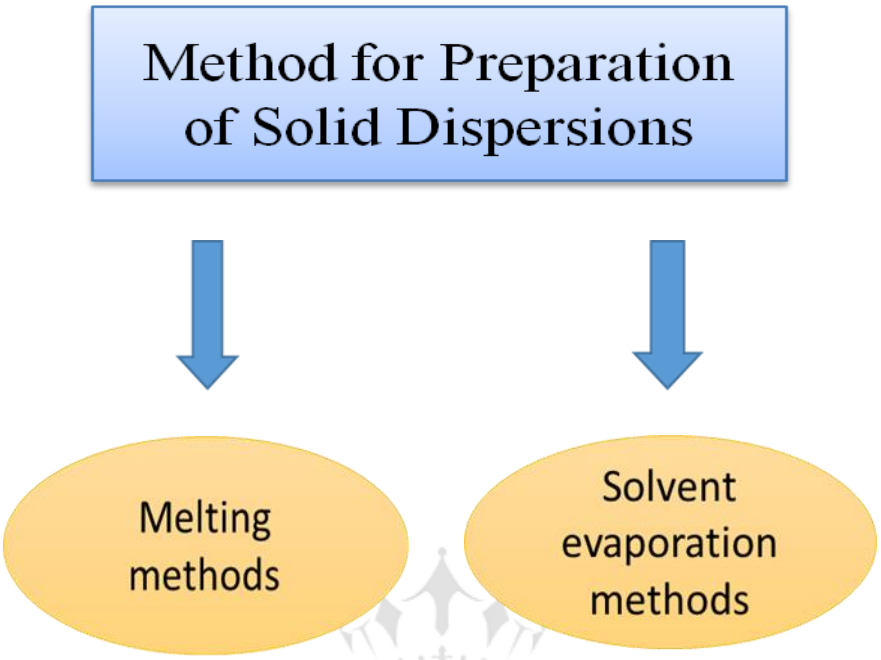

Figure No. 1: Methods for Preparation of Solid Dispersions

The absorption of drugs from a solid dosage form, when taken orally, can be divided into two steps - (1) the process of dissolution of the drug in vivo which leads to a solution; and (2) the transport of the dissolved drug from the solution across the gastrointestinal membrane. Each step involved in the process of absorption of the drug is very crucial. The overall absorption and bioavailability of the drug may be affected by the poor performance of either step mentioned above. From among the many new active pharmaceutical ingredients introduced into the market, almost all the active pharmaceutical ingredients face the problem enumerated above. Either step one or two may lead to a decrease in the overall bioavailability of the active pharmaceutical ingredient. The biopharmaceutical Classification (BCS) system classifies these active pharmaceutical ingredients into four classes as given below:

Table No. 1: BCS classification of drug

Class I High solubility High Permeability eg. Diltiazem Propranolol Theophylline Enalapril	Class II Low solubility High permeability eg. Nifedipine Flurbiprofen Ketoconazole Phenytoin
Class III High Solubility Low permeability eg. Insulin Atenolol Acyclovir Cimetidine	Class IV Low Solubility Low permeability eg. Taxol Chlorothiazide Furosemide Indinavir

It is generally recognized that poor solubility is one of the most frequently encountered difficulties in the field of pharmaceutics. Low solubility and subsequent unsatisfactory dissolution rate often compromise oral bioavailability. As a result, the improvement of solubility and dissolution rate of poorly soluble compounds is of great importance. Poor aqueous solubility and bioavailability of drugs into the body after administration are two prime issues that are faced by the pharmaceutical industry at present. This problem has been the major problem hampering the release of new chemical entities into the market. Therefore, pharmaceutical companies are focusing on finding a method or technology by which they can enhance the aqueous solubility and bioavailability of the drug. To date, various methods for modification of active pharmaceutical ingredients have included physical, chemical, and controlled solid-state methods. Each of the methods given above has its drawbacks which restrain their use to modify the active pharmaceutical ingredient to improve its aqueous solubility and bioavailability. Some other conventional methods used to improve aqueous solubility and bioavailability include the use of surfactants; pH modification; solid dispersion technique; co-solvent and hydrotropic formation; co-crystallization techniques; and many more.

Solid dispersions are defined by Chiou and Riegelmann; as "a dispersion of one or more active ingredients in an inert carrier or matrix at solid-state prepared by melting (fusion), solvent or melting-solvent method."

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration, for example, parenteral.

Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for several reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach the systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate-limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate-limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include enhancing the solubility and dissolution rate of poorly water-soluble drugs and enhancing the permeability of poorly permeable drugs.

Aim & Objective

- To study preformulation parameters of amlodipine besylate to increase its solubility by using the solid dispersion method.
- To enhance the solubility of amlodipine besylate by using a PEG 4000 and PEG 6000.
- To enhance the bioavailability of amlodipine besylate.
- To formulate the solid dispersion by using a PEG 4000 and PEG 6000 in solvent evaporation and physical mixture method.
- To study the effect of polymers and polymer composition on the solubility of the drug.

➢ To evaluate, compare and select suitable carrier systems for solubility enhancement of drug.

➢ Finally, to characterize prepared solid dispersion for their morphology.

MATERIAL AND METHODS

Drug & polymer profile

Amlodipine besylate

Table No. 2: Drug profile

Description	A white or almost white powder. Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol. No polymorphism has been encountered.
Structure	$C_{26}H_{31}ClN_2O_8S$ Molecular weight: 567.1
IUPAC Name	3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2- chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate.
Pharmacokinetics	Well-absorbed, with peak blood levels between 6-12 hours post-dose, Absolute bioavailability has been estimated to be between 64 and 80%, Terminal plasma elimination half-life is about 35-50 hours
Drug Interactions	*In vitro* data indicate that amlodipine does not affect the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Polyethylene glycol

Table No. 3: Polymer profile

Synonyms	Carbowax; CarbowaxSentry; Macrogola; PEG; Pluriol; Polyoxyethylene glycol
Structural Formula	Average molecular weight: 3000-4800 Chemical Name: α-Hydro-ω-hydroxypropyl (oxy-1,2-ethanediyl)
Density	1.080
Melting point	69.0-84.0 °C
Solubility	All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols
Functional Category	Ointment base; plasticizer; solvent; suppository base; tablet and Capsule lubricant
Applications	used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations.

Preparation of solid dispersion

Preparation of physical mixture with PEG 4000

For the preparation of a physical mixture Amlodipine, besylate, and PEG 4000 were weighed accurately in various ratios 1:1, 1:3, 1:5, 1:7, and 1:10 and mixed for 5 min with use of a pestle and mortar and sieved through a 100 μm mesh. Amlodipine besylate PEG 4000 physical mixtures were used for further investigations.

Preparation of physical mixture with PEG 6000

For the preparation of a physical mixture Amlodipine, besylate, and PEG 6000 were weighed accurately in various ratios 1:1, 1:3, 1:5, 1:7, and 1:10 and mixed for 5 min with use of a pestle and mortar and sieved through a 100 μm mesh. Amlodipine besylate PEG 6000 physical mixtures were used for further investigations.

Preparation of solid dispersion with PEG 4000 by Solvent evaporation method

Amlodipine besylate and PEG 4000 were weighed accurately in various ratios 1:1, 1:3, 1:5, 1:7, and 1:10) and transferred to a china dish containing a sufficient quantity of methanol to dissolve. Methanol was evaporated on the heating mantle at 40^0C. The resulting solid dispersions were stored for 24 hrs in desiccators. The mass obtained was crushed, pulverized. Finally, dispersions were sieved through a 100 □m mesh and were used for further investigations.

Preparation of solid dispersion with PEG 6000 by Solvent evaporation method

Amlodipine besylate and PEG 6000 were weighed accurately in various ratios 1:1, 1:3, 1:5, 1:7, and 1:10) and transferred to a china dish containing a sufficient quantity of methanol to dissolve. Methanol was evaporated on the heating mantle at 40^0C. The resulting solid dispersions were stored for 24 hrs in desiccators. The mass obtained was crushed, pulverized. Finally, dispersions were sieved through a 100 □m mesh and were used for further investigations.

