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Research

Solid Dispresion Strategies For Improved Amlodipine Besylate Performance: Preparation And Assessment

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Abstract

Solid dispersion techniques have emerged as promising strategies for enhancing the dissolution rate and bioavailability of poorly water-soluble drugs like amlodipine besylate. This review explores various solid dispersion approaches, including solvent evaporation, melting method, co-precipitation, spray drying, and supercritical fluid technology. These methods offer advantages such as increased drug solubility, improved dissolution kinetics, and enhanced oral bioavailability. Factors influencing the formulation and performance of solid dispersions, such ascarrier selection, drug-carrier interactions, and processing parameters, are discussed. Additionally, recent advancements in solid dispersion technology, such as nanostructured dispersions and inclusion complexation, are highlighted. Overall, solid dispersion techniques represent versatile and effective strategies for optimizing the therapeutic efficacy of amlodipine besylate formulations.

Keywords: Solid Dispersion, Amlodipine Besylate, Bioavailability Enhancement, Solubility Improvement, Pharmaceutical Formulation.

INTRODUCTION

The drug solubility enhancement, bioavailability at the target site of therapeutic action are of the numerous challenges in pharmaceutical formulation. Poorwater solubility tops the list of critical compound properties among the five key physicochemical parameters in early compound screening viz. dissociation constant, solubility, permeability, stability and lipophilicity [1].

Advances in combinatorial chemistry and high throughput screening have ledto 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 weights [2].

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. Theenhancement of oral bioavailability for poorly water soluble drugs remains one of themost challenging aspects of drug development [3].

Biopharmaceutics Classification System (Bcs)

The biopharmaceutics classification system (BCS) is the scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is a drug development tool that allows estimation of the contributionsof three major factors, dissolution, solubility and intestinal permeability that affect oral absorption of drugs. BCS class II and IV drugs which have low solubility provide a number of challenges for formulation scientists workingon oral delivery of drugs [4].

Numerous methodologies have been suggested and practically applied to improve the market ability of such drug candidates. These include the use of particlesize manipulation via micronization and nanonization, use of complexing agents suchas cyclodextrins, preparation of high energy drug states related to polymorphic or amorphic transformation, use of co-solvents, micellar solutions and lipid based systems for lipophilic drugs [5].

Solubility in quantitative terms is defined as the concentration of the solute ina saturated solution at a certain temperature. It is defined in qualitative terms as the spontaneous interaction of two or more substances to form a homogeneous moleculardispersion [6].

The property of a solute i.e, solid, liquid, gaseous or chemical substances which is to be dissolved in a solvent i.e, in a solid, liquid, or gaseous solvent to form a homogeneous solution is called as solubility. The solubility of a solute in a solvent depends on the solvent used as well as on temperature and pressure [7]. Solubility varies over an extended range from infinitely soluble such as ethanol in water, to poorly soluble, such as silver chloride in water. The poorly or very poorly soluble compounds are often termed as insoluble [8]. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for showing pharmacological response. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Most of drugs are weakly acidic and weakly basic with poor aqueous solubility. 130 orally administered drugs on the WHO list, 61 could be classified with certainty. 84% of these belong to class I (highly soluble, highly permeable), 17% to class II (poorly soluble, highly permeable), 24 (39%) to class III.(highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble,poorly permeable) [9]. Drug release is an important and rate limiting step for oralbioavailability, particularly for drugs with low solubility and highpermeability i.e. BCS class II drugs.By improving the drug release profile ofBCS class II drugs, it is possible to enhance their bioavailability and reduceside effects [10].

