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FORMULATION AND EVALUVATION OF AMLODIPINE BESYLATE SOLID DISPERSION

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ABSTRACT

Amlodipine besylate is a drug that is used for treating high blood pressure, certain types of angina and coronary heart failure. One of the major problem with this drug is its low solubility in biological fluids, which result into poor bioavailability after oral administration. The purpose of the presenting investigation was to increase the solubility and dissolution rate of Amlodipine besylate by the preparation of its solid dispersion with polyethylene glycol 6000 and hydroxyl Propyl methyl cellulose (HPMC) by using solvent evaporation method and physical mixture method in the 1:1, 1:2 and 1:3 ratio of the drug and carrier respectively. The prepared solid dispersion were characterized by FT-IR Spectroscopy no interaction of drug with carriers. The solid dispersion were evaluated for percentage practical yield, drug content and invitro dissolution study. The formulation code F3 of Amlodipine besylate solid dispersion prepared by solvent evaporation method using polyethylene glycol 6000 at 1:3 ratio drug and carrier is highest improvement in the dissolution profile, at the end of 60 minutes, formulation F3 gave the highest drug release that is 89.50%.

KEYWORDS: Solid dispersion, Amlodipine besylate, Hydroxypropyl methy cellulose, polyethylene glycol 6000, acetone and hydrochloric acid.

INTRODUCTION

Advances in combinatorial chemistry and high throughput screening have led to the development of large number of molecules with requisite pharmacological activity. However these immobilized receptor techniques lead to the selection of compounds with undesirable physicochemical attributes like high lipophilicity, poor aqueous solubility and high

molecular. The drug solubility enhancement, bioavailability at the target site of therapeutic action are of the numerous challenges in pharmaceutical formulation. Poor water solubility tops the list of critical compound properties among the five key physicochemical parameters in early compound screening viz. dissociation. The progress in treatment of diseases has been evident with the upsurge in development of new drugs. Approximately more than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. The enhancement of oral bioavailability for poorly water soluble drugs remains one of the most challenging aspects of drug development solid dispersion refers to a group of solid products consisting of atleast two different components, generally a hydrophilic matrix and ahydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles .Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Solid dispersions should preferably be designated according to their molecular arrangement. Although a great research interest in solid dispersion in the past fourdecades, the commercial utilization is very limited. Problems of solid dispersion involve The physical and chemical stability of drugs and vehicles, Method of preparation, Reproducibility of Its, physicochemical properties Formulation of solid dispersion into dosage forms, Scale-up of manufacturing processes.

MATERIAL AND METHODS

MATERIALS

Amilodipine besylate and polyethylene glycol 6000 were provided by nickon pvt.ltd,Villupuram, Hydroxy Propyl methyl cellulose and acetone were obtained from Merck Specialties' pvt.ltd.Mumbai, Hydrochloric acid were obtained from S.D. Fine Chem.Ltd.Mumbai

METHODS

preparation of standard stock solution

Standard stock solution of Amlodipine pure drug was prepared by accurately weighing about 10mg of each drug in 10ml volumetric flask. The drugs were dissolved with 5ml of methanol and sonicated to dissolve it completely and made up to the mark with the same solvent; results1000µg/ml solution was obtained. From this 1ml was taken and diluted to10ml to get a concentration of 100µg/ml. from 100µg/ml solution 2ml was taken and made up to 20ml to

get a final working stock solution of10µg/ml required concentrations or dilutions needed for UV and visible estimation was prepared from 10µg/ml solution.

Preparation of calibration curve

From the prepared standard stock solution, a series of calibration standards were prepared by selected dilutions. From the sock solution, 1µg/ml, 2, 4, 6, 8, 10µg/ml was prepared. The absorbance of the prepared solutions was measured at 239nm against a regent blank. At each concentration triplet readings were measured and mean value was used for the Construction of calibration curve. Calibration curve was constructed by taking concentration of the prepared solution on x-axis and corresponding absorbance on y-axis.

