ORIGINAL ARTICLE

Solubility Enhancement of a Poorly Water-Soluble Drug, Amlodipine Besylate and its Formulation Development into Solid Dispersion using Mixed Solvency Concept and Evaluation of Prepared Solid Dispersions

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Abstract

Introduction: In recent generation, the difficult task is to overcome solubility problems in the formulation development of the drug. The lower water solubility of drugs causes various challenges in developing formulations and the use of harmful organic solvents produces toxicity. So, this problem is overcome by the mixed solvency concept proposed by Dr R.K. Maheshwari in 2009. In this work, amlodipine besylate was chosen as a model drug and solubilizers selected were sodium benzoate, sodium acetate, sodium citrate, sodium caprylate, poloxamer 407, l-lysine, β-cyclodextrins and niacinamide. The solid dispersions are proposed to be formulated using these expectedly safe water-soluble additives as per mixed solvency concept. **Materials and Methods:** Solid dispersions were prepared using solvent evaporation method, amlodipine besylate was chosen as a model drug and solubilizers selected were sodium benzoate, sodium acetate, sodium citrate, sodium caprylate, poloxamer 407, l-lysine, β-cyclodextrins and niacinamide. The amlodipine besylate used for the preparation of solid dispersion was characterized and identified by UV spectrophotometric analysis, melting range determination and comparative dissolution studies. **Results and Discussions:** The amlodipine besylate used for the preparation of solid dispersion was characterized and identified by UV spectrophotometric analysis and melting range determination. The observed values were in accordance with the reported values in the literatures. For pre-formulation studies, the solubility studies of the drug were done in different blends. Also, calibration curves in water and 0.1N HCl were prepared. Interaction studies of drug-solubilizers have shown no interaction and incompatibility between drugs and solubilizers. Solubility of amlodipine besylate drug sample was reported in different blends. UV spectrophotometric study of drugs and solubilizers indicated no drug-solubilizer interference at 368 nm. Different blends of solubilizers were prepared by varying their concentrations. Out of these prepared blends, blend V, blend O and blend C were selected on the basis of the drug solubility at 80-90. Different solid dispersions were prepared with different drug and solubilizers ratios. One of three trail batches of solid dispersions were selected for comparative dissolution studies. The formulated solid dispersions were compared with marketed tablet (tablet powder) and pure drug. **Summary and Conclusion:** The main objective of the present study is to explore the concept of mixed solvency to formulate the solid dispersion of model drug, amlodipine besylate and also to propose mixed solvency concept as a tool to overcome the situation of limiting resources to increase solubility of poorly soluble substances. The drug content and drug release studies were assessed. Based on the above findings, it may be concluded that the solubility and release of a poorly water-soluble drug can be enhanced using various

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solid solubilizers by the application of mixed solvency concept.

Key words: Amlodipine besylate, bioavailability, mixed solvency concept, solid dispersion, solubility

INTRODUCTION

The most common, convenient, and simplest method of administering medication is through oral route. Oral solid dosage forms have a number of advantages over other forms of orally administered dose formulations, including exact dosage, less volume, improved stability, and ease of production. The physicochemical characteristics of the medication are impacted by the excipients used in formation of solid oral dosage forms. The major barriers to the biological performance of poorly water-soluble (PWS) medications are their poor solubility and dissolution rate. The solid dispersion technique improves the dissolution rate of less water-soluble drugs and includes several applications. The rate of absorption and total bioavailability of less water- soluble drugs are improve the solid dispersion can be prepared by common methods like solvent evaporation, melting, and fusion-solvent evaporation methods. They help in decreasing the drug particle size, increase drug wettability, create porous systems, and decrease drug crystallinity, Solid dispersion (SD) is one of the most promising methods for increasing drug solubility. Mixtures with at least two components an API and a hydrophilic carrier are referred to as SDs. In this system, the hydrophilic carrier matrix in which the API is disseminated is solid. SDs have been prepared using a variety of techniques, including ball milling, hot-melt extrusion, spray-drying, precipitation, and solvent evaporation.[1-3]