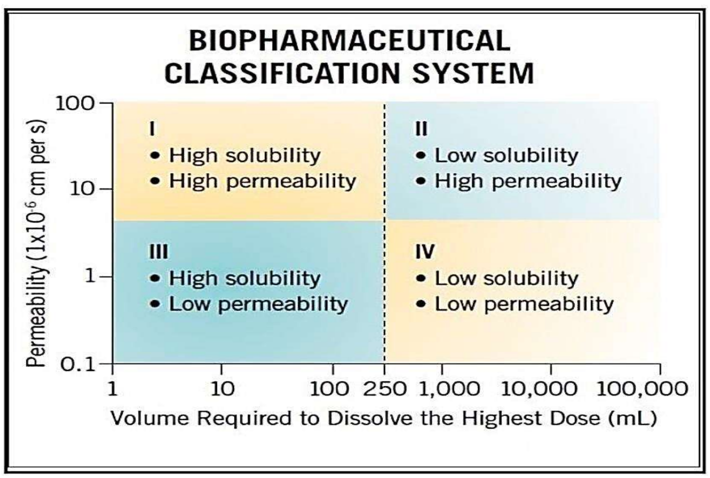


Fig 1: Bcs And Viable Formulation Option BasedOnthebcs

Mechanism Of Action

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist orslow-channel blocker) that inhibits the transmembraneinflux of calcium ions into vascular smooth muscle and cardiac muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellularcalcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Withinthe physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and itskinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Pharmacodynamics Hemodynamics

Following administration of therapeutic doses to patients with hypertension, NORVASC produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasmacatecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial bloodpressure and increases heart rate in hemodynamic studies of patients with chronicstable angina, chronic oral administration of amlodipine in clinical trialsdid not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina. In hypertensive patients with normal renal function, therapeutic doses of NORVASC resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

Drug Interactions Sildenafil

When amlodipine and sildenafil were used in combination, eachagentind ependently exerted its own blood pressure lowering effect.

Pharmacokinetics

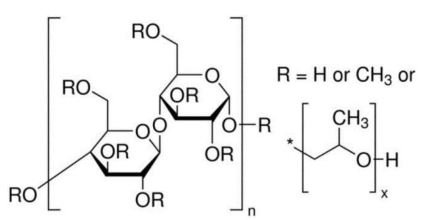
After oral administration of therapeutic doses of NORVASC, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has beenestimated to be between 64 and 90%.The bioavailability of NORVASC is not alteredby the presence of food. Amlodipine is extensively (about 90%) converted to inactivemetabolites via hepatic metabolism with 10% of the parent compound and60% of the metabolites excreted in the urine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasmaproteins in hypertensivepatients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-stateplasma levels of amlodipine are reached after 7 to 8 days of consecutivedaily dosing. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose. Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required. A similarincrease in AUC was observed in patients with moderate to severe heartfailure.

Drug profile

In vitro data indicate that amlodipine has no effect on the humanplasma protein binding of digoxin, phenytoin, warfarin and indomethacin.
SYNONYMS: PMC; MHPC; hpmcd; goniosol; HPMC/MHPC; methocelhg; HPMC/HEMC; Isoptoplain; Isoptotears; HYPROMELLOSE.

Empirical formula: C8H15O8-(C10H18O6)n-C8H15O

Molecular weight: 86000
Structure: Hydroxypropylmethylcellulose



Description: HPMC is an odorless and tasteless, white or creamy-white fibrous orgranular powder.
Melting point:browns at 190–200ºC; chars at 225–230ºC.Glasstransitiontemperature is 170-180ºC.
Density: Bulk Density: 0.341 g/cm, Tapped Density: 0.557 g/cm, True Density:1.326 g/cm.
Solubility: soluble10 mg/mL, clear to almost clear, colorless. Itcan be dissolvedin water, and formed a transparent to milky white andhas a certain viscosity colloidalsolution.
Category: Coating agent; film-former; rate-controlling polymer forsustained release; stabilizing agent; suspending agent; tablet binder;viscosity increasing agent.

MATERIALS AND METHODS

Various chemicals used for the preparation and evaluation of AmlodipineBesylate Solid Dispersion are listed in table as follows

Table 1: List Of Chemical Used

S.No	Materials	Manufactures
1.	Amlodipine Besylate	Nickon Pvt. Ltd.Villupuram.
2.	Poly Ethylene Glycol 6000	Nickon Pvt. Ltd.Villupuram.
3.	Hydroxy Propyl MethylCellulose	Merck Specialities Pvt.Ltd. Mumbai
4.	Acetone	Merck Specialities Pvt.Ltd. Mumbai
5.	Hydrochloric acid	S.D. Fine Chem. Ltd. Mumbai