Formulation of solid dispersions

Solid dispersion of Amlodipine Besylate was prepared by solvent evaporation method and physical method

S.no	Formulation code	Drug	Carrier	Drug: Carrier	Method
1.	F1	Amlodipine Besylate	PEG 6000	1:1	Solvent Evaporation Method
2.	F2	Amlodipine Besylate	PEG 6000	1:2	
3.	F3	Amlodipine Besylate	PEG 6000	1:3	
4.	F4	Amlodipine Besylate	HPMC	1:1	Solvent Evaporation Method
5.	F5	Amlodipine Besylate	HPMC	1:2	
6.	F6	Amlodipine Besylate	HPMC	1:3	
7.	F7	Amlodipine Besylate	PEG 6000	1:1	Physical Mixture
8.	F8	Amlodipine Besylate	PEG 6000	1:2	
9.	F9	Amlodipine Besylate	PEG 6000	1:3	
10.	F10	Amlodipine Besylate	HPMC	1:1	Physical Mixture
11.	F11	Amlodipine Besylate	HPMC	1:2	
12.	F12	Amlodipine Besylate	HPMC	1:3	

Solvent evaporation method

In solvent evaporation method, the drug and carrier Poly Ethylene Glycol 6000 (PEG 6000) and Hydroxy Propyl Methyl Cellulose (HPMC)were mixed in 1:1, 1:2 and 1:3 ratios in acetone separately. Solvent was removed by evaporation under reduced pressure. The mass was sieved and passed through sieve # 100

Preparation of physical mixtures

For the sake of comparison, physical mixtures having the same composition of the solid dispersions were prepared by simply triturating the drugs and the polymers in a porcelain mortar. The mixtures were then sieved (420 µm) and stored in amber-glass capped containers.

Evaluation of prepared solid dispersion determination of percent practical yield (py):

To determine the efficiency of any method of production, Percentage practical yield was calculated. In this method pre weighed dispersions were collected to determine practical yield (PY) from the following equation.

Percent Practical Yield (PY) = (Weight of Practical solid dispersions × 100)/ Theoretical weight (Amlodipine Besylate + Polymer

Estimation of drug content

The formulation equivalent to 500 mg of drug was weighed and diluted suitably with distilled water. The absorbance was measured at239 nm for the amount of drug in each formulation was calculated. The percent drug content is calculated using the following formula.

% Drug content = Actual drug content × 100/Theoretical drug content

Compatibility studies by ftir between drug and thepolymer

The Drug Polymer Interaction was studied using the Fourier Transform Infra -Red Spectroscopy (FTIR). One to Two mg of pure drug was mixed with the weighed polymer samples (PEG 6000 / HPMC) then this is mixed properly with the potassium bromide to uniform mixture .From this powder a small quantity as compressed into a thin semitransparentpellet by applying pressure (Pressed Pellet Technique). The IR Spectrum of the pellet was recorded taking air as the reference and compared to study the interference.

Determination of dissolution

Invitro release profiles for each batch was performed using USP dissolution apparatus. Solid dispersions of Amlodipine Besylate prepared by ALL techniques were kept in the basket of dissolution apparatus and immersed in 900 ml distilled 0.01MHydrochloric Acid at 37 ± 0.5° C and stirred at 100 rpm. Aliquot of 5 ml was withdrawn at time intervals of 15, 30, 45 and 60 min. The same amount of withdrawn volume was replaced with the dissolution medium in order to maintain the sink condition. The sample withdrawn was analyzed at 239nm spectrophotometrically.