Table No. 4: Method and formulation code of solid dispersion

Sr. No.	Polymer	Ratio	Method	Formulation code
1		1:1		PM41
2	PEG-4000	1:3	Physical	PM43
3		1:5	Mixture	PM45
4		1:7		PM47
5		1:10		PM410
6		1:1		PM61
7	PEG-6000	1:3	Physical	PM63
8		1:5	Mixture	PM65
9		1:7		PM67
10		1:10		PM610
11		1:1		SE41
12	PEG-4000	1:3	Solvent	SE43
13		1:5	Evaporation	SE45
14		1:7	Method	SE47
15		1:10		SE410
16		1:1		SE61
17	PEG-6000	1:3	Solvent	SE63
18		1:5	Evaporation	SE65
19		1:7	Method	SE67
20		1:10		SE610

Preformulation study

Identification and characterization of drug

- ✓ Organoleptic properties
- ✓ Melting point determination

- ✓ Determination of λ max of Amlodipine besylate
- ✓ Calibration curve of Amlodipine besylate in methanol
- ✓ Determination of Solubility
- ✓ Fourier Transform Infra-Red (FTIR) Spectroscopy
- ✓ Differential Scanning Calorimetry (DSC)
- ✓ Powder X-ray diffraction (PXRD)
- ✓ Scanning electron microscopy (SEM)

Characterization of Solid Dispersion

- ✓ Percent Practical Yield
- ✓ Drug content
- ✓ Solubility studies

RESULTS AND DISCUSSION

Identification and characterization of drug

Organoleptic properties

Table No. 5: Results of organoleptic Properties

Test	Specification/Limits	Observations
Colour	White to off white	White
Odour	Unpleasant	Unpleasant
Nature	Crystalline powder	Crystalline powder
Taste	Metal	Metal

Melting Point determination

Table No. 6: Melting point determination

Apparatus	Observed Value	Reference Value
Melting Point Apparatus	193-195^{0}C.	195-204 ^{0}C

Determination of λ max of Amlodipine besylate

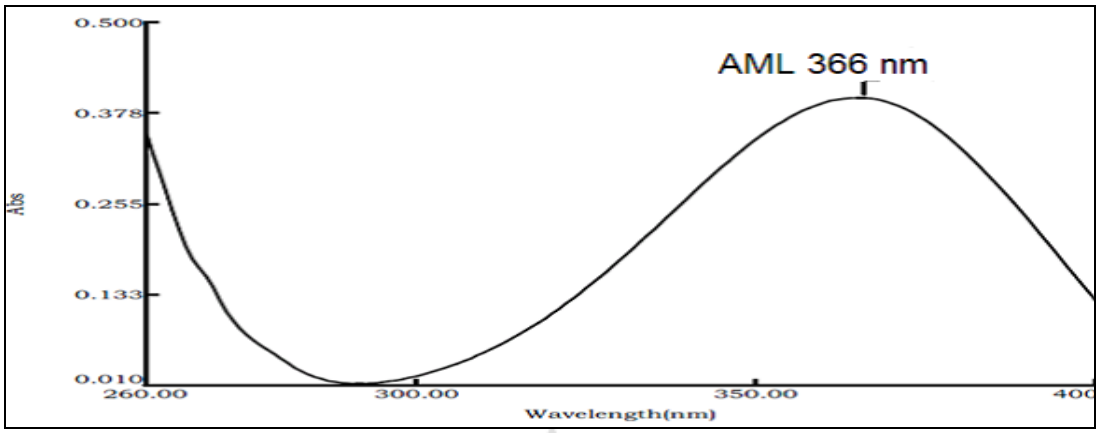

Figure No. 2: λmax of amlodipine besylate in methanol

Calibration curve of amlodipine besylate in methanol

Table No.7: Absorbance and conc. data of amlodipine besylate at 366 nm

Sr. No.	Conc. µg/ml	Absorbance at 366 nm
1	2	0.317
2	4	0.5248
3	6	0.7706
4	8	0.9791
5	10	1.2117
6	12	1.5288