MIXED SOLVENCY CONCEPT

In current scenario, it is difficult to overcome solubility problem in formulation development of the drug. The less water solubility of drugs causes various challenges for developing formulations and use of harmful organic solvents produces toxicity. Hence, this problem is overcome by the mixed solvency concept proposed by Dr. R. K. Maheshwari in 2009 because one of the numerous benefits of the mixed solvency concept is that it lessens the risk of using hazardous and damaging organic solvents because it is a safe and environmentally friendly solution. In addition, it provides the anticipated improvement in drug solubility, potentially increasing the possible drug load. Combining several excipients is likely to result in additive and synergistic solubilizer effects, which has the benefit of lowering the toxicities. Large quantity of single solubilizer may be harmful to humans when used to increase drug solubility to the desired level. However, the problem of toxicity can be overcome by combining many excipients in safe and lower quantities. The mixed solvency approach has been used to study a wide variety of medications for solubility enhancement.[4-18]

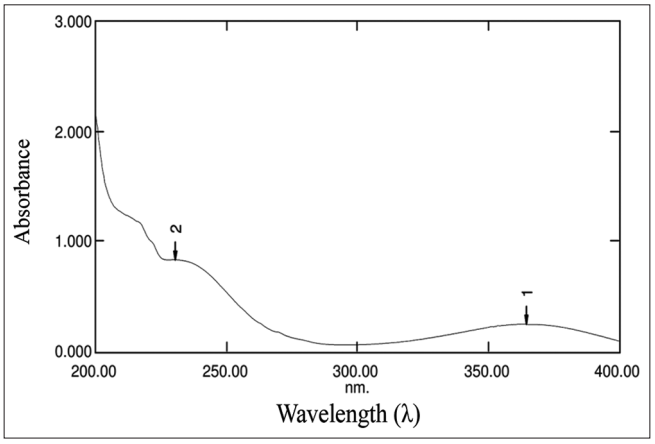

Figure 1: Ultraviolet spectra of amlodipine besylate in D.M. water

CHEMICALS AND REAGENTS

A gift sample of amlodipine besylate was received from MCW Healthcare Private Limited, Indore. Other solubilizers such as sodium benzoate, sodium acetate, sodium citrate, sodium caprylate, poloxamer 407, l-lysine, β-cyclodextrins, and niacinamide used were of analytical grade.

DRUG CHARACTERIZATION

UV spectrophotometric analysis in D.M. water

100 mg of amlodipine besylate drug was weighed accurately and transferred into a 1000 mL volumetric flask. Then, 700 mL of D.M. water was added to it and the flask was shaken to dissolve the drug completely. After that, the volume was made up to 1000 mL with D.M. water to obtain a solution of 100 µg/mL. Then, 10 mL of solution was pipetted out from the stock solution into a 50 mL volumetric flask, and the volume was made up to 50 mL with D.M. water to obtain a solution of 20 µg/mL. The resulting solution was scanned between 200–400 nm on Shimadzu-1700 UV spectrophotometer against D.M. water. The spectrum is displayed in Figure 1. The drug showed peaks at 231 nm and 368 nm. The peak at 368 nm was selected for further studies to avoid interference with solubilizers. This peak was similar as reported peak in the literature.

Melting range determination

The melting range of the drug was determined using open capillary method. The drug sample was filled in the capillary and the melting range was determined by analogue melting test apparatus. The melting range of drug sample was found

Table 1: Absorbance data for calibration curve of amlodipine besylate in D.M water at 368 nm

S. No.	Concentration (µg/mL)	Absorbance (mean±SD) (*n*=3)
1	0	0
2	20	0.217±0.0020
3	40	0.438±0.0010
4	60	0.632±0.0015
5	80	0.832±0.0032
6	100	1.016±0.0049

Table 2: Absorbance data for calibration curve of amlodipine besylate in 0.1 N HCl at 368 nm

S. no.	Concentration (µg/mL)	Absorbance (mean±SD) (*n*=3)
1	0	0
2	20	0.225±0.0030
3	40	0.444±0.0041
4	60	0.643±0.0032
5	80	0.858±0.0020
6	100	1.051±0.0036

to be 200–202°C which was similar to the value reported in the literature.

