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Formulation and Development of Fast Dissolving Film of a Poorly Soluble Drug Azelnidipine with Improved Drug Loading Mixed Hydrotropy Concept and Its Evaluation

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ABSTRACT

During the formulation development of new drug molecules, the major problem is the low aqueous solubility. Azelnidipine is an anti-hypertensive drug categorized in BCS class II drug (low aqueous solubility and high permeability). Azelnidipine is poorly soluble in water, has poor bioavailability and slow onset of action, and therefore cannot be given in emergency conditions. Therefore, the purpose of this research was to provide a fast-dissolving film of Azelnidipine. Fast dissolving film can provide quick onset of action by using the concept of mixed hydrotropy. Solubility of Azelnidipine was determined in an individual solution of nicotinamide, sodium benzoate, urea, ammonium acetate, and sodium acetate at concentrations 10, 20, 30, 40 % w/v solutions using purified water as solvent. The highest solubility was obtained in a 40 % nicotinamide solution. The highest solubility was obtained in the 5:5:10:20 ratio of urea: ammonium acetate: sodium benzoate: nicotinamide. This optimized combination was utilized in the preparation of solid dispersion with Azelnidipine by using distilled water as solvent. Solid dispersion was evaluated for X-ray diffraction, FTIR, and drug content to show no drug-hydrotropes interaction has occurred. This solid dispersion is used in the development of fast dissolving film. Dissolution studies of prepared fast dissolving film were done using USP Type II apparatus. The batch B4 films show 98.25±0.87 % cumulative drug release within 14 min and *in vitro* disintegration time was 34.33±0.471 sec. It was concluded that the concept of mixed hydrotropic solid dispersion is a safe and cost-effective technique for enhancing the bioavailability of poorly water-soluble drugs. The miraculous enhancement in solubility and bioavailability of Azelnidipine by mixed hydrotropy concept.

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INTRODUCTION

Low aqueous solubility is a major problem faced during the formulation development of new drug molecules. The low solubility of a drug in an aqueous medium has poor bioavailability and slow onset of action. Azelnidipine is the antihypertensive drug categorized as a BCS Class II drug (low aqueous solubility and high permeability). Various solubility enhancement techniques help to solve the issue and make the drug bioavailable. A compatible combination of drug and excipients alters the physical characteristics of the drug making them fit the model that alters the solubility of the drug. Due to the poor bioavailability of the drug, the formulator may select an injection route instead of the oral route. For better oral bioavailability drug must be soluble in gastrointestinal fluids so, the drug should be soluble in an aqueous medium also possess permeability properties for good membrane diffusion to reach the bloodstream.

Hydrotropy is the solubilization process where the addition of a large amount of the second solute increases the aqueous solubility of another solute. The other solute may be a poorly water-soluble drug. Hydrotropes may be an anionic, cationic or neutral molecule, and also possess a hydrophilic as well as a hydrophobic group. Finding the right hydrotropic agent is the major task that requires screening of a large number of hydrotropic agents to increase the water solubility of the drug. Enhancement of solubility of drug can easily be achieved by selecting a correct hydrotropic agent. In hydrotropic solubilization, chemical modification of drug, preparation of emulsion system, and use of organic solvents are not required. This technique is a promising approach that has great potential for the poorly soluble drug.

Solubility of Azelnidipine is increased by the mixed hydrotropic solid dispersion method. In mixed hydrotropy, we use two or more hydrotropic agents, which may give an enhancement effect on the solubility of poorly water-soluble drugs. Utilization of this technique in the formulation to increase the solubility of poorly water-soluble drugs helps in reducing the individual concentration of hydrotropic agents, therefore, minimize their side effects.

Fast dissolving drug delivery systems have gained popularity because they are easily dissolving film disintegrate or dissolves rapidly in saliva without the need for water. Drugs dissolve in saliva that can bypass enterohepatic circulation and first-pass metabolism. If the drug is absorbed in the mouth, which improves the bioavailability of the drug that reduces the dosing frequency and dose-related untoward effects.

The main objective of this study was to increase the solubility of poorly water-soluble drug Azelnidipine in water by using hydrotropic agents and their combinations so that oral bioavailability can be increased and to prepare a fast-dissolving film of the same.

MATERIALS AND METHODS

MATERIALS:

Azelnidipine was obtained as a gift sample from Glenmark Ltd, Nashik. HPMC E5 purchased from Yarrow Chem products and all other Chemicals purchased from Modern Science, Nashik.

METHODS

Determination of Solubility: Saturation solubility of Azelnidipine was determined in Distilled water and Phosphate buffer pH 6.8. An excess quantity of drug Azelnidipine was added in 10 ml of glass vials containing 5 ml of distilled water. The resultant mixture was shaken vigorously for 10 min and stirred on a magnetic stirrer plate at RT 12 h. The solution was allowed to equilibrate for 24 h. Further, samples were withdrawn and centrifuged at 10,000 RPM for 15 min. The supernatant was filtered through filter paper. The filtrate was diluted up to 10 ml with distilled water and analyzed using UV Visible spectrophotometer (Shimadzu UV2600) at 270 nm and solubility was calculated.

