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ENHANCEMENT OF AQUEOUS SOLUBLITY OF AZELNIDIPINE USING SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT

The present study was aimed to improve the solubility and bioavailability of water insoluble antihypertensive agent Azelnidipine by solvent evaporation method. Chemically Azelnidipine is dihydropyridine analogue. Azelnidipine is voltage dependent inhibitor of trans-membrane Ca2+ influx in vascular smooth muscles. Solid dispersion of Azelnidipine was prepared using hydrophilic polymers by solvent evaporation technique. Further preparations were analysed for solubility study, FTIR study, PXRD study, and Stability Studies. Based on physical characters and drug release patterns formulations F3C, F7C and F11C exhibited best results when compared to pure dug.

KEYWORDS: Solid dispersion, Solvent evaporation, Solubility, BCS Class II, Antihypertensive.

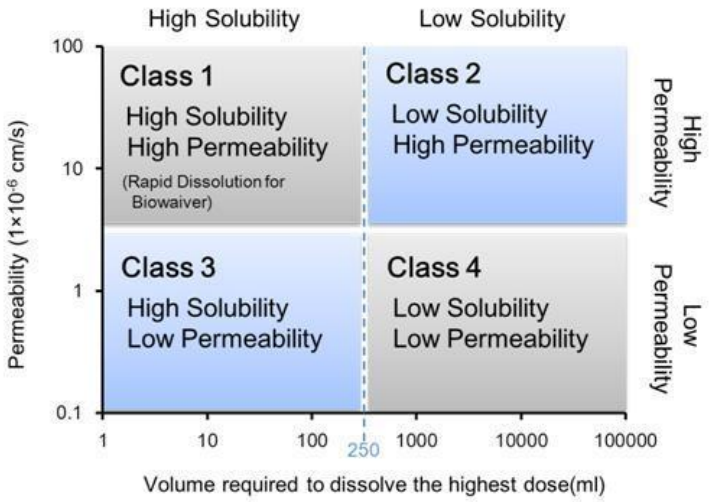
INTRODUCTION

Oral drug delivery is very popular due to its ease of administration, high patient compliance, cost effectiveness, reduced sterility constraints, and flexibility of dosage form design.[1] When a drug is administered orally, it has to cross certain barriers (varies from drug to drug) within the biological system including dissolution in gastrointestinal fluids, permeation across the GI membrane, and first pass metabolism to reach its actual site of action via systemic circulation.

For the drugs which are administered orally, solubility is an important physicochemical factor which affect the drug absorption as well as its therapeutic effectiveness. The low water solubility and low dissolution of the drug Gastrointestinal fluid ultimately leads to the poor oral bioavailability. This poor oral bioavailability of the drug is the major challenging task for

the oral dosage form development. While designing of oral dosage form usually one third percent of drugs are hydrophobic i.e. water insoluble and one-half percent of drugs fail in clinical trials due to underprivileged pharmacokinetics.

On the basis of solubility and permeability of drugs across the GIT Amidon et al (1995) classified active pharmaceutical ingredients (API) into 4 groups known as Biopharmaceutical classification system (BCS).[2] In the Biopharmaceutical classification system low water-soluble drugs belongs to BCS class II and class IV group. Due to low water solubility and slow dissolution of BCS Class II and Class IV drug have been investigated in wide range.



Techniques to improve solubility[3]

There are various techniques available to improve the solubility of poorly soluble drugs such as:

- Micronization
- Nanosuspension
- Modification of the crystal habits
- Eutectic mixtures, solid dispersions
- Microemulsions
- Self-micro emulsifying drug delivery systems
- Cyclodextrin inclusion
- Lipid-based delivery systems

SOLID DISPERSION

Sekiguchi and obi were the first to introduce Solid dispersion as unique technique by report of an improved dissolution of the drug from sulfamethazole-urea solid dispersion.[4] Solid dispersion is one of the approaches employed to improve dissolution of hydrophobic drugs whose absorption is dissolution rate limited.

Solid dispersion technology refers to the dispersion of one or more active ingredients in an inert matrix in the solid stage in order to achieve improved dissolution rate, sustained release of drugs, altered solid state characters, and enhanced solubility and stability.[5] The solid dispersion was first introduced to overcome the low bioavailability of lipophilic drugs by forming a eutectic mixture of drugs with hydrophilic carriers.

ADVANTAGES OF SD[6]

Following are some advantages of solid dispersion technique

1. Particles with reduced particle size: In solid dispersion particle size is reduced, a high surface area is formed, resulting in an increased dissolution rate and consequently an improved bioavailability is observed.
2. Particles with improved wettability: The solid dispersion improves the wettability and solubility. Moreover, polymers can affect the drug dissolution profile by direct dissolution or co-solvent effects.
3. Particles with higher porosity: Particles in solid dispersions possess higher degree of porosity and hasten the drug release profile. The increase in porosity also depends on the polymer properties.
4. Drugs in amorphous state: The enhancement of drug release can be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process.
5. In solid dispersions drugs are available in super saturated solutions which are considered to be metastable polymorphic form. Thus, the drugs in amorphous form increase the solubility of the particles.
6. Rapid dissolution rates that results in an increase in the rate and extent of the absorption of the drug, and a reduction in presystemic; both can lead to the need for lower doses of the drug.
7. Cost effective
8. Less time required for production

DISADVANTAGES[7]

1. The key disadvantages of solid dispersion are related to their instability.
2. Moisture and temperature have more of a deteriorating effect on solid dispersions than physical mixtures. Some solid dispersion is not easy to handle because of tackiness.
3. Two fixed dose combination is required.
4. Drug-drug solid dispersion, it is compulsory that one of the drugs is highly soluble.
5. It leads to the poor scale-up for the purpose of manufacturing.
6. The polymers used in solid dispersion can absorb moisture and cause phase-separation, crystal growth and convert amorphous form into crystalline form. Thus, result in decrease solubility and dissolution rate.