PREFORMULATION STUDIES

Preparation of calibration curve of amlodipine besylate in D.M. water

100 mg of amlodipine besylate dug was weighed accurately and transferred into a 1000 mL volumetric flask. Then, 700 mL of D.M. water was added and the flask was shaken to dissolve the drug completely. After that, the volume was made up to 1000 mL with D.M. water to obtain a solution of 100 µg/mL. Appropriate dilutions were made from stock solution with D.M. water to obtain standard solution of concentrations 20, 40, 60, 80, and 100 µg/mL. The resulting solution was scanned at 368 nm on Shimadzu-1700 UV spectrophotometer against the respective reagent blank. The data are written down in Table 1.

Preparation of calibration curve of amlodipine besylate in 0.1 N HCl

100 mg of amlodipine besylate drug was weighed accurately and transferred into a 1000 mL volumetric flask. Then, a sufficient quantity of 0.1N HCl was added and the flask was shaken to dissolve the drug completely. After that, the volume was made up to 1000 ml with 0.1 N HCl to obtain a solution of 100 µg/ml. Appropriate dilutions were made from stock solution with 0.1N HCl to obtain standard solution of concentration 20, 40, 60, 80, and 100 µg/ml. The resulting solution was scanned at 368 nm on Shimadzu-1700 UV spectrophotometer against the respective reagent blanks, the absorbance of the resulting drug solutions was observed. The data are written down in Table 2.

Determination of approximate solubility of drug in different blends AT 80–90°C

Preparation of blends

On the basis of a review of mixed solvency concept initiatives, some solid solubilizers were screened. For blend 1, sodium benzoate (1 g), sodium citrate (1 g), and sodium acetate (1 g) were taken in 10 mL of volumetric flask and approximately 8 mL of D.M. water was added to it and vigorous shaking was done until a clear solution was obtained. Then, volume was made with D.M. water up to 10 mL. Then pH of blend 1 was determined using pH papers. Some procedure was followed for other blends.

Procedure for approximate solubility study

To a 5 mL vial, 1 mL blend was taken and 5 mg drug was added to it. Using water bath, the vial was heated at temperature maintained at 80–90°C. Shaking was done until the drug was dissolved. Again 5 mg drug was added and the vial was shaken (keeping the temperature 80–90°C) to dissolve the drug. The same procedure was repeated until a suspension was obtained. A similar procedure was followed for all the blends and the approximate solubilities of the drug were determined in each blend. The data are written down in Table 3.

Determination of partition coefficient

The partition coefficient assesses the drug lipophilicity and its ability to cross cell membranes. The partition coefficient was estimated by determining the difference concentrations of the drug in D.M. water and octanol, and log value of partition coefficient was used to derive log P. In a separating funnel combination of 20 mL octanol and 20 mL D.M. water was taken. To this 20mg drug was added. The separating funnel was shaken for 30–40 min. After shaking the observation was done and it was found that drug was not fully dissolved. Then, 10–10 mL of both octanol and D.M. water was again added to the funnel followed by 30 min shaking. After 30 min, the drug was fully dissolved. Both the aqueous and organic phase were separated and they were taken out in different beakers. Then, aqueous layer was taken and its absorbance was measured in UV spectrophotometer at 368 nm. The absorbance value was kept in regression equation and the concentration was found out. Using concentration value of aqueous phase, the concentration of octanol phase was found out. The concentration of drug in aqueous phase it was found to be 15.91 mg/30 mL and octanol was found out to be 4.09 mg/30 mL.