Instruments And Equipments Used

Various Instruments and equipment's used for the preparation andevaluationof Amlodipine Besylate Solid Dispersion are listed in table asfollows

Table 2: List Of Instrument Used

S.No	Industrument Used	Manufactures
1.	Digital balance	Mettle Toledo DR-203, Switzerland
2.	FTIR	Agilent Cary 630 FTIR spectrometer,
3.	Digital Dissolution Apparatus	Lab India DS-8000, India
4.	UV Visible Spectrophotometer	Double beam ELICO SL-210, India

Methods Used

Preparation Of Standard Stock Solution [11]

Standard stock solution of Amlodipine pure drug was prepared byaccurately weighing about 10mg of each drug in 10ml volumetric flask.The drugs were dissolvedwith 5ml of methanol and sonicated to dissolveit completely and made up to the markwith 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 solution2ml wastaken and made up to 20ml to get a final working stock solution of10µg/ml required concentrations or dilutions needed for UV and visibleestimation was prepared from 10µg/ml solution.

Preparation Of Calibration Curve [12]

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 preparedsolutions was measured at 239nm against a regent blank. At eachconcentration triplet readings were measured and mean value was usedfor the Construction of calibration curve. Calibration curvewasconstructed by taking concentration of the prepared solution on x-axis andcorresponding absorbance on y-axis.

Preparation Of 0.01 M Hydrochloric Acid

0.01 M Hydrochloric acid was prepared by taking 0.82 ml ofhydrochloricacid in 1000 ml volumetric flask and then distilled water wasadded to volume.

Formulation Of Solid Dispersions [13]

Solid dispersion of Amlodipine Besylate was prepared by solvent evaporation method and physical mixtures. The composition is shown in table 5.

Table 3: Formulation Of Solid Dispersions

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 EthyleneGlycol 6000(PEG 6000) and Hydroxy Propyl Methyl Cellulose (HPMC)were mixed in 1:1,1:2 and 1:3 ratios in acetone separately. Solvent wasremoved by evaporation under reduced pressure. The mass waspulverised and passed through sieve # 100.

Preparation Of Physical Mixtures

For the sake of comparison, physical mixtures having the samecomposition ofthe solid dispersions were prepared by simplytriturating the drugs and the polymers in a porcelain mortar. Themixtures were then sieved (420 µm) and storedin amber- glass cappedcontainers.

Evaluation Of Prepared Solid Dispersion

Determination Of Percent Practical Yield (Py)

To determine the efficiency of any method of production,Percentage practicalyield was calculated. In this method pre weigheddispersions were collected to determine practical yield (PY) from thefollowing equation.
Percent Practical Yield (PY) = (Weight of Practical solid dispersions × 100)/ Theoretical weight (Amlodipine Besylate + Polymer

Estimation Of Drug Content [14]

The formulation equivalent to 500 mg of drug was weighed anddiluted suitably with distilled water. The absorbance was measured at239 nm for the amountof drug in each formulation was calculated. Thepercent 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 [15]

The Drug Polymer Interaction was studied using the FourierTransform Infra -Red Spectroscopy (FTIR). One to Two mg of pure drugwas mixed with the weighedpolymer samples (PEG 6000 / HPMC) thenthis is mixed properly with the potassiumbromide to uniform mixture.From this powder a small quantity as compressed into a thin semitransparentpellet by applying pressure (Pressed Pellet Technique). The IRSpectrum of the pellet was recorded taking air as the reference andcompared to study the interference.

Determination Of Dissolution

Invitro release profiles for each batch was performed using USPdissolution apparatus (Lab India DS-8000, India). Solid dispersions ofAmlodipine Besylate prepared by ALL techniques were kept in the basketof dissolution apparatus and immersed in 900 ml distilled 0.01MHydrochloric Acid at 37 ± 0.5° C and stirred at 100 rpm. Aliquot of 5 mlwas withdrawn at time intervals of 15, 30, 45 and 60 min. The sameamount of withdrawn volume was replaced with the dissolution mediumin order to maintain the sink condition. The sample withdrawn wasanalyzed at 239 nm spectrophotometrically.