RESULTS AND DISCUSSION

Calibration curve for amlodipine besylate

Calibration curve for Amlodipine Besylate was developed from the stock solution. From the stock solution, 1µg/ml, 2, 4, 6, 8, 10µg/ml. The absorbance of the prepared solutions was measured at 239nm against are agent blank Using UV Spectrophotometer. At each

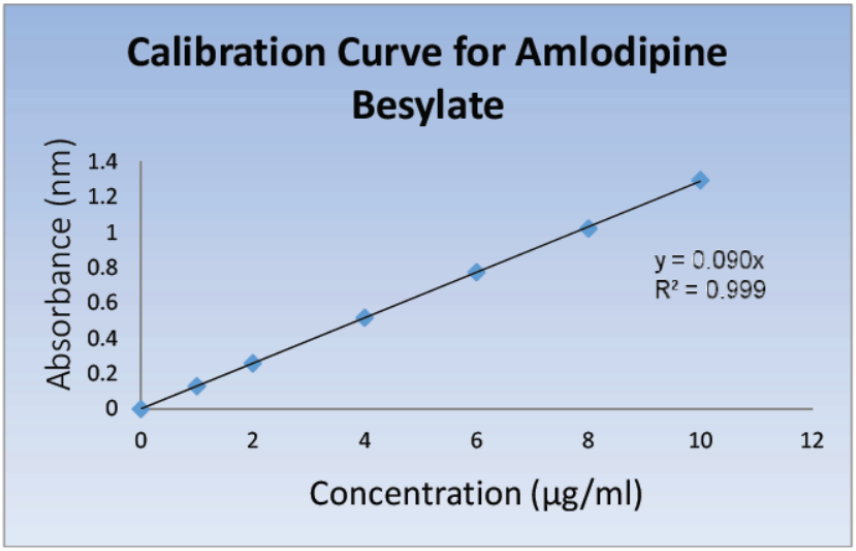
concentration triple treadings were measured and mean value was used for the Construction of calibration curve. Calibration curve was constructed by taking concentration of the prepared solution on x-axis and corresponding absorbance on y-axis.

The λmax was found to be 239 nm for Amlodipine Besylate, at which the absorbances of standard solutions (0-10µg/ml) were measured. Calibration between the concentration and absorbance were developed with a regression coefficient of 0.999, which showed linearity between 0-10µg/ml ranges for Amlodipine Besylate.

Data for calibration curve for amlodipine besylate;

S. no	Concentration (µg/ml)	Absorbance At 239 nm
1.	0	0.000
2.	1	0.129
3.	2	0.259
4.	4	0.517
5.	6	0.775
6.	8	1.022
7.	10	1.296

λmax =239 nm r = 0.999



Calibration curve for amlodipine besylate.

Determination of percent practical yield

The Formulation Code F1 (Amlodipine Besylate: PEG 6000 (1:1) solid dispersion by solvent evaporation method was found to have the Highest Percent Practical Yield of 96.26%. The

least Percent Practical Yield of87.45% was found in the Formulation Code F6 (Amlodipine Besylate :HPMC (1:3) solid dispersion by solvent evaporation method.

Data for percent practical yield

S. no	Formulation code	Percentage practical yield
1.	F1	96.26%
2.	F2	92.83%
3.	F3	88.50%
4.	F4	93.60%
5.	F5	89.20%
6.	F6	87.45%
7.	F7	93.10%
8.	F8	91.06%
9.	F9	90.34%
10.	F10	91.56%
11.	F11	92.78%
12.	F12	91.75%
13.	F13	90.82%
14.	F14	90.10%
15.	F15	90.26%