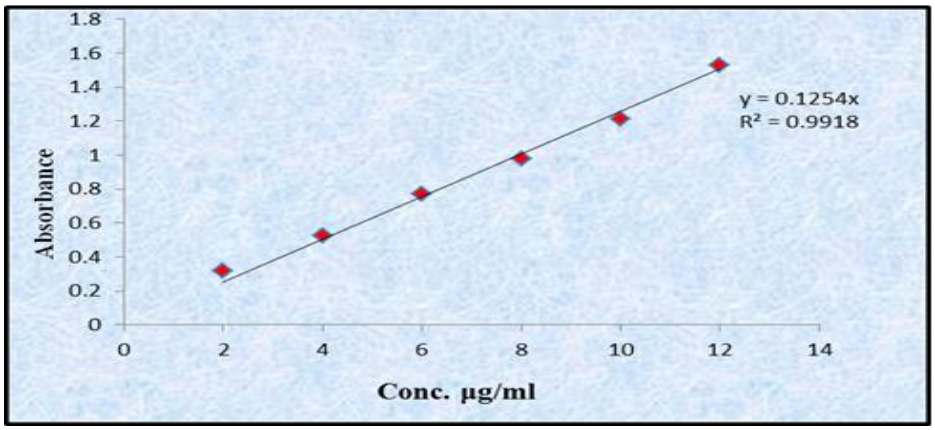

Figure No. 3: Calibration curve of Amlodipine besylate

FT-IR spectral study

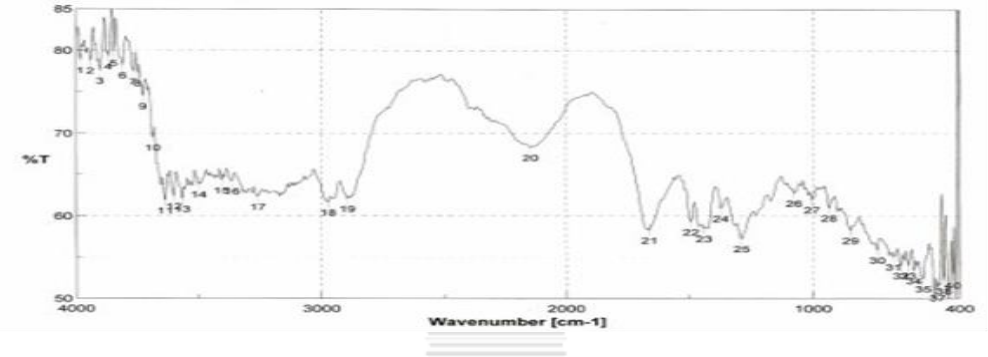

Figure No. 4: FT-IR-spectra of amlodipine besylate pure drug

Table No. 8: IR interpretation data

Compound	Frequency (cm^{-1})	Type of vibration
Amlodipine besylate	3020 (m)	Ar-CH str
	1599, 1507, 1474, 1434 (s)	Ar –C=C
	1214 (s)	C-F – str
	1272 (s)	C-O-C str
	3420 (m)	NH str
	3374 (m)	NH_2str
	1696 (s)	C=O str
	2983 (s)	CH_3(CH) str

Differential scanning calorimetry (DSC)

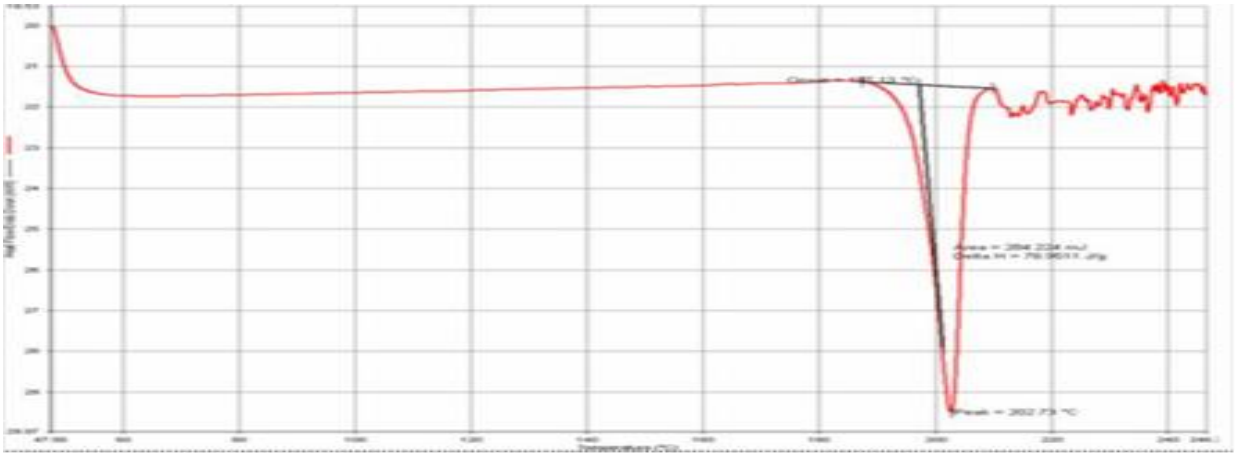

Figure No. 5: DSC spectra of amlodipine besylate

X-ray powder diffraction (XRD)