AZELNIDIPINE[8]

IUPAC Name

3-(1-Benzhydrazetidine-3-yl)-5-isopropyl-2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Molecular Weight: 582.657g/mol

Chemical formula: C_{33} H_{34} N_4 O_6

Chemical structure

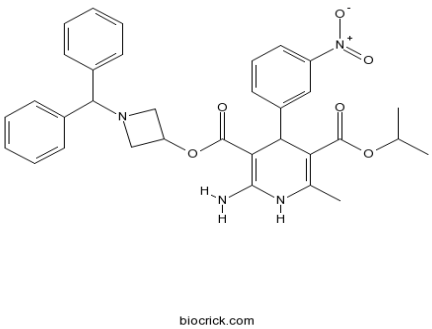


Fig. 1: Chemical structure of Azelnidipine.

Mechanism of action

Azelnidipine inhibits trans-membrane Ca2+ influx through the voltage-dependent channels of smooth muscles in vascular walls. Ca2+ channels are classified into various categories, including L-type, T-type, N-type, P/Q-type, and R-type Ca2+ channels. The L-type Ca2+

channels [L1382]. Normally, calcium induces smooth muscle contraction, contributing to hypertension. When calcium channels are blocked, the vascular smooth muscle does not contract, resulting in relaxation of vascular smooth muscle walls and decreased blood pressure.

Pharmacodynamic

Azelnidipine is a vasodilator that induces a gradual decrease in blood pressure in hypertensive patients. Unlike other members of its drug class, Azelnidipine does not induce reflex tachycardia due to vasodilation. This is likely due to the fact that it elicits a gradual fall in blood pressure. It also exhibits a prolonged hypotensive effect and has been shown to have a strong anti-arteriosclerotic action in vessels due to its high affinity for vascular tissue and antioxidative activity. Clinical studies have demonstrated that Azelnidipine markedly reduced heart rate and proteinuria in hypertensive patients by inhibiting sympathetic nerve activity. The drug has also been confirmed to have cardio-protective, neuroprotective, and anti-atherosclerotic properties, and has also been found to prevent insulin resistance.

Table 1: Drug Profile.

Drug	**Parameters**	
Azelnidipine	Category	Anti-hypertensive
	Pharmacologic class	Dihydropyridine analogue
	Appearance	Yellow crystalline powder
	Melting point	193-195˚C
	Log p	4.7
	pKa	7.89
	Solubility	insoluble in water
	Permeability	High permeability
	Dose	8mg, 16mg
	Brands	Calblock®,

MATERIALS AND METHODS

Azelnidipine was obtained as the gift sample from Mylan Pharmaceutical limited (Hyderabad), Kollidone VA64 (PVPVA), Soluplus, PVP K 30, Ethanol, Phosphate buffer pH 4, Distilled water. All other chemicals were used of analytical grade.

Instruments used

Electronic Balance, Magnetic stirrer, UV/visible spectrophotometer, Dissolution Apparatus.

Preparation of Solid Dispersion

Method of estimation of Azelnidipine

Analytical method development[9]

Analytical method was developed to determine the concentration of Azelnidipine in different media; 0.1N HCl, pH 4.0+0.01% Tween 80 and water by UV spectrophotometer.

Estimation of drug in different medium by UV spectrophotometer

Standard Stock: 100 mg equivalent drug was taken and added to respective media in a 100 mL volumetric flask and volume was made up to 10 mL, resulting in stock solution of 1mg/mL.

Sub Stock: From the standard stock solution, 10 mL was taken and added to respective buffer media in a 100mL volumetric flask and volume made up to 100 mL.

Working Stock: From the sub stock solution, different aliquots were taken in series if 10 mL volumetric flasks and volume made up with buffer to get a series of working standard solution of concentration, range of 2 µg/mL to 10 µg/mL for 0.1N HCl, 2 µg/mL to 10 µg/mL for pH 4.0+0.01% Tween 80 and 2 µg/mL to 10 µg/mL water.

Determination of absorption maxima

10 µg/mL solution was scanned by UV Spectrophotometer to determine absorption maxima. Initially blank buffer solution was placed in the cuvette and scanned in the region of 200-400 nm. Then sample was scanned in the same region and absorption maxima will was determined.

Determination of Beer's law range and plotting of calibration curve

From the working stock solution 0.2, 0.4,0.6,0.8,1.0 1.2 mL of sample was taken and diluted up to 10 mL using respective buffer media in a 10 mL. volumetric flask resulting in concentrations 2, 4, 6, 8, 10, 12 14 µg/mL solutions. These samples were analysed at λ_{max} and calibration curve was plotted taking concentration in µg/mL on X-axis and absorbance units on Y-axis.

Table 2: Preparation of calibration curve (0.1N HCL).

Concentration (ug/ml)	Abs
2	0.288
4	0.415
6	0.589
8	0.743
10	0.891

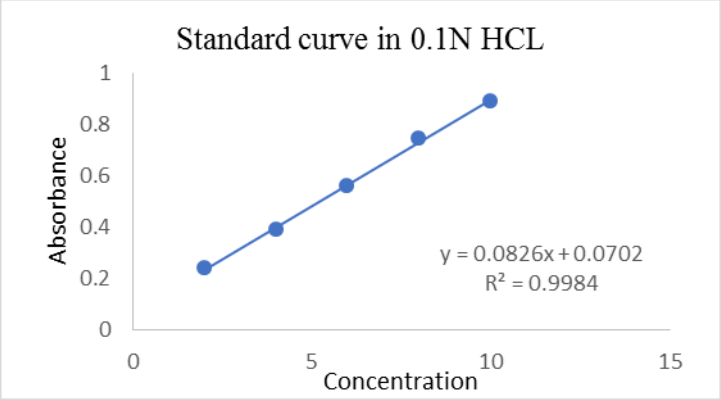


Fig. 2: Calibration curve in 0.1N HCL.

