IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

SOLUBILITY ENHANCEMENT OF DILTIAZEM BY USING SOLID DISPERSION TECHNIQUES

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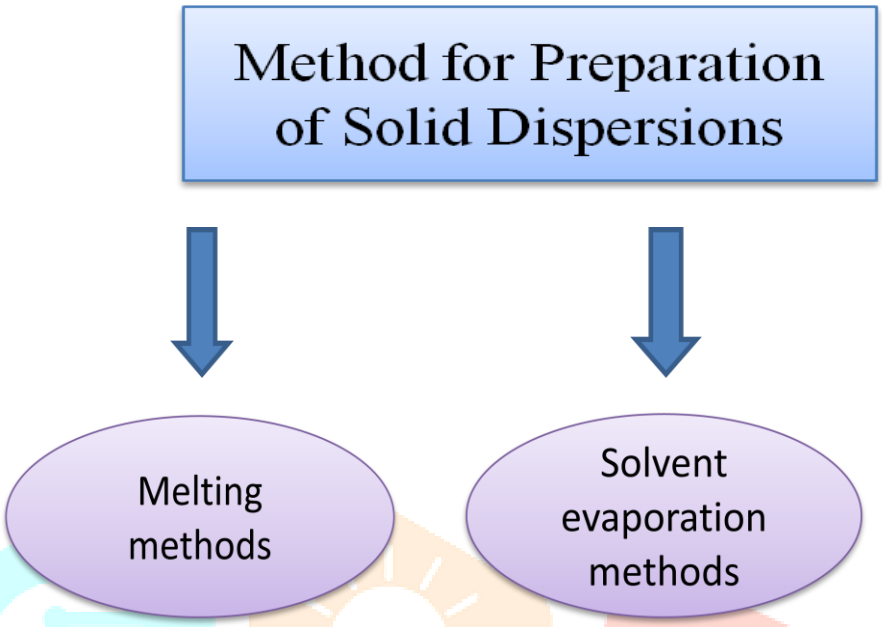
Abstract

Diltiazem 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 aim of the current study was to prepare solid dispersion of Diltiazem in order to enhance its solubility by using polymer like PEG 4000 and PEG 6000 which ultimately helps to increase bioavailability of Diltiazem. Solid dispersion of Diltiazem was prepared by using 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, there for this was optimized batch for use farther investigation. Solubility of the drug was increased by the solvent evaporation method as compared to physical mixture and pure drug. The bioavailability of solid dispersion formulation was also enhanced in comparison with Std. Diltiazem. Finally it can be concluded that the solid dispersion technique is a useful technique in improving the solubility and bioavailability of slightly water-soluble compounds such as Diltiazem.

Keywords- vasopastic angina, Diltiazem, solubility, dispersion, bioavailability.

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."



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 overall bioavailability of the active pharmaceutical ingredient. Biopharmaceutical Classification (BCS) system classifies these active pharmaceutical ingredients into four classes as given below:

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 Chlorethizide Furosemide Indinavir

Table no. 1: BCS classification of drug

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 which are faced by the pharmaceutical industry at the present time. 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 their own 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 includes: the use of surfactants; pH modification; solid dispersion technique; co-solvent and hydrotrop 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 a 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 a number of 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 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 solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly permeable drugs.

Aim & Objective

- To study preformulation parameters of Diltiazem in order to increase its solubility by using solid dispersion method.
- To enhance the solubility of Diltiazem by using a PEG 4000 and PEG 6000.
- To enhance the bioavailability of Diltiazem.
- 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 solubility of drug.
- To evaluate, compare and select suitable carrier systems for solubility enhancement of drug.
- Finally to characterize prepared solid dispersion for their morphology.

Material & Methods

Drug & polymer profile

Diltiazem

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 has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Table no. 2: Drug profile

Polyethylene glycol

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.

Table no. 3: Polymer profile

Preparation of solid dispersion

Preparation of physical mixture with PEG 4000

For the preparation of a physical mixture Diltiazem and PEG 4000 was 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. Diltiazem PEG 4000 physical mixtures were used for further investigations.