Table 3: Results of approximate solubility studies of amlodipine besylate in different blends at temperature 80–90°C

S. No.	Blend	Blend composition (%w/v)	pH	Approximate solubility (mg/mL) at 80–90°C
1	A	10% Sodium benzoate 10% Sodium citrate 10% Sodium acetate 5% Poloxamer-407	7	60
2	B	10% Sodium benzoate 10% Sodium citrate 10% Sodium acetate 5% Sodium caprylate	7	200
3	C	20% Sodium benzoate 10% Sodium citrate 10% Sodium acetate	7	More than 1000
4	D	10% Sodium benzoate 10% Sodium acetate 10% Sodium citrate 10% Poloxamer-407	7	150
5	E	10% Sodium benzoate 5% Sodium citrate 5% Sodium acetate 5% Sodium caprylate	7	155
6	F	10% Sodium benzoate 10% Sodium acetate 10% β – Cyclodextrin 10% L-lysine	7	60
7	G	10% Sodium benzoate 10% Sodium acetate 10% L-lysine 10% Niacinamide	7	55
8	H	10% Sodium benzoate 10% Sodium citrate 5% Sodium acetate 5% Poloxamer-407 10% L-lysine	7	65
9	I	5% Sodium caprylate 5% L-lysine 10% Poloxamer-407 10% Niacinamide 10% β – Cyclodextrin	8	240
10	J	10% Sodium acetate 10% Poloxamer-407 10% Sodium citrate 10% Niacinamide	7	60
11	K	10% Sodium benzoate 5% Sodium caprylate 5% Sodium citrate 5% L-lysine 10% Niacinamide	8	65
12	L	10% Sodium benzoate 10% L-lysine 10% Niacinamide 5% β – Cyclodextrin	7	80

(Contd...)

Table 3: *(Continued)*

S. No.	Blend	Blend composition (%w/v)	pH	Approximate solubility (mg/mL) at 80–90°C
13	M	5% β – Cyclodextrin 10% Niacinamide 10% L-lysine 5% Sodium caprylate	7	60
14	N	10% Sodium benzoate 5% Sodium caprylate 5% Sodium acetate 10% Niacinamide 5% L-lysine	5	60
15	O	20% Sodium benzoate 20% Sodium citrate 20% Sodium acetate	7	180
16	P	10% Sodium benzoate 10% Sodium acetate 10% L-lysine 10% Niacinamide 10% Sodium citrate	7	100
17	Q	10% Sodium benzoate 5% Sodium caprylate 5% Sodium acetate 10% Sodium citrate	7	150
18	R	5% Sodium caprylate 5% L-lysine 5% Poloxamer-407 10% Niacinamide 10% β – Cyclodextrin	7	250
19	S	10% Sodium benzoate 10% Sodium acetate 10% L-lysine 10% Niacinamide 10% Sodium citrate 10% Sodium caprylate	8	130
20	T	5% Sodium caprylate 2.5% β – Cyclodextrin 2.5% Sodium citrate 2.5% Sodium acetate	7	160
21	U	5% Sodium caprylate 5% Sodium benzoate 5% L-lysine 5% Poloxamer-407	7	140
22	V	10% Sodium benzoate 10% Sodium citrate 10% Sodium acetate	7	150

Determination of interference of solubilizers in the spectrophotometrie estimation of amlodipine besylate

For the interference investigation, various solubilizers, including sodium caprylate, sodium citrate, sodium benzoate, sodium acetate, niacinamide, poloxamer-407, sodium acetate, and beta cyclodextrin, were utilized. Drug standard solutions in both the solubilizer-free and solubilizers-containing D.M. water were produced to measure UV spectrophotometric interference. To make a stock solution of the drug (100 µg/mL), 50 mg of the drug was precisely weighed, dissolved in 450 ml of D.M. water, and then heated at 50–60°C with vigorous shaking. The solution was cooled to room temperature and then dilution was done up to the mark with D.M. water. Then, D.M. water was used to dilute 10 ml of the aforementioned solution to a final volume of 50 ml. This results in a 20 µg/mL solution. In a similar manner, solutions of excipients were created by combining 100 mg of

Table 4: Drug solubilizers interference studies in the spectrophotometric estimation of amlodipine besylate