Estimation of drug content

The drug Content of Amlodipine Besylate in PEG 6000 By Solvent Evaporation Method The drug Content of Amlodipine Besylate Solid dispersion in PEG6000 is shown in Table No: 08 and Table No 10. The percent drug content for F1, F2, and F3 was found to be 99.00%, 99.76% and 99.84%respectively for Amlodipine Besylate Solid dispersion in PEG 6000formulated using Solvent Evaporation Technique .Whereas the percent drug content for F7, F8, and F9 was found to be 99.22%, 99.69% and 99.78% respectively for Amlodipine Besylate Solid dispersion in PEG 6000 formulated using Physical Mixture Technique .The drug Content of Amlodipine Besylate Solid dispersion in HPMC is shown in Table No: 09 and Table No: 11. The percent drug content forF4, F5, and F6 was found to be 93.41%, 93.24% and 93.05% respectively for Amlodipine Besylate Solid dispersion in HPMC formulated using Solvent Evaporation Technique. Whereas the percent drug content for F10, F11, F12 was found to be93.80%, 93.60% and 93.37%respectively for Amlodipine Besylate Solid dispersion in HPMC formulated using Physical Mixture Technique.

Amlodipine besylate peg 6000 solid dispersionby solvent evaporation method.

S. no	Formulation code	Drug: Carrier (Ratio)	Drug content (%)
1.	F1	1:1	99.00%
2.	F2	1:2	99.76%
3.	F3	1:3	99.84%

Amlodipine besylate hpmc solid dispersion by solvent evaporation method.

S. no	Formulation code	Drug: Carrier (Ratio)	Drug content (%)
1.	F4	1:1	93.41%
2.	F5	1:2	93.24%
3.	F6	1:3	93.05%

Amlodipine besylate peg 6000 solid dispersionby physical mixture method.

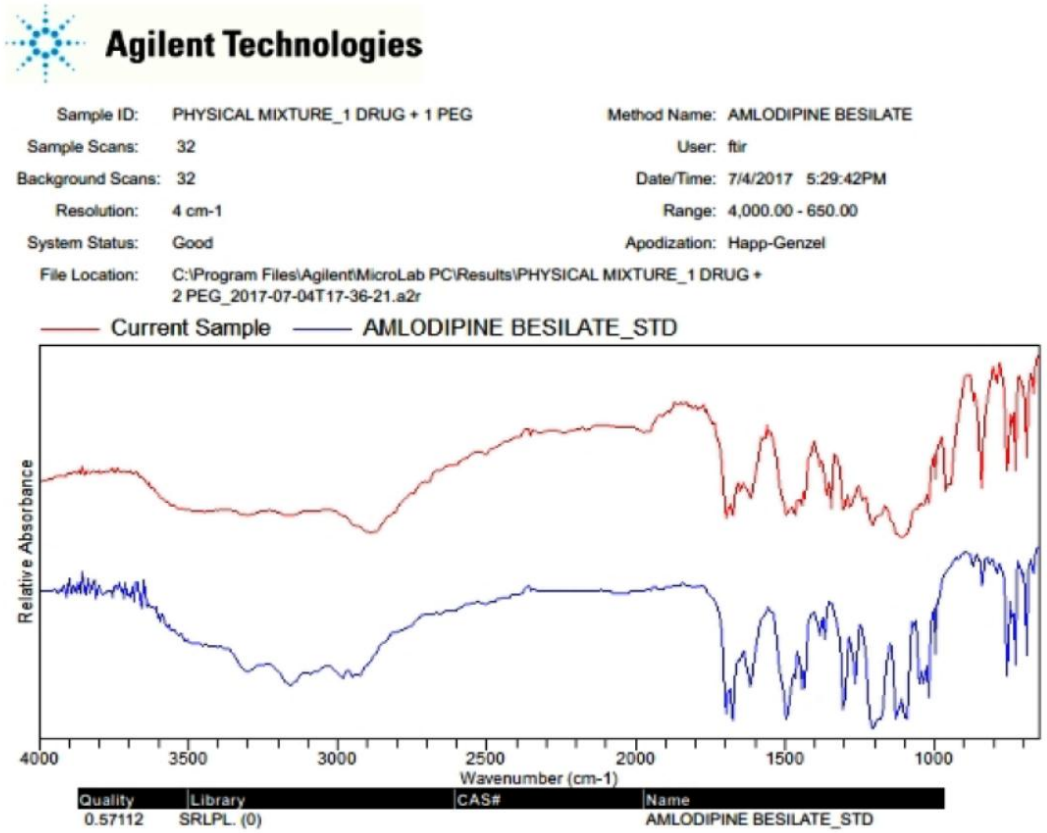
S. No	Formulation code	Drug: Carrier (Ratio)	Drug content (%)
1.	F7	1:1	99.22%
2.	F8	1:2	99.69%
3.	F9	1:3	99.78%