Preparation of physical mixture with PEG 6000

For the preparation of a physical mixture Diltiazem and PEG 6000 was 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. Diltiazem PEG 6000 physical mixtures were used for further investigations.

Preparation of solid dispersion with PEG 4000 by Solvent evaporation method

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

Preparation of solid dispersion with PEG 6000 by Solvent evaporation method

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

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

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

Preformulation study

Identification and characterization of drug

- ✓ Organoleptic properties
- ✓ Melting point determination
- ✓ Determination of λ max of Diltiazem
- ✓ Calibration curve of Diltiazem 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

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

Table no. 5: Results of organoleptic Properties

Melting Point determination

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

Table no. 6: Melting point determination

Determination of λ max of Diltiazem

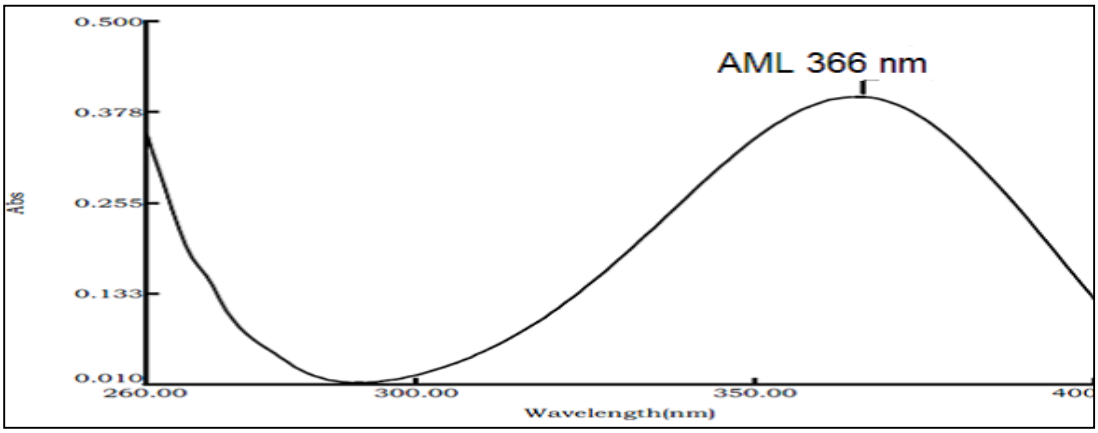


Figure no.1: λmax of Diltiazem in methanol

Calibration curve of amlodipine besylte in methanol

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

Table no.7: Absorbance and conc. data of Diltiazem at 366 nm

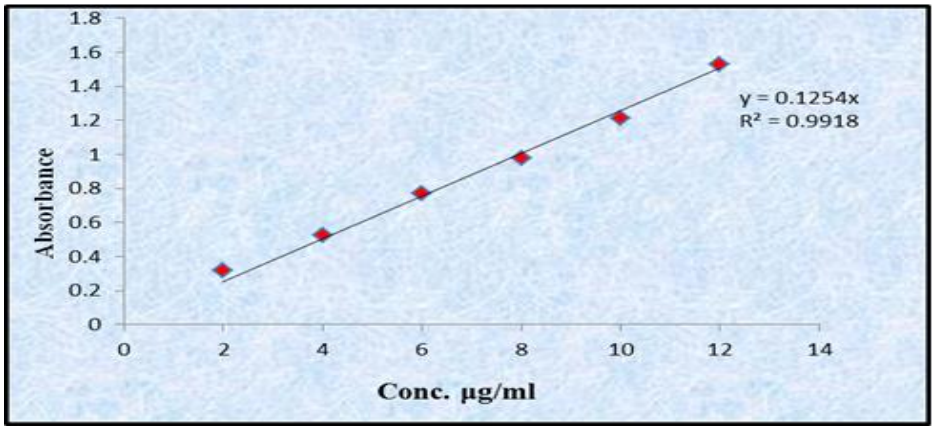


Figure no.2: Calibration curve of Diltiazem

FT-IR spectral study

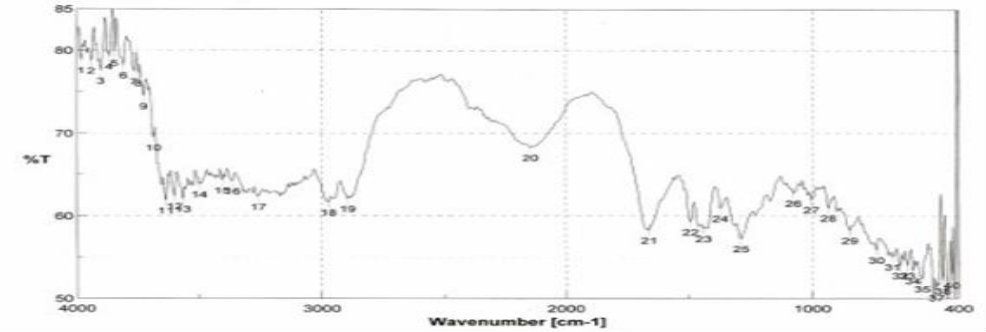


Figure no.3: FT-IR-spectra of Diltiazem pure drug

Compound	Frequency (cm^{-1})	Type of vibration
Diltiazem	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

Table no.8: IR interpretation data

Differential scanning colorimetry (DSC)

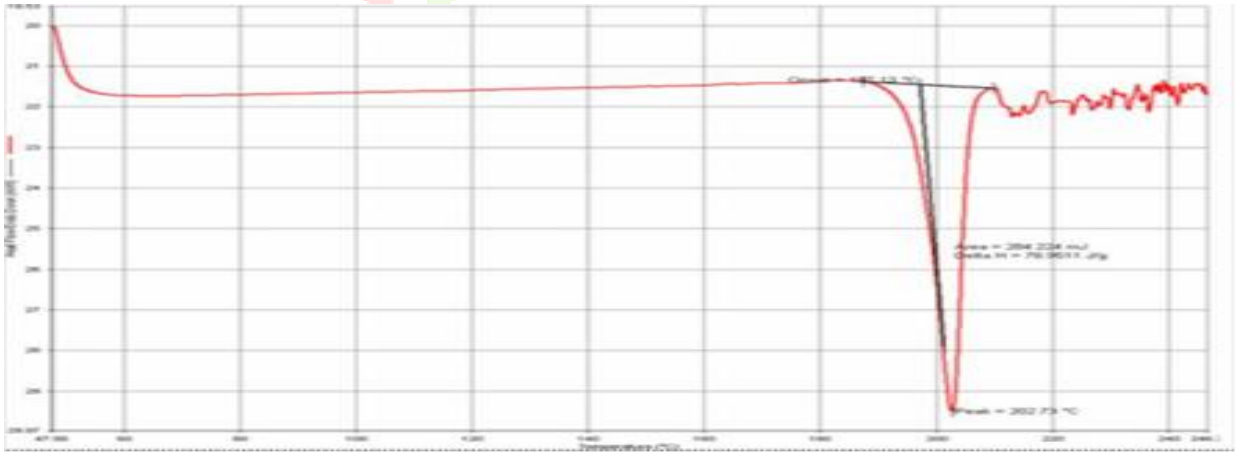


Figure no.4: DSC spectra of Diltiazem

X-ray powder diffraction (XRD)