Determination Of Release Kinetics

The kinetic models used were zero order, First order, Higuchi, Hixon –Crowell model and Korsmeyer – Peppas model.

Zero – Order Model

Drug dissolution from dosage forms that do not disaggregate and releasethedrug slowly can be represented by the equation:
$Qt = Q0 + K0t$
Where,
Qt is the amount of drug dissolved in time t, Q0 is the initial amount of drug in the solution,
K0 is the zero order release constant andt is time in hours. Expressed in units of concentration/time.
Graph: X- axis is time in hours and Y- axis is % cumulative drug release.

First order model

The release of the drug which followed first order kinetics can beexpressedby the equation:
$\log Q_t = \log Q_0 + K_t / 2.303$
Where,
Q_0 is the initial concentration of drug, Q_t is cumulative amount of drug released per unit surface area,k is the first order rate constant and t is the time.

Graph: X- axis is time in hours and Y- axis is log % cumulative drugrelease.

Hixon Crowell model
Hixson and Crowell (1931) recognized that the particles regular area isproportional to the cube root of its volume. The equation describes the releasefrom systems where there is a change in surface area and diameter of particles. They derived the equation: $W0^{1\backslash 3} - W^{1/3} = KHC * t$
Where, W0 is the initial weight of particle,W is the weight of particle, KHC is Hixon Crowell release rate constant andtis time.

Higuchi model
Higuchi model describes the drug release from several typed of matrices initially conceived for planar systems, then extended to different geometrics and porous systems. It was derived by higuchi in 1961. For higuchi release kinetics equation is,
Q = KH t 0.5
Where, Q is amount of drug released per unit surface area of the dosageform KH is Higuchi release rate constant andt is time.

Korsmeyer – Peppas model
Koresmeyer derived a simple relationship which describes drug releasefrom a polymeric system. To find out the mechanism of drug release, first 60%drug releasedata was fitted in Koresmeyer – Peppas model equation,
$(M_t/M) = Km\ tn$
where,
M_t is amount of drug released at time t, M is total amount of drug in dosage form,Km is kinetic constant, n is diffusion and release exponent andtis time in hours.

RESULTS AND DISCUSSION

Calibration Curve For Amlodipine Besylate

Table 4 : Data For Calibration Curve For AmlodipineBesylate λmax -239 nm

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

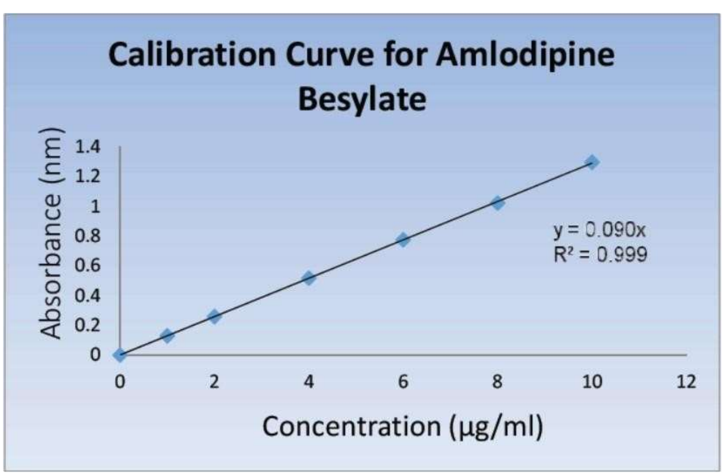


Fig 2: Calibration Curve For Amlodipine Besylate

Determination Of Percent Practical Yield

Table 5: Data For Percent Practical Yield

S.No	FormulationCode	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

Table 6: Amlodipine Besylate Peg 6000 Solid Dispersion by 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%

Table 7: Amlodipine Besylate Hpmc Solid DispersionBy 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%