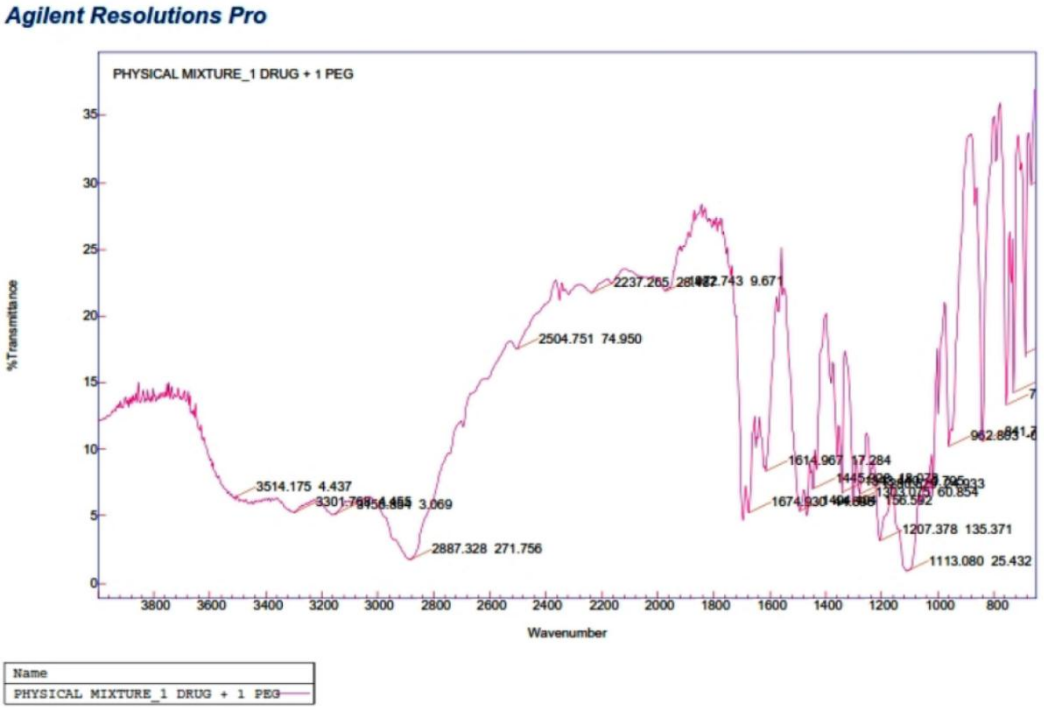
Amlodipine besylate hpmc solid dispersion by physical mixture method.