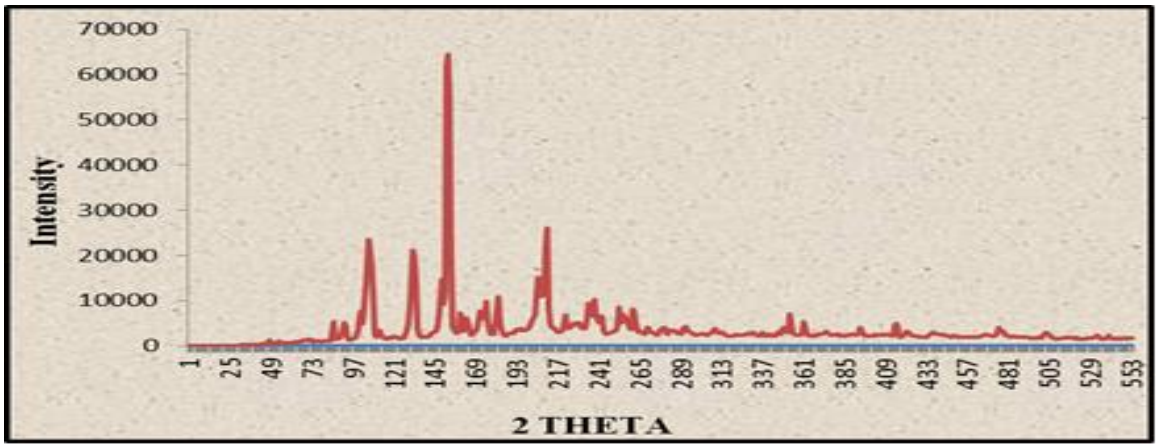


Figure no.5: XRD of Diltiazem

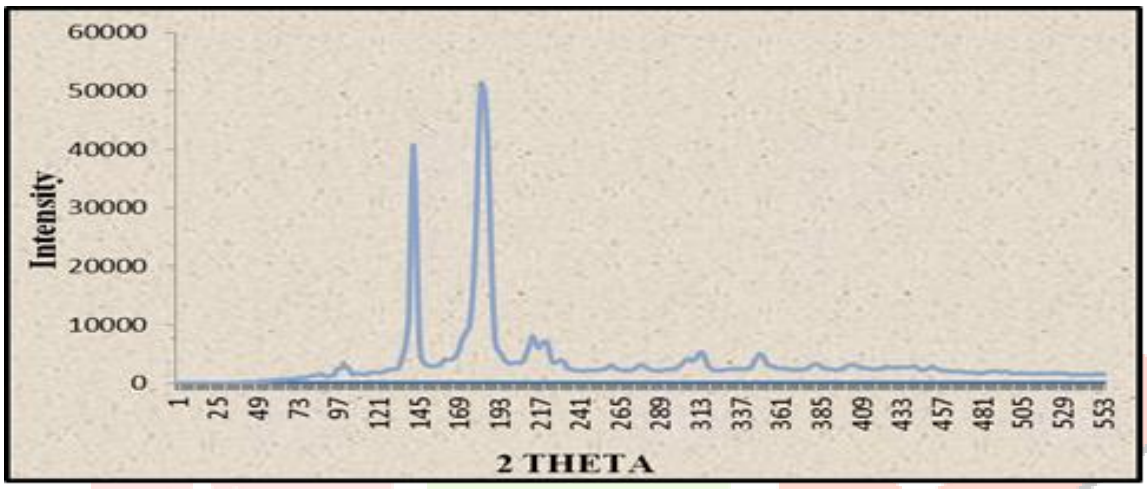


Figure no.6: XRD of PEG 4000

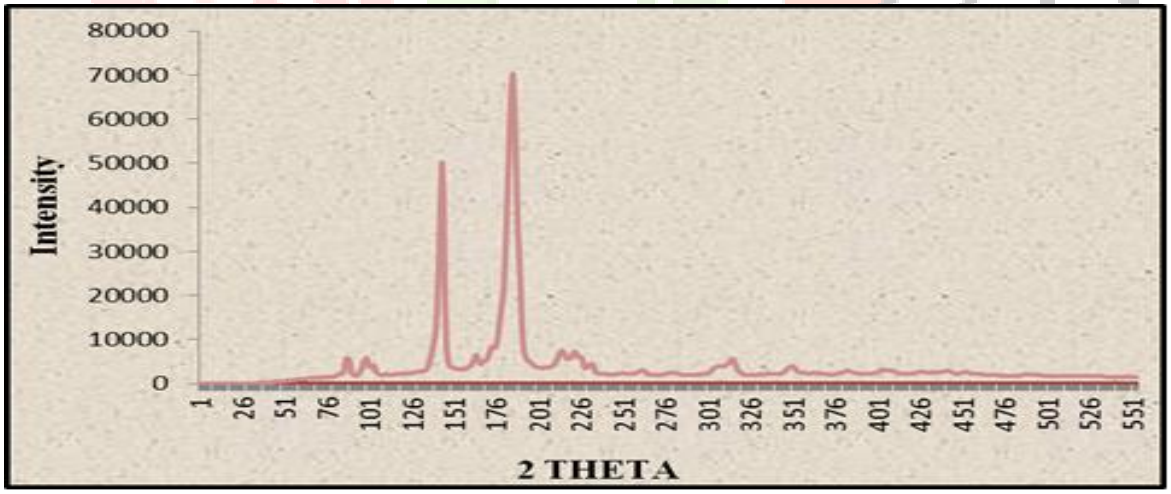


Figure no.7: XRD of PEG 6000

SEM

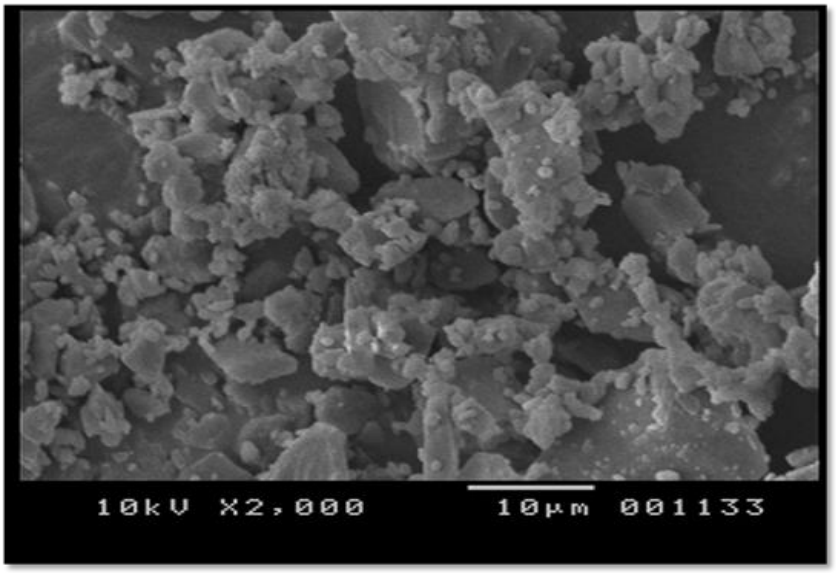


Figure no.8: SEM of Diltiazem

Characterization of Solid Dispersion

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

Drug content

Solubility studies

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

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

Solubility of Diltiazem 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

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

Table no.10: Stability study data of Formulation

Conclusion

Solid dispersions prepared by using different methods were effective for improving drug dissolution rate.Current study investigates the suitability of PEG 4000, PEG 6000 as a carrier for solid dispersions of Diltiazem study. The purpose of the present investigation was to evaluate the effect of polymer composition and solvent characteristics on the dissolution behaviour of Diltiazem. Develop the solid dispersion by solvent evaporation method and physical mixture method. Solvent evaporation method was preferred for development of solid dispersion because of their 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, there for this was optimized batch for use farther investigation. Solubility of the drug was increased by the solvent evaporation method as compared to physical mixture and pure drug. The percent practical yield was found to be in the range 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, there for this was optimized batch use for farther investigation. Solid dispersions showed no diffraction peaks, suggesting that the drug was in amorphous state. The results of SEM images concluded that the solid dispersion prepared were uniform in size and shape, smaller in size than 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 exposing to stress conditions of temperature and moisture. The bioavailability of solid dispersion formulation was also enhanced in comparison with Std. Diltiazem.

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

Acknowledgement

We are thankful to Yashica Pharmaceuticals Private, Thane for providing gift sample of Diltiazem & 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.

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