Table 3: Preparation of calibration curve (Ph 4 + Tween 80).

Concentration (ug/ml)	Abs
2	0.289
4	0.423
6	0.568
8	0.726
10	0.875

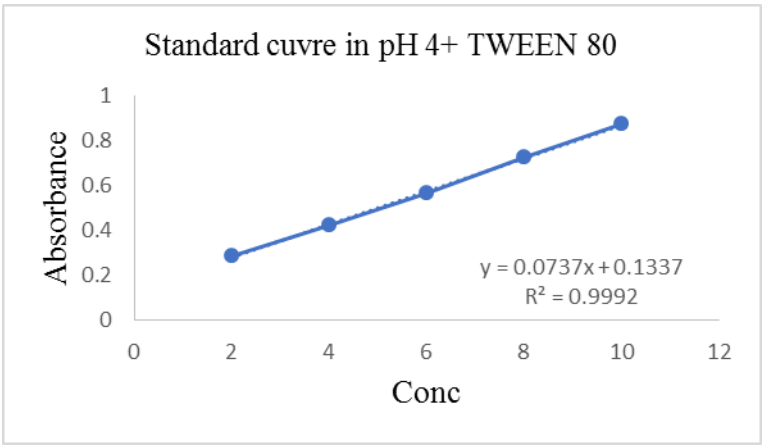


Fig. 3: Calibration Curve In pH4 + Tween 80.

Table 4: Preparation of calibration curve (water).

Concentration (ug/ml)	Abs
2	0.288
4	0.415
6	0.589
8	0.743
10	0.891

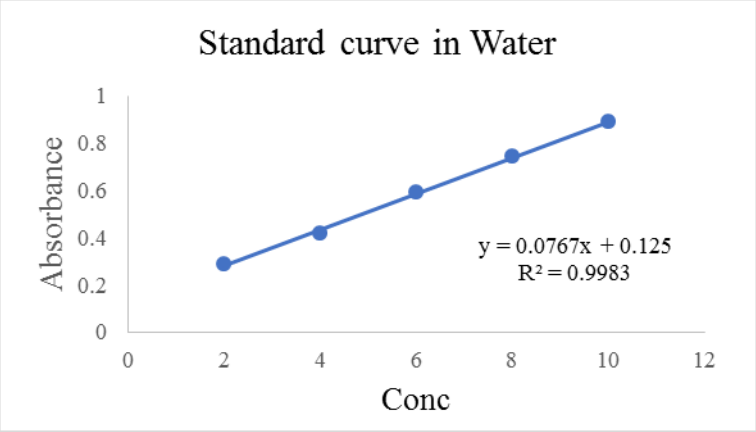


Fig. 4: Calibration curve in water.

Preparation of solid dispersion by solvent evaporation method[10]

Solid dispersion of Azelnidipine were prepared by Solvent evaporation method. The polymer used in the study was PVPVA, Povidone k-30 and Soluplus. SDs was prepared in drug: carrier concentrations of 1:0.5, 1:1, 1:2 and 1:3 for drug: Kollidon VA 64, Povidone k-30 and Soluplus respectively.

Preparation of physical mixture

Physical mixture were prepared by mixing the appropriately weighed amount of Azelnidipine and carriers/polymers in pestle and mortar then pass through Sieve no 60.

Preparation of solid dispersion

The Azelnidipine and all other polymers (PVPVA, Povidone k-30 and Soluplus) were weighed according to requirement for the preparation of solid dispersion of different ratios. Solution of Azelnidipine: polymer (10% w/w) was prepared by dissolving different ratios (1:0.5, 1:1; 1:2 and 1:3) of drug: polymer in the sufficient amount of absolute ethanol with continuous stirring. This solution is then kept on magnetic stirring for 30-35 min. and then the mixture was poured slowly in the petridish. Then petridish was kept in oven until the solvent evaporated. The resultant solid dispersions were scraped out with spatula, fine

powder was obtained by passing through sieve no 60 and stored it until further evaluation. The compositions of various solid dispersions were given in table no 3. Solubility studies were performed for all the formulations prepared. Based on the solubility results, formulations were selected for further optimization. Practical yield calculated by using below formula.

Table 5: Composition of solid dispersion.

FC	D:P	Polymer used		
		PVPVA	Soluplus	PVP K-30
F1	1:0.5	Y		
F2	1:1	Y		
F3	1:1	Y		
F4	1:2	Y		
F5	1:0.5		Y	
F6	1:1		Y	
F7	1:1		Y	
F8	1:2		Y	
F9	1:0.5			Y
F10	1:1			Y
F11	1:1			Y
F12	1:2			Y

Characterization of solid dispersion

Solubility studies of solid dispersion

Solubility studies were performed by taking SDs of Azelnidipine: carrier ratios (1:0.5, 1:1, 1:2, 1:3) in 250 mL of buffer and subjected to mechanical shaking at 200 rpm for 24 hrs. The resultant dispersions were collected and filtered through 0.45 µ PVDF filters and the concentration of drug was determined from absorbance at 261 nm. The solubility was performed with different medias like 0.1N HCl, water and pH 4.0 + 0.01% Tween 80.