Azelnidipine-Hydrotropic Agent Interference study:

Ultraviolet spectrophotometric Study: For determination of interference of hydrotropic agent in the UV spectrophotometric estimation of Azelnidipine, the absorbance of the standard solution of Azelnidipine was determined in distilled water alone. For the interference study absorbance was determined using a standard solution of Azelnidipine in the presence of hydrotropic solution for the formulation purpose. The absorbance was recorded against the respective reagent blank at the appropriate wavelength. Absorbance was measured using a UV visible spectrophotometer (Shimadzu UV 2600).

Fourier Transform Infrared Spectrophotometry of drug and with Polymer: The drug was subjected to FTIR studies (Shimadzu 8400S) for characterization. IR technique is one of the most powerful techniques of chemical identification. Drug and Physical mixture with polymer (HPMC E5) and other excipients were mixed with potassium bromide in 1:99

proportion and spectrum was obtained in a range of 400-4000cm^{-1}. Potassium bromide was used as a blank while running spectrum.

Equilibrium solubility studies in different hydrotropic agents: 10, 20, 30, 40 % w/v solution of each hydrotropic agent such as Urea (U), Nicotinamide(N), Sodium Benzoate(SB), Ammonium Acetate(AA), Sodium Acetate(SA) were prepared in water. For determination of solubility accurately measured 5 ml of an above particular solution of hydrotropic agents was taken in 10 ml vial and an excess amount of drug Azelnidipine was added and shaken until a saturated solution was formed. Each vial was shaken vigorously for 10 min and stirred on a magnetic stirrer plate at RT 12 h, hence equilibrium solubility can be achieved. This solution was allowed to equilibrate for 24 h. The solution was further centrifuged at 10,000 rpm for 15 min and further filtered through filter paper. The filtrate was diluted up to 10 ml using distilled water and analyzed using UV Visible Spectrophotometer at 270 nm.

Enhancement solubility ratio was calculated by the following formula:

$$Enhnacement\ ratio = \frac{solubility\ of\ drug\ in\ hydrotropic\ solution}{solubility\ of\ drug\ in\ water}$$

Equilibrium solubility studies in mixed hydrotropic blends: 2-3 hydrotropic agents were mixed in 1:1 ratio and dissolved in water to get a clear solution, excess amount of drug azelnidipine was added in hydrotropic solution and vigorously shaken for 10 min to get a saturated solution. This solution was stirred on a magnetic stirrer plate at RT 12 h, hence equilibrium solubility can achieve. This solution stood for 24 h. The solution was further centrifuged at 10,000 rpm for 15 min and further filtered through filter paper. The filtrate was diluted up to 10 ml using distilled water and analyzed using UV Visible Spectrophotometer at 270 nm.

Formulation of hydrotropic solid dispersion of Azelnidipine: For the preparation of hydrotropic solid dispersion, accurately weighed 0.5 gm Urea, 0.5 gm Ammonium acetate, 1 gm Sodium Benzoate, 2 gm Nicotinamide, and 1 gm of the drug (Azelnidipine) so that total weight of mixture was 5 gm (drug: hydrotropic agent ratio was 1:4) were taken in a 100 ml beaker and properly mixed. Further, a minimum quantity of warm distilled water sufficient to dissolve the above hydrotropic blend was added. A minimum amount of water approx. 5 ml

is used lesser will be the time required to evaporate and chemical stability of drug may not be affected adversely during removal of water.

Dissolution of the hydrotropic mixture facilitated by a magnetic stirrer. After complete dissolution of the hydrotropic blend, 1 gm of Azelnidipine was dissolved in the above solution, and the temperature was maintained at 45-50^0 C to facilitate the water evaporation. After complete evaporation of water indicates viscous solution and this indicates the formation of wet solid dispersion. The wet solid dispersion was spread on the Petri plate and this Petri plate was kept in a hot-air oven maintained at 50^{0}C±2^0 C so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss due to evaporation could be obtained. After complete drying, hydrotropic solid dispersion was crushed using a glass mortar pestle and passed through sieve 60, and was stored in an airtight glass bottle.

Evaluation of hydrotropic solid dispersion of Azelnidipine:

Fourier Transform Infrared Spectrophotometry Study: Fourier Transform Infrared spectrum (FTIR) of Azelnidipine and its hydrotropic solid dispersion was recorded over a range 4000-400 cm^{-1} to study principle peaks using FTIR spectrophotometer (Shimadzu 8400s).

X-ray powder diffraction analysis of Azelnidipine and its solid dispersion: The X-ray powder diffraction spectra of Azelnidipine was recorded using an X-ray diffractometer with Cu as target filter having a voltage/current 40kV/30mA at a scan 4^0/min. The sample was analyzed at a 2Ɵ angle range of 10-80^0. Step time was 0.20 s and time acquisition was 1 h.

Drug content/ Assay: Solid dispersion containing 100 mg of drug was dissolved in 100 ml of Phosphate Buffer pH 6.8 to achieve a solution that has a concentration of 1000 µg/ml. 10 ml from this stock solution was taken and diluted to 100 ml using Phosphate buffer pH 6.8 to get 100 µg/ml. further, 10 µg/ml solution was prepared by taking 1 ml from the stock solution and diluted up to 10 ml. Absorbance was measured using UV Visible Spectrophotometer.