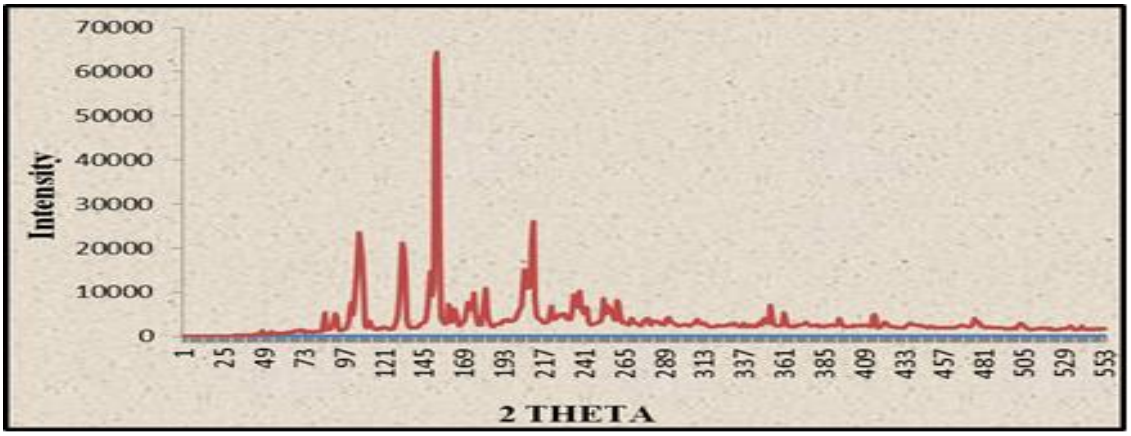

Figure No. 6: XRD of Amlodipine besylate

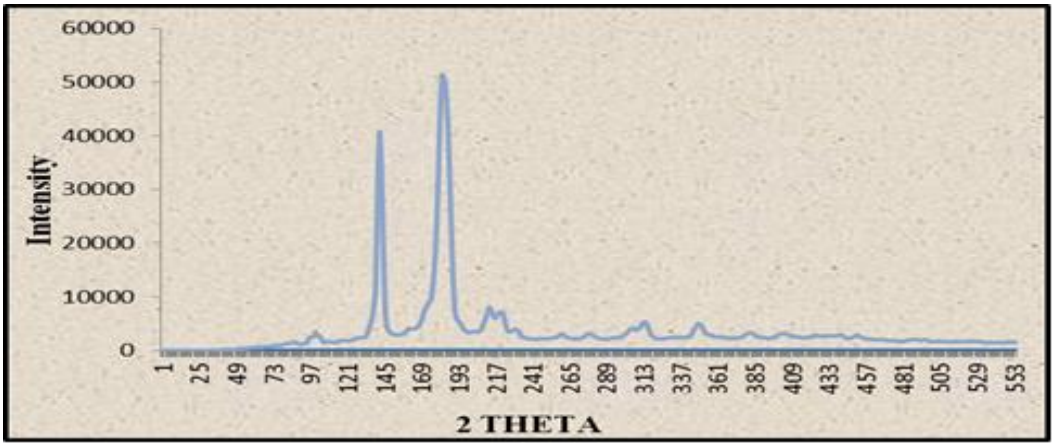

Figure No. 7: XRD of PEG 4000

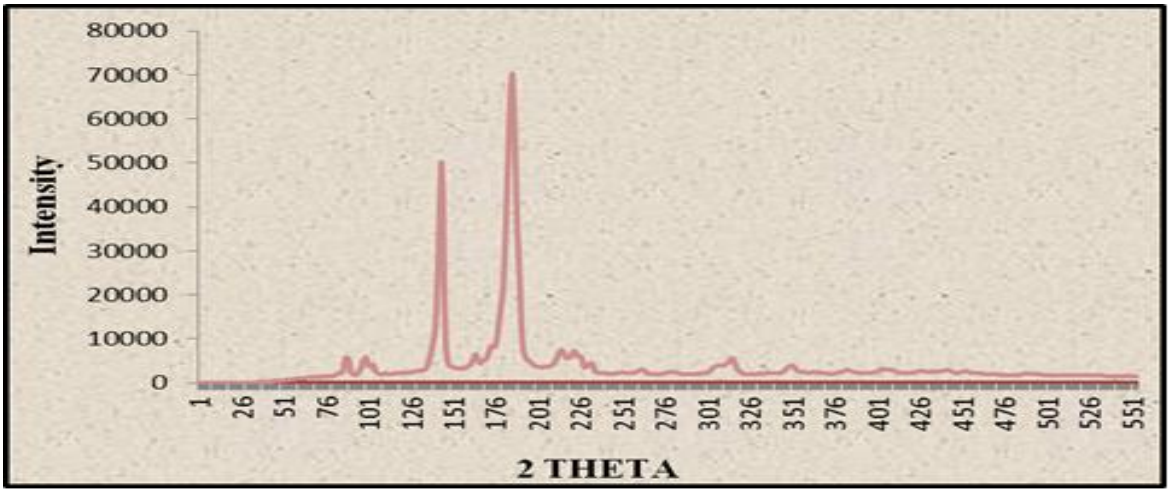

Figure No. 8: XRD of PEG 6000

SEM

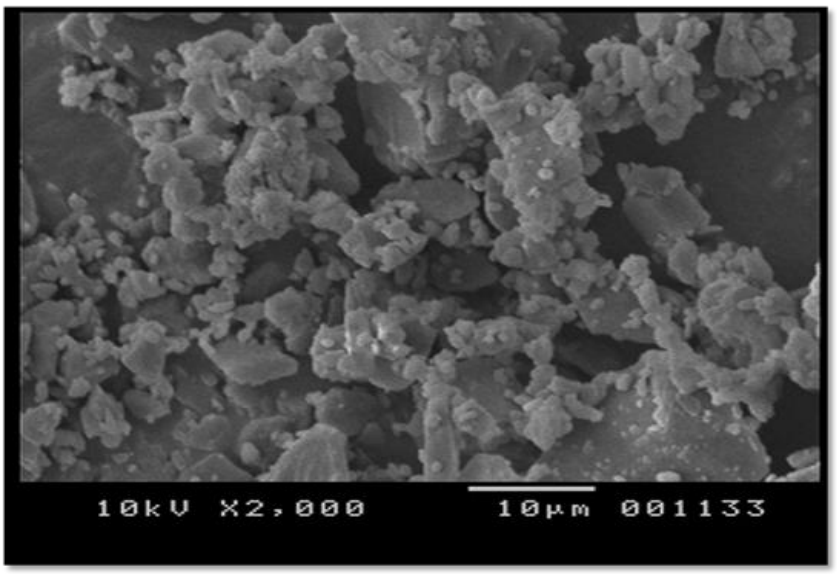

Figure No. 9: SEM of Amlodipine besylate

Characterization of Solid Dispersion

Percent Practical Yield -The percent practical yield was found to be in the range of 68.50 - 91.25%.

Drug content

Solubility studies

Table No. 9: % Practical Yield, Solubility and % Drug content of Formulation

Sr.No.	Formulation code	Ratio	%Practical Yield	Solubility (µg/ml)	% Drug content
1	PM41	1:1	85	40.76	91.77
2	PM43	1:3	85.25	93.67	86.47
3	PM45	1:5	88.16	147.43	88.93
4	PM47	1:7	89	113.8	91.01
5	PM410	1:10	86.09	100.5	90.31
6	PM61	1:1	82.5	130.09	87.02
7	PM63	1:3	90.25	132.59	90.54
8	PM65	1:5	90.83	141.51	92.64
9	PM67	1:7	91.25	134.35	91.55
10	PM610	1:10	87.09	117.69	85.73
11	SE41	1:1	70.5	121.2	95.04
12	SE43	1:3	77	142.5	91.79
13	SE45	1:5	83	325.95	101.9
14	SE47	1:7	80.62	207.6	83.12
15	SE410	1:10	79.09	204.5	82.09
16	SE61	1:1	68.50	137.36	86.9
17	SE63	1:3	79.25	253.3	85.03
18	SE65	1:5	80.5	264.3	90.06
19	SE67	1:7	78.25	248.0	94.29
20	SE610	1:10	74.72	232.6	105.1