Fourier Transforms infrared spectroscopy

FT-IR spectra obtained using FT-IR spectrophotometer obtaining with spectrum software, which is employed to characterize the possible interaction between the Azelnidipine and polymer in the solid state. Sample about 2 mg mixed with 100 mg of potassium bromide and then compressed to from disc. The spectra of plain drug, polymer, physical mixture of drug and polymer and SDs were scanned over a frequency range of 4000 to 450 cm^{-1}.

LOD (Loss on drying)

The Moisture Analyzer works according to the thermo-gravimetric principle, also often referred to as the 'Loss on Drying' (LOD) principle. For residual solvent by using Halogen moisture analyser (HX204) At temp 60°C, Time -5min and sample quantity 1-2 gm**.**

P-X-ray diffraction

The powder crystallinity of drug and prepared SDs were investigated using BRUKER D8 advance XRD with Cu kα radiation (wavelength 1.5406 Å). All the samples were scanned from 2° to 50° 2θ at a step size 0.009 with time 15.5 S.

Assay

Accurately, equivalent weighed quantity of prepared SDs dissolved in 10ml of ethanol and sonicated for 30min. The resulting solution was filtered, and the filtrates were analysed by UV spectrophotometer at 261nm after appropriate dilutions in water. The above assay done in triplicate.

Stability study

Before subjecting to stability studies, solid dispersion samples were analysed by XRD studies and initial thermograms were recorded. Then samples were subjected to accelerated conditions, 40ºC + 2º C/75% RH + 5% RH. After one month, XRD patterns of solid dispersion samples were recorded and compared with initial XRD patterns of respective samples.

***In-vitro* Dissolution Studies[11]**

In vitro dissolution studies of solid dispersions were performed by maintaining sink condition in a USP paddle apparatus (USP type II). USP paddle apparatus is standard dissolution test apparatus. The dissolution medium was 900mL pH 4.0 + 0.01% tween 80 kept at 37˚C ± 0.5˚C. The solid dispersion equivalent to dose of Azelnidipine was taken in dissolution apparatus with paddle stirrer at 75 rpm. At specific time intervals, samples of 5mL was withdrawn by means of syringe fitted with prefilter. The Drug release from solid dispersion were analysed spectrophotometrically by measuring absorbance at 261nm after suitable dilutions. All samples were tested in triplicate and then mean values were calculated.

RESULTS AND DISCUSSION

The study was undertaken to formulate a dosage form of poorly soluble drug by the preparation of Solid dispersion using solvent evaporation method. The attempt made to improve solubility and dissolution of Azelnidipine using Kollidon VA64, Soluplus and PVP K30. The study involves preformulation studies of drug and excipients. The prepared samples of solid dispersion were evaluated for various parameters such as Solubility, FTIR, PXRD, Dissolution study.

Solubility Studies

Solubility of the crystalline form of drug and solid dispersion of Azelnidipine containing various polymer in different media like 0.01N HCl, water and pH4.0 were performed to determine the improvement in solubility of pure drug. Drug Azelnidipine showed solubility of 1.21 µg/mL. All polymers except PVP K30 showed an increase insolubility with at 1:2 ratio. This enhancement in solubility can be attributed to conversion of crystalline form of drug into amorphous form as well as the presence of a hydrophilic polymer in the solid dispersion.

Table 6: Saturation Solubility of Drug And Formulations In Different Media (PVPVA).

Media	***Solubility (µg/mL)***				
	Azelnidipine	***F1 (1:0.5)***	***F2 (1:1)***	***F3 (1:2)***	***F4(1:3)***
Water	-	3.88	4.22	10.39	9.89
0.1N HCl	0.68	5.69	6.31	15.72	14.72
pH 4.0 + 0.01% Tween 80	1.21	6.89	7.29	29.89	27.83
pH 6.8 + 0.01% Tween 80	0.91	4.37	4.88	18.36	16.89

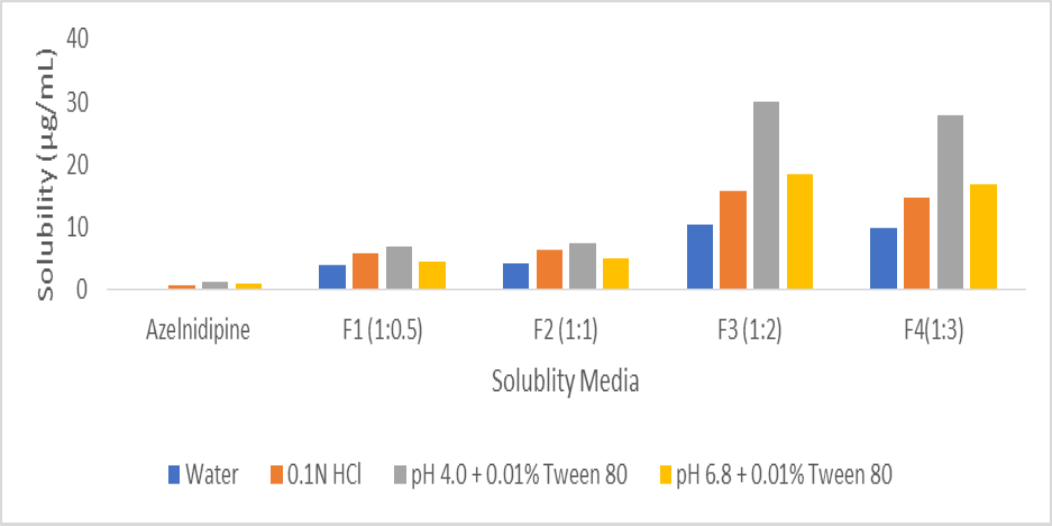


Fig. 5: Saturation solubility of drug and formulation in different media (PVPVA).

Table 7: Saturation solubility of drug and formulations in different media (SOLUPLUS).