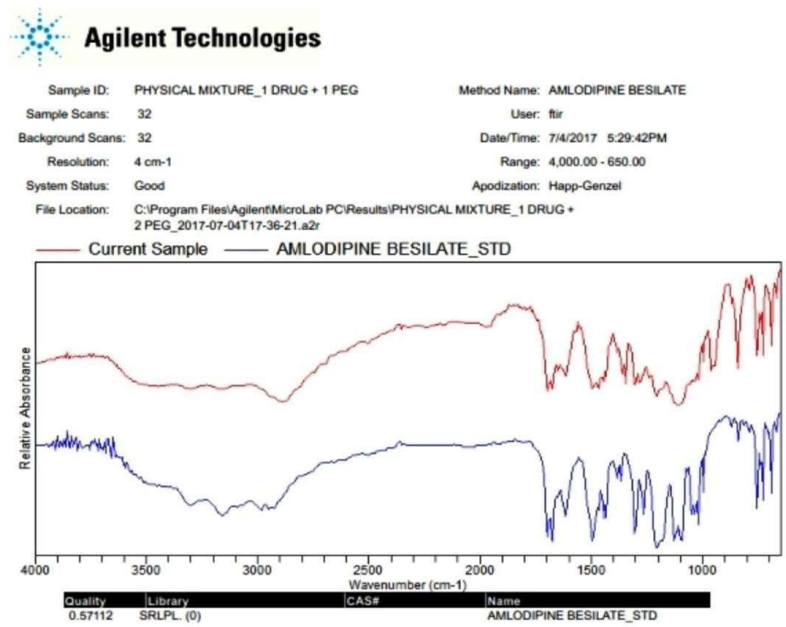
Table 8: Amlodipine Besylate Peg 6000 Solid Dispersionby Physical Mixture Method

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%

Table 9: 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 ThePolymer



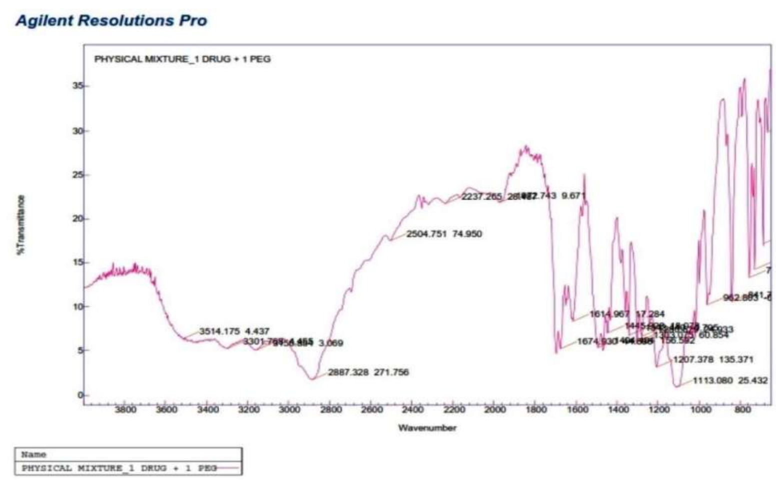
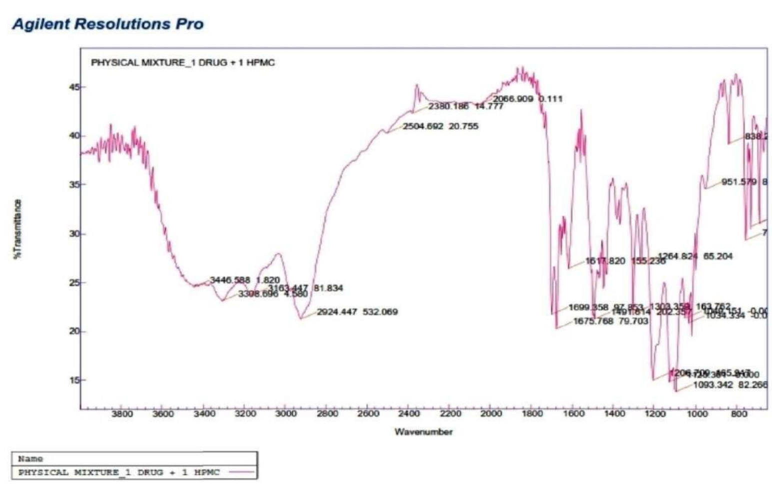