Drug	Solubilizers	Drug conc.(µg/mL)	Solubilizers (µg/mL)	Wavelength (nm)	Absorbance against water
Amlodipine besylate	-	20	-	368	0.217
Amlodipine besylate	Sodium benzoate	20	100	368	0.216
Amlodipine besylate	Sodium acetate	20	100	368	0.211
Amlodipine besylate	Sodium citrate	20	100	368	0.213
Amlodipine besylate	Sodium caprylate	20	100	368	0.218
Amlodipine besylate	L-lysine	20	100	368	0.212
Amlodipine besylate	Poloxamer-407	20	100	368	0.219
Amlodipine besylate	β – Cyclodextrin	20	100	368	0.215
Amlodipine besylate	Niacinamide	20	100	368	0.212

Table 5: Results of approximate solubility of amlodipine besylate in D.M. water at 80–90ºC

Solvent	Solubility (mg/mL)
Demineralized water	255 mg/5 mL (51 mg/mL)

each solubilizer with 50 mL of D.M. water to create a volume that had 1000 µg/mL of stock solution. A 100 mL volumetric flask was filled with D.M. water to a volume of 100 mL after adding 20 mL of the drug stock solution (100 µg/mL) and 10 mL of the excipient stock solution (1000 µg/mL) from the aforementioned solution. The results of the absorbance measurements made against water at 368 nm are displayed in the Table 4. The absorbances of drug solutions and those in the presence of solubilizers were nearly same. Therefore, it was clear that the solubilizers were not interfering with the drug at 368 nm in UV spectrophotometric examination.

Determination of approximate solubility of amlodipine besylate in d.m. water and selected blends at temperature 80–90°C

Procedure for approximate solubility in D.M. water

Amlodipine besylate approximate solubility was assessed in D.M. water. To a test tube 5 mL D.M. water was taken and 5 mg of drug was added to it using water bath, the test tube was heated at temperature maintained at 80–90°C. Shaking was done until the drug was dissolved. Again 5 mg drug was added and the test tube was shaken (keeping the temperature 80–90ºC) to dissolve the drug. The same procedure was repeated until a suspension was obtained. The results of approximate solubility are mentioned in Table 5.

Procedure for approximate solubility in blends

Amlodipine besylate approximate solubility was assessed in selected blends. To a test tube 1 ml blend was taken and 5 mg drug was added to it. Using water bath, the test tube was heated at temperature maintained at 80–90ºC.

Table 6: Results of approximate solubility of amlodipine besylate in selected blends at 80–90ºC

Blend	Blend composition	Solubility (mg/mL)
C	20% Sodium benzoate 10% Sodium citrate 10% Sodium acetate	1000
V	10% Sodium benzoate 10% Sodium citrate 10% Sodium acetate	150
O	20% Sodium benzoate 20% Sodium citrate 20% Sodium acetate	180

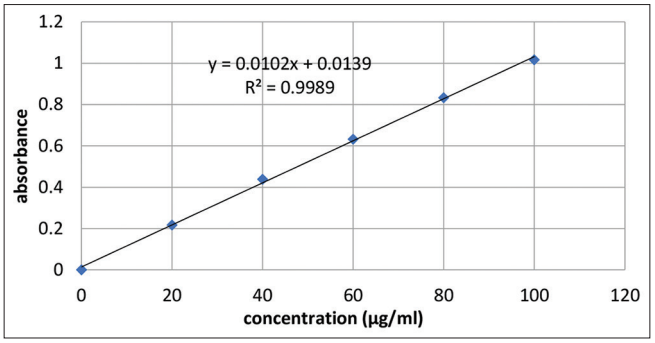

Figure 2: Calibration curve of amlodipine besylate in D.M. water

Shaking was done until the drug was dissolved. Again 5 mg drug was added and the test tube was shaken (keeping the temperature 80–90ºC) to dissolve the drug. The same procedure was repeated until a suspension was obtained. A similar procedure was followed for all the selected blends and the approximate solubilities of the drug were determined in each blend. The data are written down in Table 6.