Media	Solubility (µg/mL)				
	Azelnidipine	**F9 (1:0.5)**	**F10 (1:1)**	**F11 (1:2)**	**F12 (1:3)**
Water	-	3.11	3.86	8.39	7.89
0.1N HCl	0.68	4.69	5.31	12.72	11.72
pH 4.0+0.01Tween 80	1.21	6.19	6.79	23.89	21.83
pH 6.8+0.01Tween 80	0.91	3.77	3.88	18.36	16.89

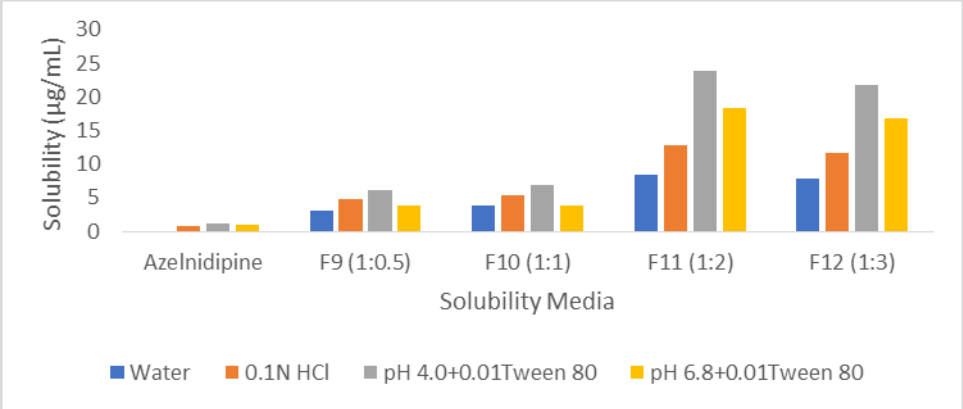


Fig. 6: Saturation solubility of drug and formulations in different media (SOLUPLUS).

Table 8: saturation solubility of drug and formulations in different media (PVP K-30).

Media	Solubility (µg/mL)				
	Azelnidipine	**F5 (1:0.5)**	**F6 (1:1)**	**F7 (1:2)**	**F8 (1:3)**
Water	-	0.14	0.35	0.65	0.61
0.1N HCl	0.68	0.52	0.79	0.81	0.79
pH 4.0 + 0.01Tween 80	1.21	1.57	1.81	2	1.77
pH 6.8 + 0.01Tween 80	0.91	1.01	1.21	1.89	1.12

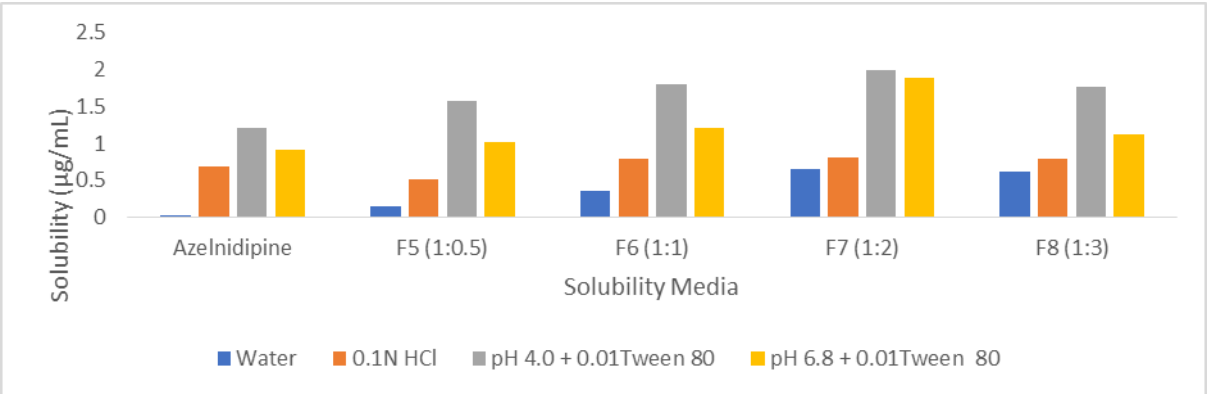


Fig. 7: Saturation solubility of drug and formulations in different media (PVP K-30).

Table 9: Saturation solubility of optimized formulations in different media.

Media	Solubility (µg/mL)											
F.C.	F3A	F3B	F3C	F3D	F7A	F7B	F7C	F7D	F11A	F11B	F11C	F11D
Water	3.88	4.22	10.39	9.89	0.51	0.52	0.51	0.66	3.11	3.86	8.39	7.89
0.1NHCl	5.69	6.31	15.72	14.72	0.69	0.66	0.66	0.82	4.69	5.31	12.72	11.72
pH 4.0+0.01% Tween 80	6.89	7.29	29.89	27.83	0.85	0.89	1.39	2.01	6.19	6.79	23.89	21.83
pH 6.8+0.01% Tween 80	4.37	4.88	18.36	16.89	0.71	0.89	1.11	1.89	3.77	3.88	18.36	16.89