S. no	Formulation code	Drug: Carrier (Ratio)	Drug content (%)
1.	F10	1:1	93.80%
2.	F11	1:2	93.60%
3.	F12	1:3	93.37%

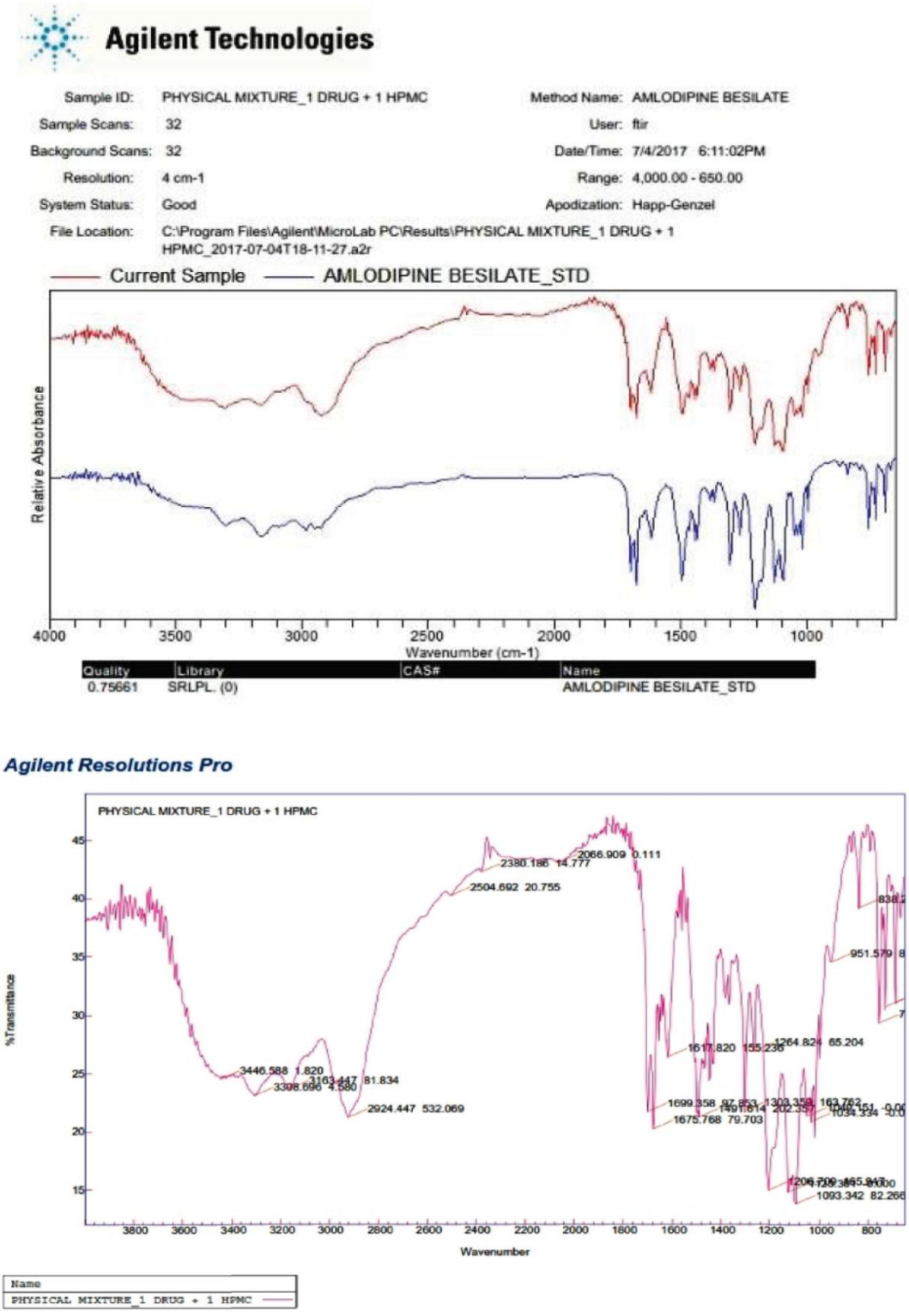
Compatibility studies by ftir between drug and the polymer

Compatibility of Amlodipine Besylate PEG 600 and HPMC were studied by IR spectral matching approach. By comparing the spectra, it was concluded that there was no significant change in spectral pattern of physical mixtures of drug and polymer, which confirmed the compatibility of Amlodipine Besylate with the polymers. The Principal peaks obtained in IR spectra of samples were almost similar to that of pure drug, indicating no interaction between drug and polymers.





Ftir spectrum for amlodipine besylate and peg6000.



Ftir spectrum foramlodipine besylate and hpmc.