Formulation Fast Dissolving Film:

Calculation of drug quantity for one film:

Dose of Azelnidipine: 8 mg

Outer diameter of Petri plate: 8.5 cm

Inner diameter of Petri plate: 8.3 cm

Inner radius of Petri plate: 4.15 cm

Area of petriplate: Area of circle= πr^2= 3.13*$(4.15)^2$

= 54.0708 cm^2

10 ml of polymeric solution contains 500 mg of drug.

Therefore 2 ml of polymeric solution contains 100 mg of drug.

This 2 ml polymeric solution spread over 54.0708 cm^2 area of petri plate.

Therefore, 100 mg of drug present in 54.0708 cm^2 area of petri plate.

So, 8mg of drug present in 54.0708/100 mg* 8mg= 4.3256 cm^2

Area of circle= Area of square= a^2 (a= length of side of square)

$4.3256cm^2 = a^2$

$a = \sqrt{4.3256cm^2}$

a= 2.079cm

By this calculation 8 mg dose of drug present in 2.0 * 2.0 cm^2area of film.

Formulation method: (Solvent casting Method):

A specified amount of polymer was weighed and dissolved in 5 ml of distilled water. The solution was kept 5-6 h for swelling of the polymer. Further required quantity of Glycerin was added in 5 ml distilled water. In this solution, a specified amount of solid dispersion was dissolved. After complete dissolution specified amount of citric acid, tween80, and sucralose were added. 2 ml of polymeric solution was cast in a Petri plate. The film was dried in an oven at 40^0 C. The dried film was separated from the Petri plate and cut 2 cm^2. Dried film stored in a desiccator. Table No. 1 outlines the composition of various Fast Dissolving Film formulations.

Table No. 1: Composition of mouth dissolving film of Azelnidipine

Ingredients	Category	B-I	B-II	B-III	B-IV	B-V
Drug equivalent to 500mg in Solid dispersion						
HPMC E-5	Polymer	10%	12%	15%	17%	20%
Glycerin	Plasticizer	5%	7%	10%	12%	15%
Citric acid	Saliva stimulating agent	3%	3%	3%	3%	3%
Tween 80	Surfactant	0.3%	0.3%	0.3%	0.3%	0.3%
Sucralose	Flavoring agent	3%	3%	3%	3%	3%
Distilled water	Solvent	10ml	10ml	10ml	10ml	10ml

Evaluation of mouth dissolving Film:

Physical appearance: The film of each formulation was randomly selected and inspected visually as well as by feel or touch for texture.

Thickness: Three films of each formulation were taken and the film thickness was measured by using a micrometer screw gauge. Mean thickness and standard deviation were calculated.

Weight variation: For the weight variation test, 3 films of every formulation were randomly selected and weighed individually to determine the average weight and standard deviation was also calculated.

Percent elongation: When stress is applied, a strip sample stretches referred to as a strain. Strain is the deformation of a strip divided by the original dimension of the sample.

$$\%\ Elongtion = \frac{Increased\ in\ length\ of\ strip}{Initial\ length\ of\ strip} \times 100$$

Moisture content (by weighing method): For the moisture content test, three films of each formulation were taken. Initially, these selected films were weighed accurately and kept in a hot-air oven at temperatures of 100-120^{0}C until they attain constant weight. Finally, the weight of the final sample was taken and percent moisture loss and standard deviation were calculated.

$$\%\ moisture\ content = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

Swelling property: Three films of each formulation batch were selected. Initially, these selected films weighed and it was subjected to immersion in simulated physiological fluid for a predetermined time. After that, the sample was taken out, wiped off to remove the excess water on the surface, and weighed. Percent swelling and standard deviation were calculated.

$$Swelling\ index = \frac{final\ weight - initial\ weight}{initial\ weight} \times 100$$

Drug content uniformity: content uniformity is determined by estimating the API content in an individual strip. Three films from each formulation were taken and individually dissolved in 10 ml of phosphate buffer pH 6.8 to give 100 µg/ml solution. Further from 100 µg/ml, 1ml solution was withdrawn and diluted to 10 ml by phosphate buffer pH 6.8 and absorbance of each solution was recorded at 270 nm (λ_{max} of Azelnidipine) using placebo film (film without drug) solution as blank. The percent drug content was determined. The mean of the percentage drug content and standard deviation were calculated.

Disintegration time: Three films from each formulation were taken and performed disintegration test by placing the film in the cylindrical tube of disintegration apparatus containing phosphate buffer pH 6.8. The time at which the film disintegrated is noted. Mean and standard deviation was calculated.

Folding endurance: Three films of each formulation were selected and folding endurance was determined repeatedly folding a small strip of film at the same place till it breaks. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of three reading and standard deviation were calculated.

Surface pH: The film was taken and placed in a Petri plate containing 5 ml of distilled water. After wetting the film, the surface pH of the film was checked by using a pH electrode.