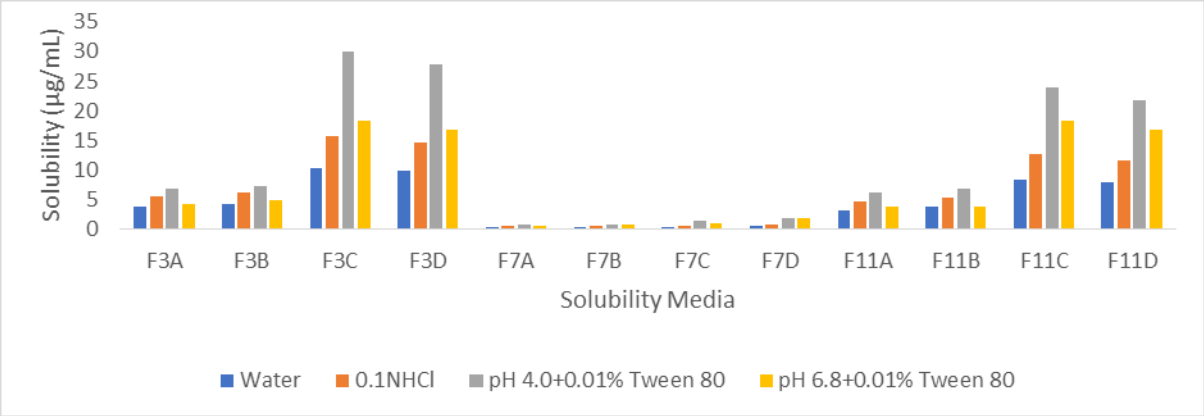


Fig. 8: Saturation solubility of optimized formulations in different media.

Fourier Transforms infrared spectroscopy

The interaction of drug and polymer was investigated by FTIR spectroscopy. Azelnidipine and SDs were analysed. FTIR spectrum of drug showed an N-H stretching absorption peak at 3448.62cm^{-1}, C-H stretching at 2978.62 cm^{-1}. The shift and broadening of peak at N-H stretching region of Azelnidipine with polymer PVPVA, PVP K-30 and Soluplus was observed respectively.

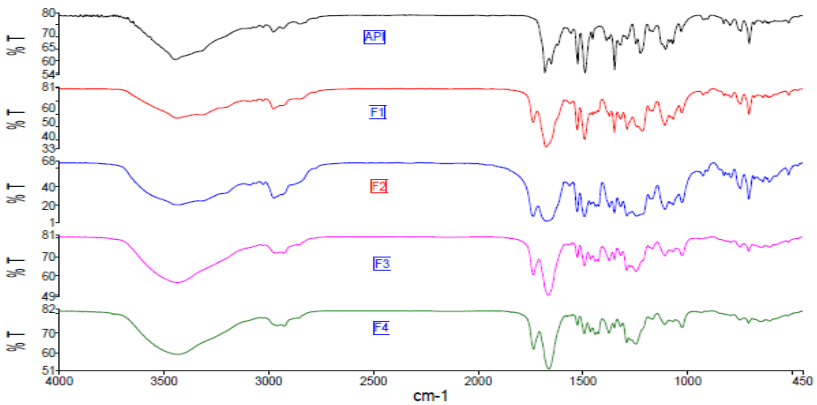


Fig. 9: FTIR spectra of drug with polymer (PVPVA).

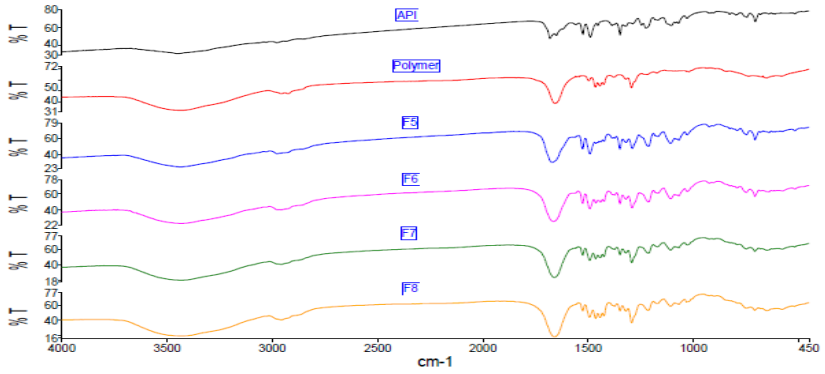


Fig. 10: FTIR spectra of drug with polymer (soluplus).

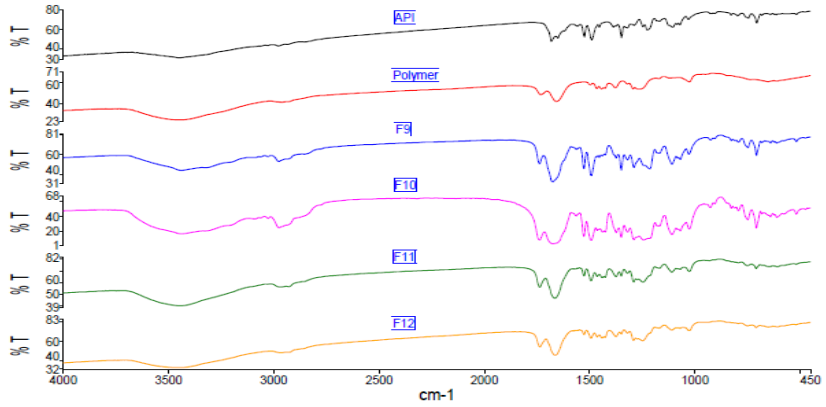


Fig. 11: FT-IR spectra of drug with polymer (POVIDONE K-30).

X-ray powder diffraction

The prepared SDs were investigated using powder X-ray diffraction. With the help of X-ray diffraction pattern the physical form of Pure drug, Physical mixture and prepared Solid dispersion were determined.