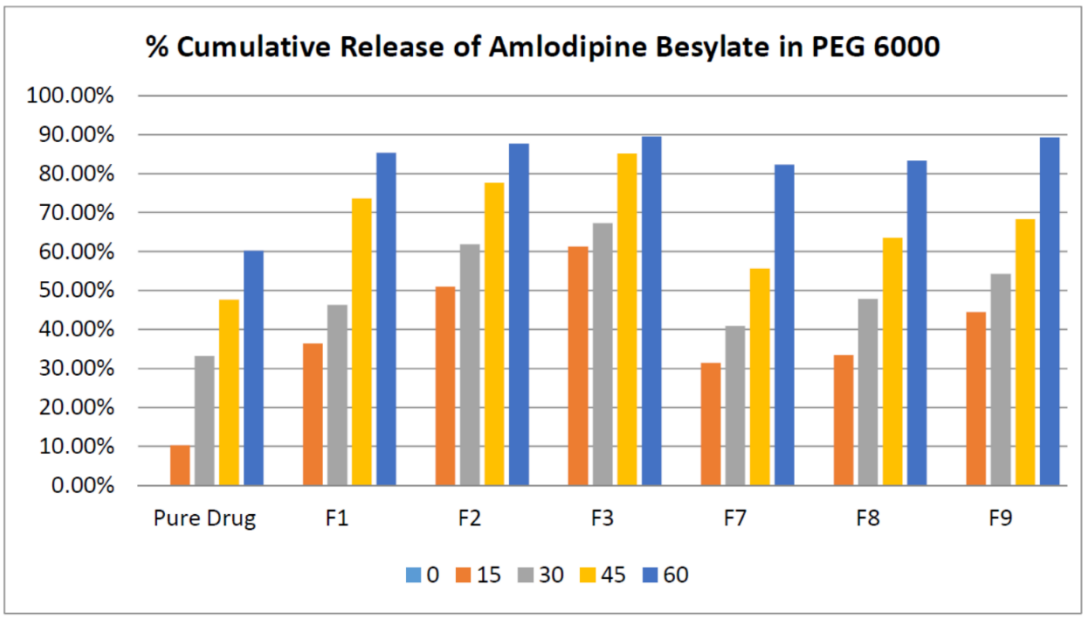
In vitro release study

The dissolution of Amlodipine Besylate Solid dispersion in PEG 6000. Cumulative percent drug released after 60 min for F1, F2, F3 was found to be 85.33%, 87.63% and89.50%

respectively for Amilodipine Besylate Solid dispersion in PEG 6000formulated using Solvent Evaporation Technique and Pure drug was found to be 60.11%.The dissolution of Amilodipine Besylate Solid dispersion in HPMC. Cumulative percent drug released after 60 min for F4, F5, F6 was found to be 32.70%, 42.29% and 62.39%respectively for Amilodipine Besylate Solid dispersion in HPMC formulated using Solvent Evaporation Technique and Pure drug was found to be60.11%.Whereas the Cumulative percent drug released after 60 min for F10,F11, F12 was found to be 55.36%, 60.70% and 68.20% respectively for Amlodipine Besylate Solid dispersion in HPMC formulated using Physical Mixture Technique and Pure drug was found to be 60.11%

In vitro release profile of amlodipine besylatesolid dispersions in peg 6000.