***In-vitro*-Drug Release:** Dissolution testing performed in phosphate buffer pH 6.8 (dissolution media) using the standard basket apparatus 37±0.5^{0}C and 50 rpm. A single film was placed in 900 ml dissolution media. 5 ml of sample were withdrawn at a suitable time interval and replaced with a fresh dissolution medium. The sample was determined using UV Visible Spectrophotometer at 270 nm and cumulative drug release was calculated.

Cumulative percent drug release was calculated using an equation obtained from the standard curve.

RESULT AND DISCUSSION:

Determination of Solubility: The solubility of Azelnidipine as observed in distilled water and Phosphate buffer pH 6.8 is presented in Table No. 2.

Table No. 2: Solubility of Azelnidipine

Solvent	Solubility (mg/ml)
Distilled water	0.0130±0.014
Phosphate buffer pH 6.8	0.0195±0.026

Azelnidipine hydrotropic agent interference study

Ultraviolet Spectrophotometric Study: The UV absorbance of spectra of Azelnidipine was determined in distilled water and the presence of hydrotropic agent solutions shown in Table No. 3. The result indicates no change in the wavelength of maximum absorbance of Azelnidipine in any of the solutions. Hence, it was concluded there was no drug-hydrotropic agent interference.

Table No. 3: Drug- Hydrotropic agent interference study by UV method

Drug	Solvent system	Drug concentration(µg/ml)	Hydrotropic agent concentration (µg/ml)	Wavelength (nm)
Azelnidipine	Distilled water	20	1000	270
Azelnidipine	Distilled water+ Nicotinamide	20	1000	269
Azelnidipine	Distilled water+ Sodium Benzoate	20	1000	272
Azelnidipine	Distilled water+ Urea	20	1000	271
Azelnidipine	Distilled water+ Ammonium Acetate	20	1000	269

Fourier Transform Infrared study of Drug and Drug+Polymer: FTIR was employed to characterize the possible interaction of Azelnidipine and Polymer and other excipients. FTIR spectrum of Azelnidipine shows characteristics peaks at 3444.86 of N-H stretch, 3034.39 of Aro C-H stretch, 2984.59 of Ali C-H stretch, 1681.93 of C=O stretch, 1489.93 of Aro C=C stretch, 1595.13 of Aro (N-O) asymmetric stretch, 1417.68 of Ali C-H bend, 1346.32 of Aro(N-H) symmetric stretch, 1276.88 of C-N stretch. All peaks are within the reported range indicating the purity of Azelnidipine. All the major peaks of Azelnidipine can also be seen in the physical mixture of Azelnidipine + HPMC E5 and other excipients.

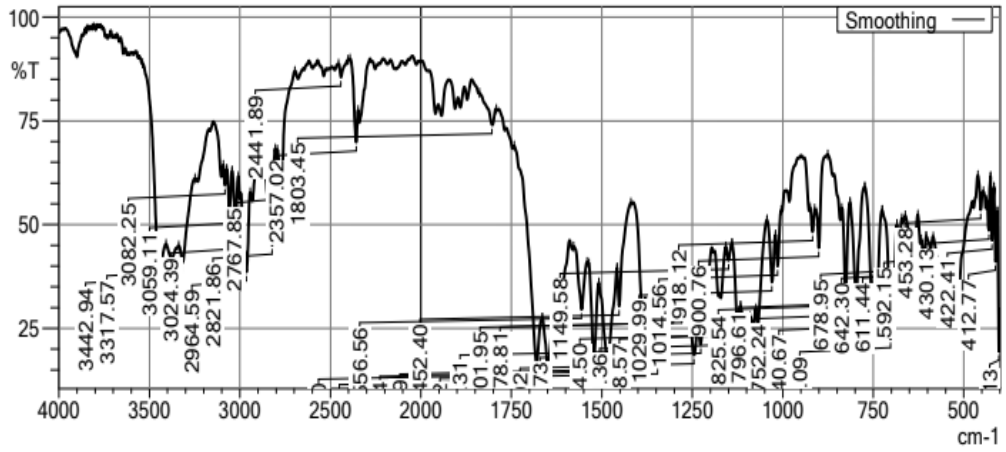

Figure No. 1: Fourier Transform Spectra of Azelnidipine

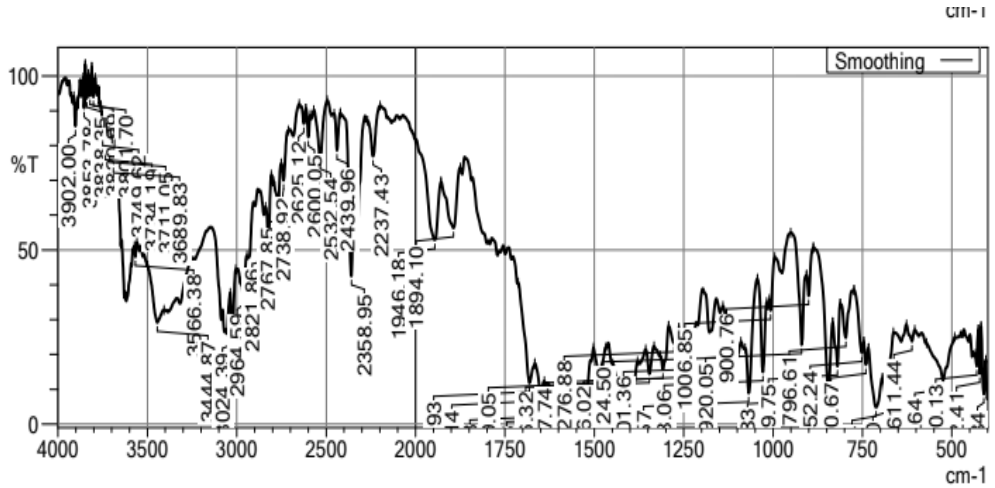

Figure No. 2: Fourier Transform Spectra of physical mixture of Azelnidipine+ HPMC E5+Citric Acid+Sucralose