Fig 3: Ftir Spectrum For Amlodipine Besylate AndPeg6000



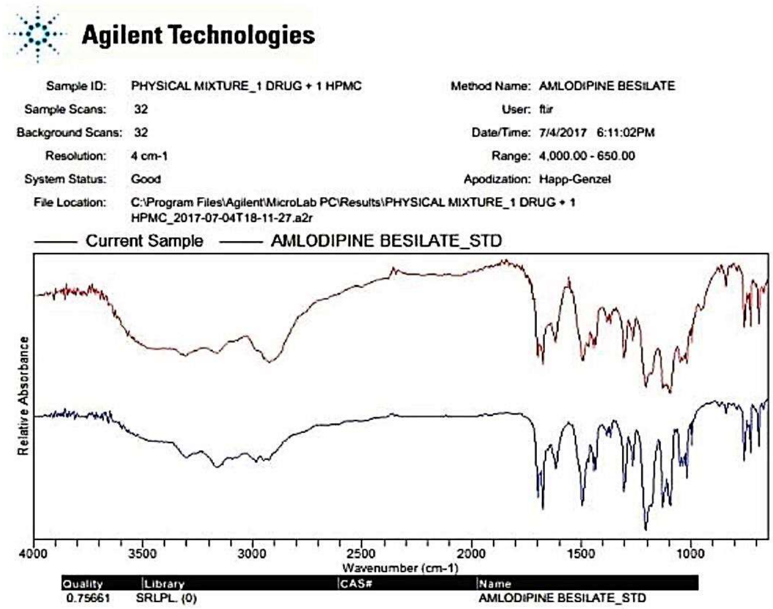


Fig 4: Ftir Spectrum Foramlodipine Besylate AndHpmc

In Vitro Release Study

Table 10: In Vitro Release Profile Of AmlodipineBesylate solid Dispersions In Peg 6000

S.no	Formulation code	% Cumulative Drug ReleaseTime (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%

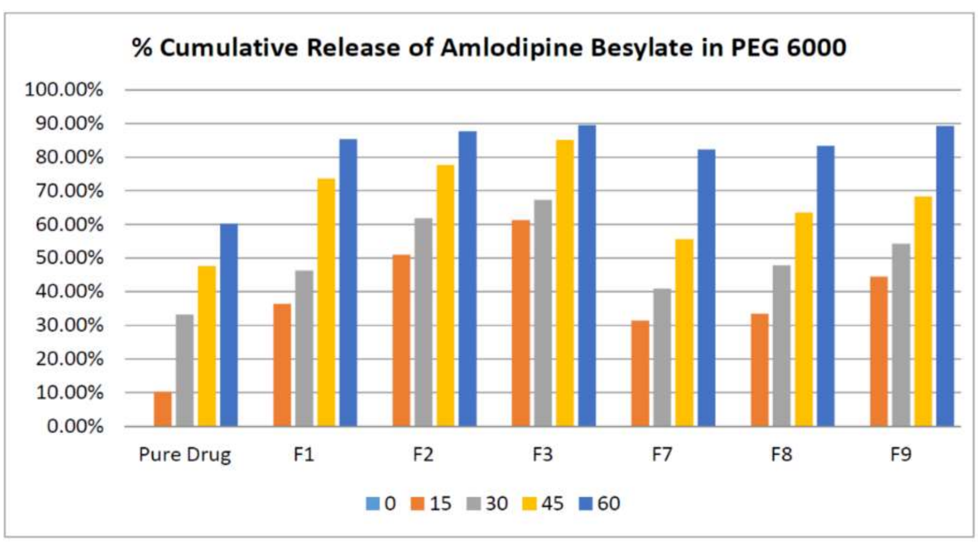


Fig 5: Graphical Representation Of In Vitro Release profile Of Amlodipine Besylate Solid DispersionsIn Peg6000

Table 11: In Vitro Release Profile of AmlodipineBesylatesolid 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%