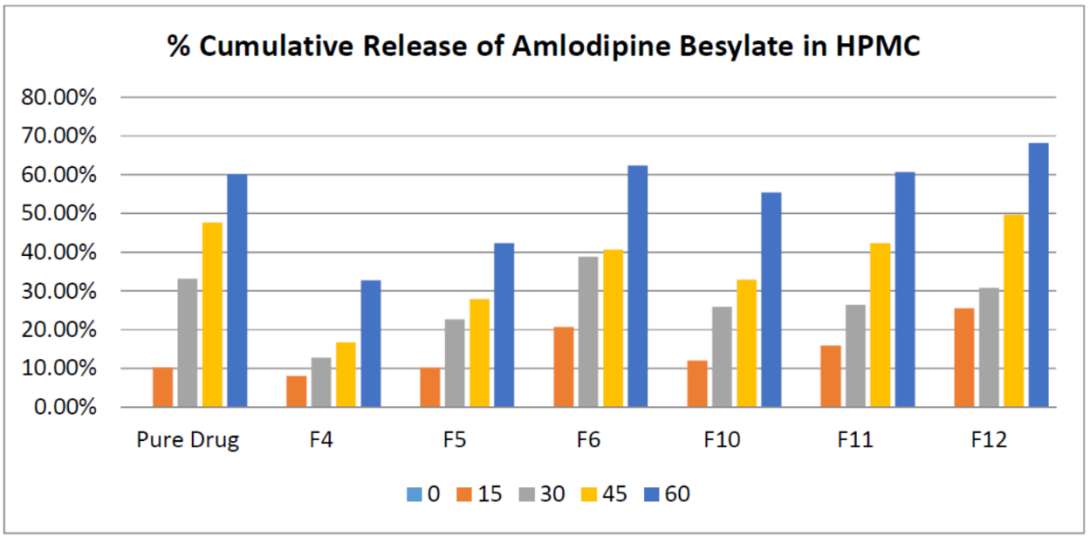
S.no	Formulation code	% Cumulative drug release Time (Minutes)				
		0	15	30	45	60
1.	Pure drug	0.0%	10.22%	33.19%	47.65%	60.11%
2.	F1	0.0%	36.36%	46.33%	73.62%	85.33%
3.	F2	0.0%	50.92%	61.84%	77.68%	87.63%
4.	F3	0.0%	61.22%	67.29%	85.20%	89.50%
5.	F7	0.0%	31.44%	4.92%	55.66%	82.30%
6.	F8	0.0%	33.42%	47.82%	63.52%	83.34%
7.	F9	0.0%	44.51%	54.28%	68.29%	89.29%



Graphical representation of in vitro releaseprofile of amlodipine besylate solid dispersions in peg6000

In vitro release profile of amlodipine besylatesolid dispersions in hpmc.

S.no	Formulation code	% Cumulative drug release time (minutes)				
		0	15	30	45	60
1.	Pure drug	0.0%	10.22%	33.19%	47.65%	60.11%
2.	F4	0.0%	8.12%	12.82%	16.73%	32.70%
3.	F5	0.0%	10.19%	22.65%	27.98%	42.29%
4.	F6	0.0%	20.70%	38.82%	4.63%	62.39%
5.	F10	0.0%	12.04%	25.89%	32.92%	55.36%
6.	F11	0.0%	15.83%	26.28%	42.28%	60.70%
7.	F12	0.0%	25.50%	30.79%	49.65%	68.20%



Graphical representation of in vitro releaseprofile of amlodipine besylate solid dispersions in hpmc.

CONCLUSION

Amlodipine Besylate is an Antihypertensive; antianginal drug used in treatment of Hypertension. The solubility and dissolution profile of Amlodipine Besylate, a poorly water soluble drug, was significantlyimproved by preparing solid dispersion with water soluble carriers like PEG 6000 and HPMC by solvent evaporation technique and Physicalmixture method.Among all the formulations the, Formulation Code F3 of Amlodipine Besylate Solid dispersion prepared by Solvent evaporation method using PEG 6000 at 1:3 drug : carrier ratio has shown highest improvement in the dissolution profile of Amlodipine Besylate..Hence it may be concluded that PEG may be used as the carrier of choice for the preparation of Solid Dispersions. The techniques explore dare relatively easy, simple, quick, inexpensive, and reproducible suggesting that solid dispersion is a trustworthy alternative for solubility enhancement of poorly water soluble drug.

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