Equilibrium solubility studies in different hydrotropic agents: Solubility of Azelnidipine in different hydrotropic solutions was evaluated as shown in Table No. 4. All hydrotropes can

enhance the solubility of Azelnidipine. The highest solubility enhancement ratio was obtained in a 40 % Nicotinamide solution. Further, to decrease the concentration of sodium benzoate, ammonium acetate, urea, sodium acetate.

Table No. 4: Equilibrium solubility of Azelnidipine in different hydrotropic agent

Hydrotropic agents	**Concentration (w/v) / SER**							
	10%	**SER**	**20%**	**SER**	**30%**	**SER**	**40%**	**SER**
Nicotinamide	0.752	**5.784**	0.766	**5.892**	0.823	**6.330**	1.480	**11.380**
Sodium Benzoate	0.651	**5.007**	0.668	**5.138**	0.685	**5.269**	0.741	**5.492**
Urea	0.679	**5.223**	0.269	**2.053**	0.121	**0.930**	0.089	**0.684**
Sodium Acetate	0.041	**0.315**	0.0374	**0.287**	0.0746	**0.5736**	0.0693	**0.5330**
Ammonium Acetate	0.610	**4.692**	0.614	**4.723**	0.663	**5.100**	0.620	**5.769**

Saturated solubility in mixed hydrotropic agent: The different combinations of hydrotropic agents in the different ratios were tried to determine enhancement in solubility. All blends were also found to increase the solubility of Azelnidipine as shown in Table No.5.

Table No. 5: Equilibrium solubility of Azelnidipine in Mixed hydrotropic blends

Blend code	**Hydrotropic combination**	**Total concentration of hydrotropic agents**	**Individual concentration**	**Conc. (mg/ml)**	**SER**
I	U+A+B	40%	13.33+13.33+13.33	5.689	43.76
II	A+B+N	40%	13.33+13.33+13.33	6.983	53.71
III	U+N+B	40%	13.33+13.33+13.33	6.618	50.90
IV	U+A+B+N	40%	10+10+10+10	66.763	513.02
V	**U+A+B+N**	**40%**	**5+5+10+20**	**84.689**	**651.45**
VI	U+A+B+N	40%	5+10+5+20	70.380	541.38

U: Urea, A: Ammonium acetate, B: sodium benzoate, N: Nicotinamide

Evaluation of hydrotropic solid dispersion of Azelnidipine:

X-ray powder diffraction analysis of Azelnidipine: The XRPD pattern of Azelnidipine and its solid dispersion is shown in Figures No. 3 and 4. XRPD pattern of Azelnidipine shown a sharp, intense peak which confirms the crystalline nature of Azelnidipine. All major peaks of pure drug can be seen in solid dispersion, but the intensity of peak decrease. This indicates the formation of an amorphous form of drug that increases solubility. This XRPD result presumed that formation of hydrotropic solid dispersion does not cause any physical and chemical interaction between Azelnidipine and hydrotropic agents at the molecular level.