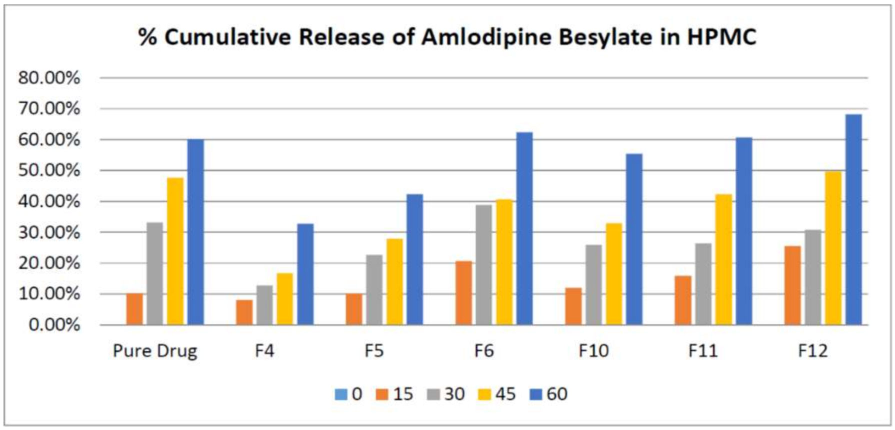


Fig 6: Graphical Representation Of In Vitro Release profile Of Amlodipine Besylate Solid DispersionsIn Hpmc

DISCUSSIONS

Calibration Curve For Amlodipine Besylate

Calibration curve for Amlodipine Besylate was developed from thestock solution. From the stock solution, 1µg/ml, 2, 4, 6, 8, 10µg/ml. Theabsorbance of the prepared solutions was measured at 239nm against aregent blank Using UV Spectrophotometer. At each concentration tripletreadings were measured and mean value was used for the Construction ofcalibration curve. Calibration curve was constructed by takingconcentration of the prepared solution on x-axis and correspondingabsorbance on y-axis. The results are given in Table No: 06 and Figure 02. The λmax wasfound to be 239 nm for Amlodipine Besylate, at which the absorbances ofstandard solutions (0-10µg/ml) were measured. Calibration between theconcentration and absorbance were developed with a regression coefficientof 0.999, which showed linearity between 0-10µg/ml ranges forAmlodipine Besylate.[16]

Determination Of Percent Practical Yield

The data for percent practical yield is given in Table No: 07. TheFormulationCode F1 (Amlodipine Besylate: PEG 6000 (1:1) soliddispersion by solvent evaporation method was found to have the HighestPercent 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.[17]

Estimation Of Drug Content

The drug Content of Amlodipine Besylate in PEG 6000 By SolventEvaporation Method Is given in table No 08. The drug Content of Amlodipine Besylate Solid dispersion in PEG6000 is shown in Table No: 08 and Table No 10. The percent drug contentfor F1, F2, and F3was 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 tobe 99.22%,99.69% and 99.78% respectively for Amlodipine Besylate Soliddispersion in PEG 6000 formulated using Physical Mixture Technique. The drug Content of Amlodipine Besylate Solid dispersion in HPMCis shownin 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% respectivelyfor Amlodipine Besylate Soliddispersion in HPMC formulated usingSolvent 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 Soliddispersion in HPMC formulated using Physical Mixture Technique.[18]

Compatibility Studies By Ftir Between Drug AndThe Polymer

Compatibility of Amlodipine Besylate PEG 600 and HPMC werestudied by IR spectral matching approach. The respective spectra aregiven in Figures 03 and By comparing the spectra, it was concludedthat there was no significant change in spectral pattern of physicalmixtures of drug and polymer, which confirmed the compatibility ofAmlodipine Besylate with the polymers. The Principal peaks obtainedin IRspectra of samples were almost similar to that of pure drug, indicating nointeraction between drug and polymers.[19]