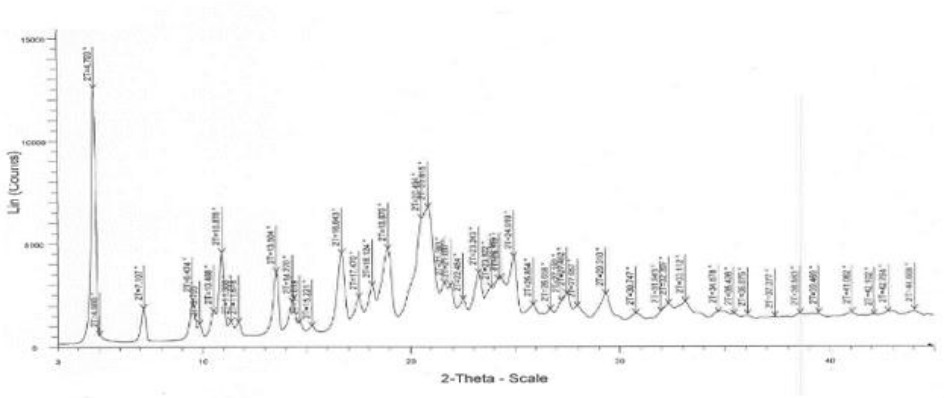


Fig. 12: P-XRD of drug.

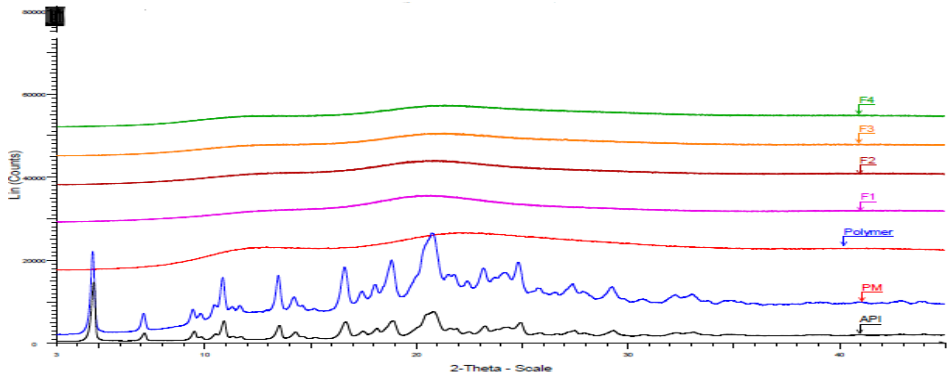


Fig. 13: P-XRD of drug with PVPVA.

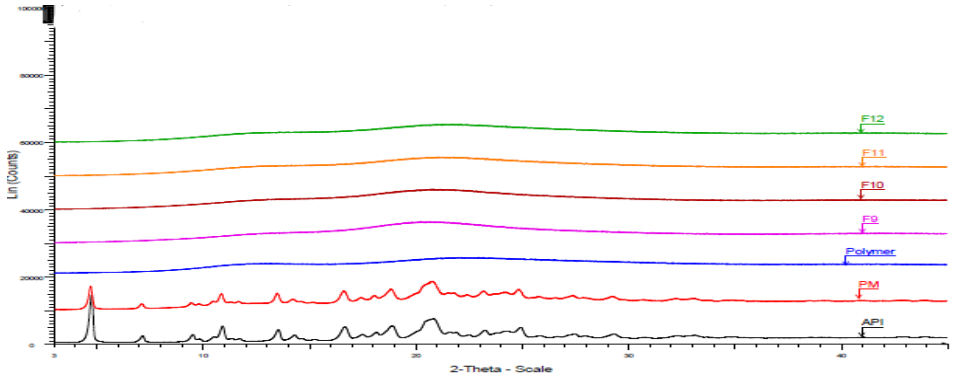


Fig. 14: P-XRD of drug with SOLUPLUS.

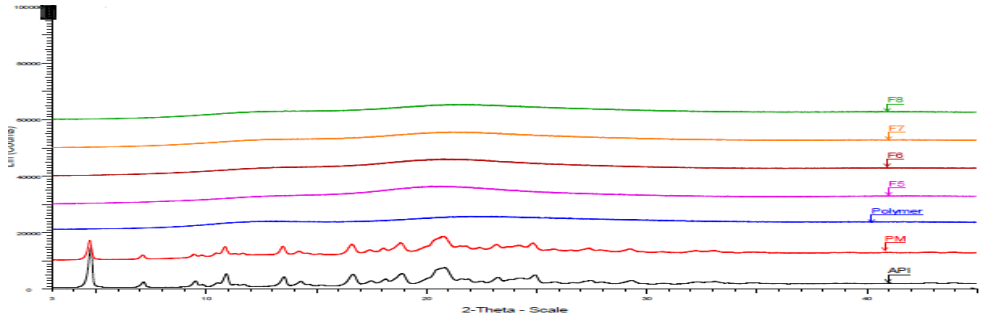


Fig. 15: P-XRD of drug with PVP K-30.

Assay

The drug content in the prepared SDs was found to be in the range of 95-105% which was acceptable.

Stability study

Stability studies were performed to check the physical stability of SDs. SDs of all the polymers in all ratios were subjected to Accelerated stability conditions. Physical stability of SDs was assessed by PXRD. Absence of diffraction peaks indicates that prepared samples were stable up-to one month.

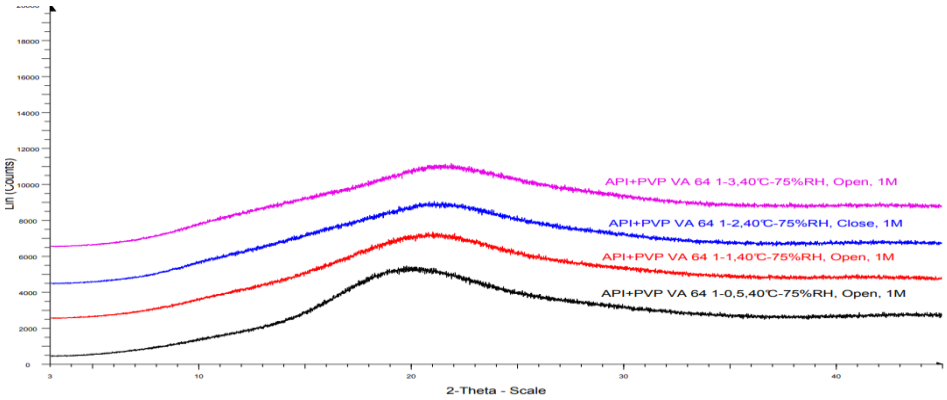


Fig. 16: P-XRD of drug with PVPVA.