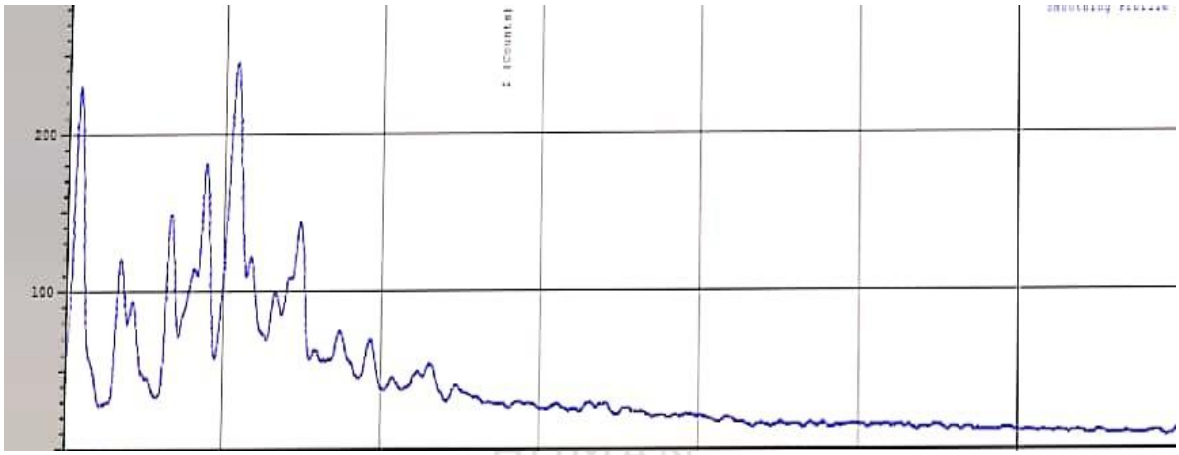

Figure No. 3: X-ray powder diffraction of pure drug Azelnidipine

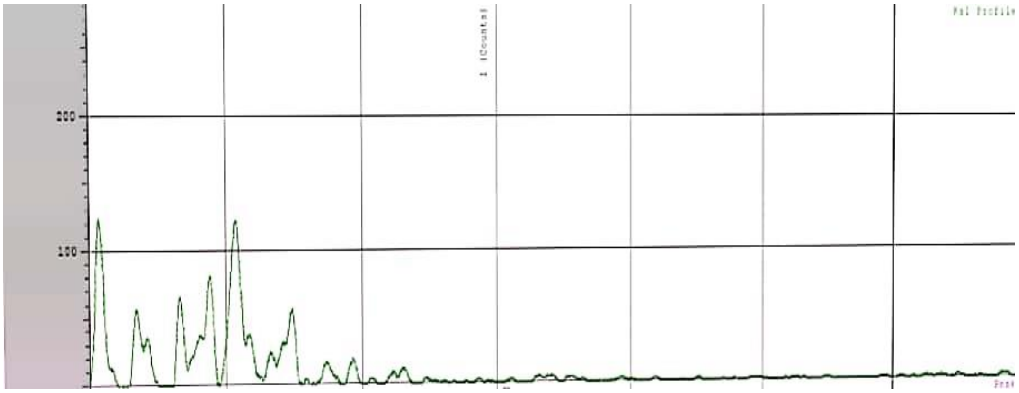

Figure No. 4: X-ray powder diffraction of hydrotropic solid dispersion of Azelnidipine

FTIR Spectroscopy of hydrotropic solid dispersion: FTIR study was performed to characterize the possible interaction of Azelnidipine and the hydrotropes. FTIR spectrum and characteristic peak as shown in Figure No. 5. All the major peaks of Azelnidipine can also be seen in the hydrotropic solid dispersion. Hence, there was no drug-excipients interaction.

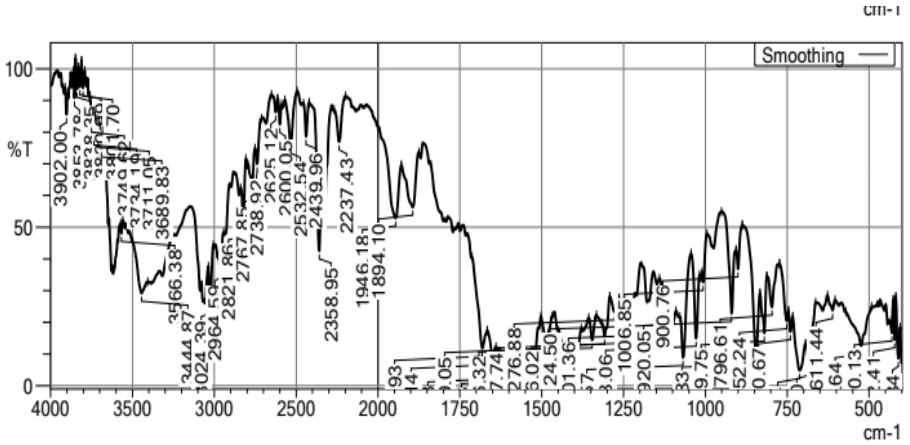

Figure No. 5: FTIR spectra of hydrotropic solid dispersion of Azelnidipine

Drug content Assay: Drug content of hydrotropic solid dispersion was found to be as shown in Table No. 6.

Table No. 6: Drug content of solid dispersion

Sample	**% Dug content (Practically observed)**	**% Drug content (Standard limit)**
Solid dispersion	97.86±2.106	85-115%

Formulation of fast dissolving film of hydrotropic solid dispersion of Azelnidipine: After the preparation of hydrotropic solid dispersion of Azelnidipine and its characterization, solid dispersion was subjected for the formulation of fast dissolving film. Fast dissolving film of hydrotropic solid dispersion of Azelnidipine was successfully formulated and evaluated for various parameters.

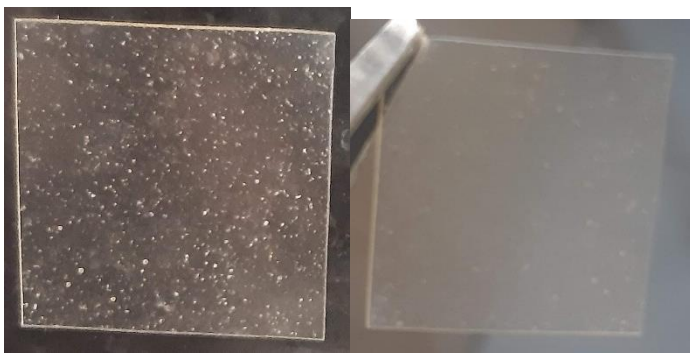

Figure No. 6: Fast dissolving film of batch 4

Evaluation of fast dissolving film: The developed fast dissolving film formulation was then subjected to various post-compression parameters and the results are depicted as shown in Table No.7.