***In Vitro* Release Study**

In-vitro drug release study for each batch was performed using USPdissolution apparatus (Lab India DS-8000, India) for Solid dispersions ofAmlodipine Besylate prepared by ALL techniques. The dissolution of Amlodipine Besylate Solid dispersion in PEG6000 is shown in Table No: 12 and Figure: 05. Cumulative percent drugreleased after 60 minfor F1, F2, F3 was found to be 85.33%, 87.63% and89.50% respectively for Amlodipine Besylate Solid dispersion in PEG 6000formulated using Solvent Evaporation Technique and Pure drug was foundto be 60.11%. Whereas the Cumulative percent drug released after 60 min for F7,F8, F9 wasfound to be 82.30%, 83.34% and 89.29% respectively forAmlodipine Besylate Soliddispersion in PEG 6000 formulated usingPhysical Mixture Technique and Pure drugwas found to be 60.11%. The dissolution of Amlodipine Besylate Solid dispersion in HPMC isshown in Table No: 13 and Figure: 06. Cumulative percent drug releasedafter 60 min for F4,F5, F6 was found to be 32.70%, 42.29% and 62.39%respectively for Amlodipine Besylate Solid dispersion in HPMC formulatedusing Solvent Evaporation Techniqueand Pure drug was found to be60.11%. Whereas the Cumulative percent drug released after 60 min for F10,F11, F12was found to be 55.36%, 60.70% and 68.20% respectively forAmlodipine Besylate Solid dispersion in HPMC formulated using PhysicalMixture Technique and Pure drug was found to be 60.11%.[20]

Drug Release Kinetics

In order to determine the release model which best describes thepattern of drugrelease, the release data was fitted in various kineticsmodels like zero order, firest order, higuchi equation and korsmeyerpeppas equation were given in Table No: 14 and shown in Figure 07, 08,09 and 10. By comparing the correlation coefficient value(R2), linearitymimicking Higuchi and korsmeyar-peppas release model. To understandthe mechanism of drug release the release data was fitted in the Higuchiequation. The corresponding plot for Higuchi kinetics also showed goodlinearity. In addition, the korsmeyer-peppas model, the value of 'n' showed(Formulation F3) greater than 1 designates a supercase –II transport.

SUMMARY

Solid dispersion of Amlodipine Besylate with PEG 6000 (F1, F2, F3)by solvent evaporation method, (F7, F8, F9) by physical mixture methodand Solid dispersion of Amlodipine Besylate with HPMC (F4, F5, F6) bysolvent evaporation method, (F10, F11, F12) by physical mixture methodwere prepared successfully.

In case of drug content determination, formulations F3 (AmlodipineBesylate PEG 6000 (1:3) Solid Dispersion by Solvent Evaporation Method)showed higher drug content of 99.84%. By increasing PEG 6000concentration the drug content concentration also increases. Whereas, formulations F6 and F12 showed decrease in drug content (93.05% and93.37%) by increasing HPMC concentration.

The FTIR spectrum of solid dispersion of Amlodipine Besylate withboth polymers, i.e PEG 6000 and HPMC showed peak similar to that ofpure Amlodipine Besylate. It revealed that there is no interaction betweendrug and polymer.

The *in-vitro* release profile of formulation F3 (Amlodipine BesylatePEG 6000(1:3) Solid Dispersion by Solvent Evaporation Method) and F9(Amlodipine Besylate PEG 6000 (1:3) Solid Dispersion by Physical MixtureTechnique) showed higher drugrelease of 89.50% and 89.29%respectively at the end of 60 mins. When compared to that of formulationF6 (Amlodipine Besylate HPMC (1:3) Solid Dispersion by SolventEvaporation Method) and F12 (Amlodipine Besylate HPMC (1:3) SolidDispersion by Physical Mixture Method), and pure drug showed only62.39%, 68.20% and 60.11% respectively at the end of 60 mins.

The in-Vitro release data was fitted to various release kinetic modelsnamely, Zero order plot, first order plot, Higuchi plot and Korsmeyer –Peppas plot. The resultrevealed that Higuchi kinetics show good linearity.In addition, the korsmeyer-peppas model, the value of 'n' showed(Formulation F3) greater than 1 designates a supercase–II transportmechanism of durg release.

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 significantly improved 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 BesylateSolid dispersion prepared by Solvent evaporation method using PEG 6000 at 1:3 drug: carrier ratio has shown highest improvement in the dissolution profile of AmlodipineBesylate. Hence it may be concluded that PEG may be used as the carrier of choice for the preparation of Solid Dispersions. The techniques explored are 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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