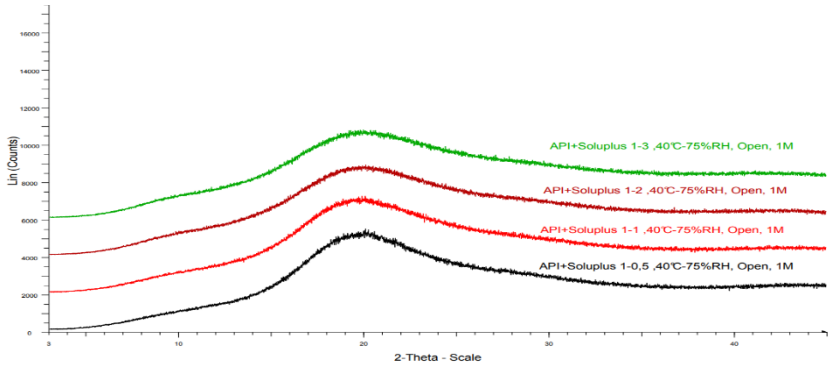


Fig. 17: P-XRD of drug with SOLUPLUS.

In-vitro Dissolution studies

Azelnidipine solid dispersion shows faster drug release than pure drug, **Fig 18** shows the plot of cumulative percent drug released as function of time for different preparations. Cumulative percent drug released after 60 minutes were 94.54, 44.32, 88.64 for F3C, F7C, and F11C receptively. While it was 37.66% in 60 minutes for pure drug Azelnidipine. Formulation F3C, F7C, and F11C were showed highest dissolution for different polymers. *In-vitro* release study revealed that there was a marked increase in the dissolution rate of Azelnidipine from all solid dispersion when compared to pure Azelnidipine itself. From *In-vitro* release profile, it can be seen that formulations F3, F7, F11 (1:2 ratio of drug: polymer) show increase in dissolution rate compared to other formulations.

Table 10: Percentage of drug release in PH4.0+0.01TWEEN 80.

Time in min	Control Tablet % Cumulative drug release ± SD	F3C % Cumulative drug release ± SD	F7C % Cumulative drug release ± SD	F11C % Cumulative drug release ± SD
5	11.33 ± 1.52	31.00 ± 2.64	14.00 ± 3.60	30.33 ± 2.08
10	14.66 ± 1.74	55.00 ± 2.00	18.33 ± 4.16	48.66 ± 2.16
15	17.40 ± 2.31	69.33 ± 2.16	22.67 ± 3.51	57.00 ± 2.00
20	23.59 ± 1.25	79.00 ± 1.00	25.68 ± 3.85	69.67 ± 2.81
30	29.18 ± 2.64	85.67 ± 1.52	33.41 ± 5.50	74.67 ± 4.04
45	31.67 ± 3.76	89.66 ± 1.47	38.64 ± 2.08	83.76 ± 4.16
60	37.66 ± 2.08	94.54 ± 2.81	44.32 ± 3.21	88.67 ± 2.51

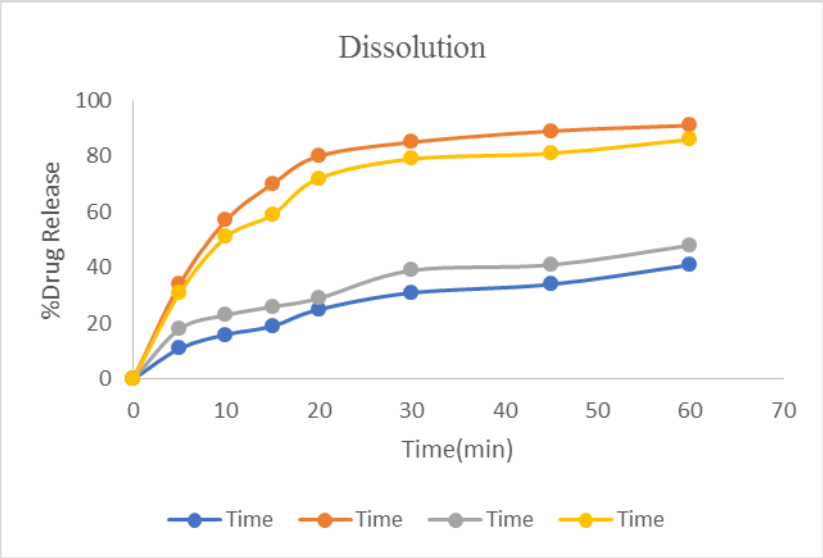


Fig. 18: In vitro dissolution profile in PH4.0+0.01%TWEEN80.

CONCLUSION

The final conclusion from data obtained from the study of formulation and evaluation of solid dispersion of Azelnidipine were prepared by solvent evaporation method with the use of different hydrophilic polymers such as PVPVA, PVP K30, Soluplus and following points can be concluded.

- The dissolution rate of Azelnidipine from solid dispersion was significantly higher for F3C, F7C, and F11C (ratio 1:2) than that of pure drug
- IR studies indicate that no chemical interaction between drug and polymer during preparation of solid dispersion of Azelnidipine
- PXRD studies showed that amorphous powder is obtained from solid dispersion
- Stability studies were performed to assure that the formulations retains its activity, and all formulations were found to be stable

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