All the formulated films were found to be of uniform weight with acceptable weight variation and thickness of tablets.

Folding endurance of optimized and validated fast dissolving film was found to be 97.66±1.24.

The moisture content of the film was found to be 1.08±0.289. The amount of moisture in the film could be crucial as it affects the mechanical strength, adhesive properties, and friability of the film.

Percent elongation of optimized and validated films was found to be 5±0.1. Results suggested the increased mechanical strength of fast dissolving film.

The percent swelling index of the optimized film was found to be 109±6.73. Higher percentage swelling of films suggested its suitability for rapid release of Azelnidipine due to increased absorption of phosphate buffer pH 6.8.

In-vitro disintegration time optimized and the validated film was found to be 34.33±0.471 s. It revealed the fast disintegration of films and it facilitated the faster dissolution of Azelnidipine.

The surface pH of the optimized and validated film was found to be 6.46±0.047. It indicates normal pH which revealed no chances of irritation to the oral mucosa after its administration.

Percent drug content of the optimized and validated film was found to be 96.87±0.51 %. The result indicates the good uniformity of content in the film without any significant variation.

Table No. 7: Results of formulated fast dissolving film of Azelnidipine(Mean±SD, n=3)

Batch No.	Weight variation	Thickness	Folding endurance	Moisture content
B1	153±1.41	0.232±0.014	67±5.09	1.09±0.304
B2	152.2±1.66	0.247.33±0.011	79.66±0.4713	1.09±0.304
B3	153.2±1.09	0.248±0.014	92±2.158	1.29±0.374
B4	**154±1.00**	**0.249.66±0.009**	**97.66±1.24**	**1.08±0.289**
B5	153.5±1.356	0.250.33±0.014	95±0.81	2.17±1.85

Percent elongation	Swelling property	Disintegration time	Surface pH	Drug content
3.33±2.355	55.55±7.85	54.33±0.4711	6.36±0.124	94.52±0.54
6.66±2.355	62.95±5.382	51±0.8160	6.36±0.124	94.11±0.74
3.33±2.35	45±8.28	40.33±0.4711	6.4±0.081	93.06±0.81
5±0.1	**109±6.73**	**34.33±0.471**	**6.46±0.047**	**96.87±0.51**
3.33±2.35	41.06±2.52	41±0.082	6.46±0.047	92.00±0.89

***In vitro* drug release:** *In-vitro* drug release study of batches B1 to B5 was conducted. B4 and B5 batch show 98.25±0.87 and 93.36± 0.90 drug release respectively. As B4 shows maximum drug release at 14 min. hence it was considered to be an optimized formulation batch.

Table No. 8: Percent cumulative drug release from the different formulation

Time (Min)	% Cumulative Drug Release				
	B1	**B2**	**B3**	**B4**	**B5**
0	0	0	0	**0**	0
2	16.12±0.13	13.19±0.51	15.38±0.38	**19.14±0.28**	12.06±0.86
4	38.45±1.31	32.53±0.42	34.70±1.02	**41.08±0.66**	29.07±1.34
6	51.89±1.31	49.43±0.81	46.24±0.55	**52.64±0.50**	43.49±0.90
8	79.03±0.73	64.84±0.55	63.76±0.50	**80.03±0.34**	58.46±0.40
10	81.20±0.50	71.41±0.83	72.20±0.48	**86.50±0.86**	77.81±0.46
12	87.20±0.51	81.42±0.73	87.00±0.40	**94.72±0.61**	84.55±0.65
14	90.18±0.13	84.81±0.73	90.3±0.13	**98.25±0.87**	93.36±0.90

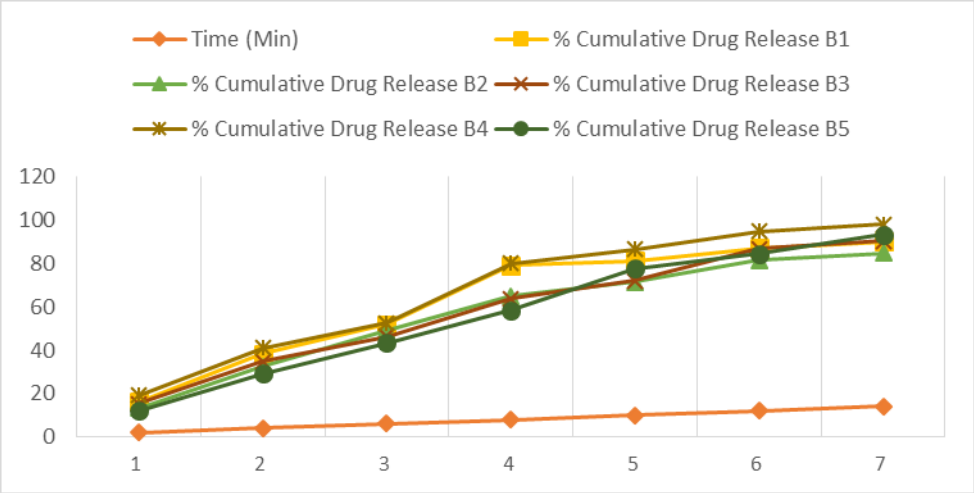

Figure No. 7: Cumulative drug release

Kinetic data treatment:

Table No. 9: Kinetic Data Treatment

Formulation code	Zero-order	First-order	Higuchi model	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
B4	0.98	0.9426	0.9572	0.9673

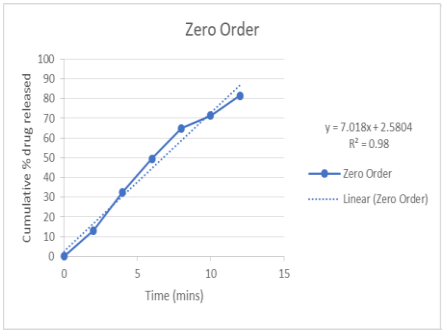

Figure No. 8: Zero order Kinetic representation of optimized batch B4

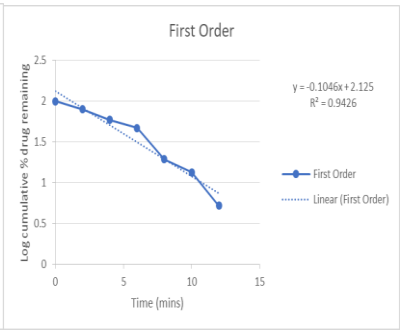

Figure No. 9: First order Kinetic representation of optimized batch B4

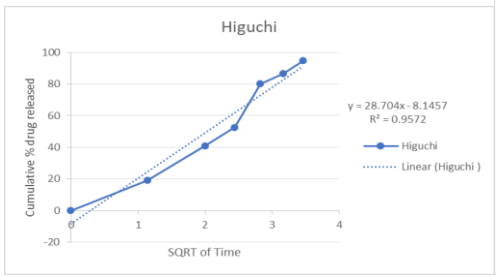

Figure No. 10: Higuchi Kinetic representation of optimized batch B4

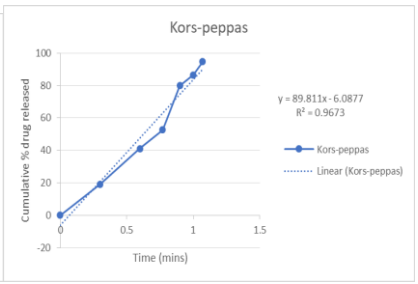

Figure No. 11: KorsmeyerPeppas Kinetic representation of optimized batch B4

The optimized formulation B4 batch follows the Zero-order and Korsmeyer Peppas equation which follows the super case II transport drug release mechanism.

CONCLUSION:

From all observation and results obtained it can be concluded that all the prepared formulations show satisfied organoleptic properties.

Azelnidipine as initially characterized for its preliminary studies such as organoleptic properties, melting point, solubility, UV Visible Spectroscopy, FTIR studies, and also drug-excipient compatibility was confirmed by FTIR.

As no uncountable peak was observed in FTIR analysis, so it was confirmed the purity of the developed formulation and no interaction of excipient with the drug.

For the selection of a hydrotropic agent for increasing the solubility of Azelnidipine, solubility studies were conducted at various hydrotropic agents and hydrotropic blend. The solubility of Azelnidipine was increased in each hydrotropic agent. A maximum solubility enhancement ratio was observed in a hydrotropic blend containing U+A+B+N (5:5:10:20).

Hydrotropic solid dispersion of Azelnidipine was characterized by XRPD analysis, FTIR analysis, and drug content analysis. FTIR and XRD analysis confirmed no interaction between drug and excipients.

The five formulations were prepared using hydrotropic solid dispersion and were subjected to physical parameters like organoleptic properties, weight variation, thickness, folding endurance, percent elongation, moisture content, swelling property, surface pH, content uniformity, disintegration test, and dissolution study.

Films show satisfactory organoleptic properties. Films also show uniform properties like thickness, uniformity in weight, percent moisture loss, percent elongation, swelling index as well as surface pH and disintegration time.

The *in vitro* dissolution study indicates that all formulation shows fast drug release in 14 min. Out of 5 Batch which B4 shows good release in 14 min. and its percentage drug release was found as **98.25±0.87** within 14 min. It follows the zero-order as well as Korsmeyer Peppas kinetic model with super case II transport. Hence, with the drug delivery system, the bioavailability of Azelnidipine could be increased with a reduction in the dosing frequency. Thus, increasing efficacy, compliance, and better clinical usefulness.

The concentration of polymer (HPMC E5) and plasticizer (Glycerine) is increased from Batch B1 to B5, so the swelling index increases as the concentration of polymer increases.

Hence, the maximum swelling index indicates the rapid release of the drug due to the higher absorption of saliva. Drug release is maximum in B4 and B5 batches but from both batches, B4 has more drug release as compared to B5. In the B5 batch, higher the concentration of polymer (HPMC E5), film produced from a highly viscous solution which shows the sticky film and based on physical properties B4 batch shows satisfactory effects. Hence B4 is an optimized batch.

Hence from all results, it was observed that all formulations are prepared well. So, it can help to bypass the hepatic first-pass metabolism and improved the bioavailability of Azelnidipine.

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