Solubility of Amlodipine besylate in water: 20.54 µg/ml

Solubility of PM 45 (1:5): 147.43 µg/ml

Solubility of PM 65 (1:5): 141.51 µg/ml

Solubility of SE 45 (1:5): 325.95 µg/ml

Solubility of SE 65 (1:5): 264.3 µg/ml

Stability Studies

Table No. 10: Stability study data of Formulation

Formulation Code	Parameters	Storage at 40°C ± 2°C/79% RH ± 5% RH			
		0 Month	1 Month	2 Month	3 Month
PM 45	Solubility (µg/ml)	147.43	147.36	146.83	146.05
	% Drug content	88.93	88.35	87.68	87.03
PM 65	Solubility (µg/ml)	141.51	141.12	140.85	140.38
	% Drug content	92.64	92.39	91.68	91.35
SE45	Solubility (µg/ml)	325.95	325.46	325.36	325.12
	% Drug content	101.9	99.95	99.12	99.08
SE 65	Solubility (µg/ml)	264.3	264.09	263.52	263.29
	% Drug content	90.06	89.18	89.02	88.95

CONCLUSION:

Solid dispersions prepared by using different methods were effective for improving the drug dissolution rate. The current study investigates the suitability of PEG 4000, PEG 6000 as a carrier for solid dispersions of Amlodipine besylate study. The purpose of the present investigation was to evaluate the effect of polymer composition and solvent characteristics on the dissolution behavior of amlodipine besylate. Develop the solid dispersion by solvent evaporation method and physical mixture method. The solvent evaporation method was preferred for the development of solid dispersion because of its low melting points.

Solubility of solid dispersion with PEG 4000 by solvent evaporation method in 1:1, 1:3, 1:5, 1:7, and 1:10 was found to be 121.2, 142.5, 325.95, 207.6, and 204.5 µg/ml respectively. Solubility of solid dispersion with PEG 6000 by solvent evaporation method in 1:1, 1:3, 1:5,

1:7, and 1:10 was found to be.137.36, 253.3, 264.3, 248.0, and 232.6 µg/ml respectively. Solubility of solid dispersion with PEG 4000 by physical mixture method in 1:1, 1:3, 1:5, 1:7, and 1:10 was found to be 40.76, 93.67, 147.43, 113.8, and 100.5 µg/ml respectively. Solubility of solid dispersion with PEG 6000 by physical mixture method in 1:1, 1:3, 1:5, 1:7, and 1:10 was found to be 130.09, 132.59, 141.51, 134.35, and 117.69 µg/ml respectively. According to their solubility study data 1:5 ratio almost increases solubility, therefore this was an optimized batch for use further investigation. The solubility of the drug was increased by the solvent evaporation method as compared to the physical mixture and pure drug. The percent practical yield was found to be in the range of 68.50-91.25%. The percent drug content of formulation in range 82.9-105.1%. According to their dissolution rate of 1:5 ratio almost increases % drug release, therefore this was optimized batch use for further investigation. Solid dispersions showed no diffraction peaks, suggesting that the drug was in an amorphous state. The results of SEM images concluded that the solid dispersion prepared was uniform in size and shape, smaller in size than a pure drug, uniformly distributed thus having good flow properties, and has good solubility than pure drug. The solid-state FT-IR studies that no chemical decomposition and no interactions between the drug and polymer, showing compatibility between them. From the stability studies of the optimized batch, it was found that the solid dispersion remained stable even after exposure to stress conditions of temperature and moisture. The bioavailability of solid dispersion formulation was also enhanced in comparison with Std. amlodipine besylate.

Finally, it can be concluded that the solid dispersion technique is useful in improving the solubility and bioavailability of the drug.

ACKNOWLEDGEMENT:

We are thankful to Yashica Pharmaceuticals Private, Thane for providing a gift sample of amlodipine besylate & Loba Chem, Pvt. Ltd, Mumbai for providing polymers. I wish to express my sincere thanks with a deep sense of gratitude, to my respected guide.

REFERENCES:

1. Peter L.D., Michael D.M. and Wildfong, Aqueous solubility enhancement through engineering of binary solid composites – Pharmaceutical applications, J. Pharm. Innov, 2009, 4, 36-49.
2. Chiou W.L, and Riegelman, S., Pharmaceutical Applications of Solid Dispersion Systems, J. Pharm. Sci., 1971, 60(9), 1281-1302.
3. Ford J.L., The Current Status of Solid Dispersions. Pharm. Acta Helv. 1986, 61, 69–88.