Drug excipient interaction studies

Physical stability studies between drug and solubilizers were carried out. The drugs and solubilizers were mixed in a separate clean glass vial in a 1:1 ratio, which was then properly sealed

Table 7: Observations of drug solubilizers incompatibility studies

S. No.	Drug solubilizer (1:1 blend)	Initial	Refrigerated condition (2-8°C)					Room temperature				
1	Amlodipine besylate	WP	1	2	3	4	5	1	2	3	4	5
2	Amlodipine besylate+Sodium benzoate	WP	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
3	Amlodipine besylate+Sodium acetate	WP	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
4	Amlodipine besylate+Sodium citrate	WP	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
5	Amlodipine besylate+Sodium caprylate	WP	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
6	Amlodipine besylate+L-lysine	WP	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
7	Amlodipine besylate+Poloxamer-407	WP	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
8	Amlodipine besylate +β – Cyclodextrin	WP	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
9	Amlodipine besylate+Niacinamide	WP	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

WP: White powder, NC: No change

and kept undisturbed under different temperature conditions for a month at room temperature and in the refrigerator. After every week (for 5 weeks), the vials were checked, and the material was noticed for any change in their physical appearance. The observations are presented in Table 7.

FORMULATION OF SOLID DISPERSIONS OF AMLODIPINE BESYLATE BY APPLICATION OF MIXED SOLVENCY CONCEPT

The formula for solid dispersion was determined in accordance with the findings of investigations into the drug's solubility in various blends. To create the solid dispersions of drug, three specific blends (blend C, blend V, and blend O) having adequate solubility were selected.

Procedure for formulation of solid dispersion

To prepare the solid dispersion (SDV) using blend V in 1:3 ratios, accurately 1 g of each solubilizer (sodium acetate, sodium benzoate, sodium citrate) were weighed and taken in a 10 ml volumetric flask. To it 8 mL of D.M. water was added and shaken well until a clear solution was obtained. Then, volume was made up to 10 mL using D.M. water. The obtained solution was transferred to china dish. One gram of amlodipine besylate drug was added and heating was done on water bath at 80–90°C so as to facilitate the dissolution of drug. Then, the removal of water from clear solution was started by use of boiling water bath with continuous heating with glass rod. After sometime, a wet mass was formed thus indicating the formation of solid dispersion (wet). The wet solid dispersion thus obtained was spread on the watch glass, and the watch glass was kept in a hot air oven maintained at 50 ± 2°C so that remaining moisture could also be evaporated out and a constant weight with no further weight loss due to evaporation could be obtained. The same procedure was used to prepare a solid dispersion in the ratio of SDC (1:4) and SDO (1:6), using appropriate quantities of solubilizers. Solid dispersions were shifted through sieve no. 100 after converting them in powder state using pestle mortars. Then, they were stored in air tight containers. Table 8 illustrates the composition of solid dispersions of amlodipine besylate.

Table 8: Composition of solid dispersion of amlodipine besylate

S. No.	Drug: solubilizers	Quantity taken (g)			
		SA	SB	SC	D
1	SDO (1:6)	2	2	2	1
2	SDC (1:4)	1	2	1	1
3	SDV (1:3)	1	1	1	1

SB: Sodium benzoate, SA: Sodium acetate, SC: Sodium citrate, D: Drug

Table 9: Composition of physical mixtures of amlodipine besylate

S. No.	Drug: solubilizers	Quantity taken (gm)			
		SA	SB	SC	D
1	1:6	2	2	2	1
2	1:4	1	2	1	1
3	1:3	1	1	1	1

SB: Sodium benzoate, SA: Sodium acetate, SC: Sodium citrate, D: Drug

Procedure for formulation of physical mixture

To prepare the solid dispersion using blend V (PMV) in (1:3) ratios, accurately weighed 1 g of each solubilizer (sodium acetate, sodium benzoate, and sodium citrate) and drug (amlodipine besylate) were used. This mixture was mixed using the geometric dilution technique and was triturated using glass pestle mortar for about 15 min. After complete mixing, the powder mass was passed through sieve no.100 and was finally stored in an airtight glass bottle. The same procedure

was used to prepare a physical mixture in the ratio of PMC (1:4) and PMO (1:6), using appropriate quantities of solubilizers. All physical mixtures were shifted through sieve no. 100. Then, they were stored in air tight containers. Table 9 illustrates the composition of physical mixtures of amlodipine besylate.