4. Serajuddin, A.T.M., Solid Dispersions of Poorly Water-Soluble Drugs, Early Promises, Subsequent Problems, and Recent Breakthroughs. J. Pharm. Sci. 1999, 88, 1058–1066.
5. Younggil Kwon, Handbook of essential pharmacokinetics, pharmacodynamics, and drug metabolism for industrial scientists, Plenum publisher, New York, 35-38.
6. Fincher J.H., Particle size of drugs and its relationship to absorption and activity, J.Pharm. Sci., 1968, 57(11), 1825-1835.
7. Habib M.J., Pharmaceutical Solid Dispersion Technology, Lancaster, P.A., Technomic Publishing company, Inc., 2001, 16-19.
8. Jones A., Pharmaceutical Eutectics, Formation, Evaluation and Relevance in preformulation studies using thermal analytical methods, Master Thesis, 2005.
9. Martin, A.N., Swarbrick, J., and Cammarata, A., Physical Pharmacy, Philadelphia PA, 1969, 2, 313.
10. Jones, G.O., Glass, New York, Wiley, 1958, 1-9.
11. Ansel C. Howard, Allen V. Loyd, Popovich A. Nicholas, Pharmacetical dosage forms and drug delivery systems.2000,7,248-252.
12. Sekikawa, H., Nakano, M. and Aritra, T., Dissolution mechanisms of drug- Polyvinylpyrollidone co-precipitates in aqueous solution, Chem. Pharm. Bull., 1979, 27(5), 1223-1230.
13. Pouton CW. Formulation of poorly water-soluble drugs for oral administration, physicochemical and physiological issues and the lipid formulation classification system, Eur. J. Pharm. Sci., 2006, 29, 278-28.
14. Ghaderi R, Artursson P,Carifors J., Preparation of biodegradable microparticles using solution enhanced dispersion by supercritical fluids, Pharm. Res., 1999, 16, 676-681.
15. Vippagunta S.R., Karin A. Maul, Siva Tallavajhala, David JW Grant. Solid-state characterization of nifedipine solid dispersions. Int. J. Pharm., 2002, 236,111-123.
16. Pravin kumar D. Arora Vandana, Solid Dispersion: A Review, Journal of Pharmaceutical and scientific Innovation, 2012, 1(3), 28.
17. Karanth H, Shenoy VS, Murthy RR. Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions, A Technical Report. AAPS Pharm Sci Tech. 2006, E1-E8.
18. D Praveen Kumar, Arora Vandana , Solid Dispersion A Aeview, JPSI 2012, (3), 27-34.
19. James L. Ford, F. Stewart and Michael H. Rubinstein, The assay and stability of chlorpropammide in solid dispersion with urea, J. Pharm. Pharmac., 1979, 31, 726-729.
20. Carcano E.C., Gana I.M., Eutectic mixtures and solid solutions of acetylsalicylic acid and urea – Stability of acetylsalicylic acid, An. R. Acad. Farm., 1974, 40 , 487-493.
21. Takeuchi H, Nagira S, Yamamoto H, Kawashima Y. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. Int. J. Pharm. 2005, 293, 155-164.
22. Kaushal A. M., Gupta P, Bansal AK.Amorphous drug delivery systems, molecular aspects, design, and performance. Crit. Rev. Ther. Drug Carrier Syst. 2004, 21, 133-193.
23. Mantsch H,H, Chapman D, Infrared spectroscopy of biomolecules. Wiley-Liss New York. 1996.
24. Buckton G, Darcy P., The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. Int. J. Pharm., 1995, 123, 265-271.
25. Bugay D.E., Characterization of the solid-state, spectroscopic techniques. Adv. Drug Deliv., 2001,48, 43-65.
26. Paraira M., Llovet X., Sufio J.M., Granulometric characterization and study of ibuprofen lysinate by means of an image processor, Drug Dev. Ind. Pharm.,1994, 20, 259-278.
27. Sebhatu T., Angberg M., Ahlneck C.Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. Int. J. Pharm., 1994, 104, 135-144.
28. Kamalakkannan V., Solubility enhancement of poorly soluble drugs by solid dispersion technique – A review, Journal of Pharmacy Research, 2010, 3(9), 2314-2321.
29. Pikal M.J., Lukes A.L., Lang J.E., Gaines K., Quantitative crystallinity determinations for betalactam antibiotics by solution calorimetry, correlations with stability, J. Pharm. Sci., 1978, 67.
30. Verheyen S., Blaton N., Kinget R., Mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions, International Journal of Pharmaceutics, 2002, 24945-2458.
31. Swati Rawata, Sanjay K. Jainb, Solubility enhancement of celecoxib using b-cyclodextrin inclusion complexes, European Journal of Pharmaceutics and Biopharmaceutics, 2004, 57, 263–267.