EVALUATION OF SOLID DISPERSION AND PHYSICAL MIXTURE

Determination of drug content of solid dispersion and physical mixture

To determine the drug content of powdered solid dispersion or physical mixture, powder equivalent to 20 mg drug was taken in a 1000 ml volumetric flask. About 800 ml of 0.1N HCl was added to the volumetric flask, and the flask was shaken continuously for 30 min to get a clear solution. Then, the volume was made up to 1000 ml with 0.1N HCl. The absorbances of solutions were recorded at 368 nm in a UV spectrophotometer (Shimadzu-1700) against 0.1N HCl as blank. Results of drug content are mentioned in Table 10.

Table 10: Drug content of solid dispersions and physical mixtures

S. No.	Drug: solubilizers	Amount of drug present in powder analysed (20 mg)		Present drug estimated %	
		SD	PM	SD	PM
1	1:6	19.73	19.60	98.65	98.00
2	1:4	19.56	19.32	97.80	96.60
3	1:3	19.48	19.21	97.40	96.05

SD: Solid dispersion, PM: Physical mixture

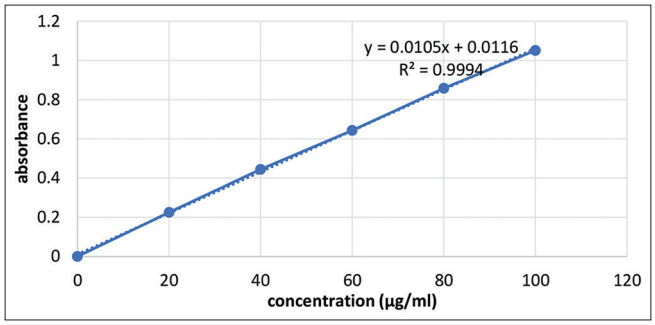

Figure 3: Calibration curve of amlodipine besylate in 0.1N HCl water

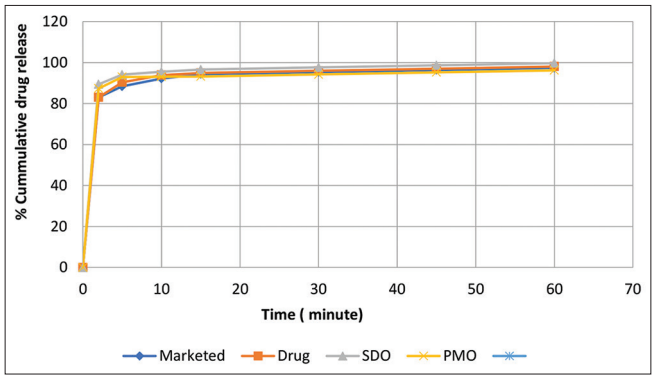

Figure 4: Comparative dissolution study in 0.1N HCl of marketed tablet (tablet powder), pure drug, SDO (1:6), PMO (1:6)

Dissolution profile

Dissolution profile of marketed tablet (tablet powder) and pure drug

- The dissolution profile of marketed tablet, Amlokind-5 was studied and compared. Five tablets were taken. All the tablets were weighed and the average weight was calculated. The tablets were triturated to get a fine powder and powder was sieved through sieve no. 100. From the sieved powder, tablet powder containing 20 mg of drug was weighed and its dissolution rate study was done.
- For the dissolution rate study of pure drug, excess amount of pure drug was taken and sieved through sieve no. 100. From the sieved pure drug, 20 mg was weighed and remaining drug was stored in an air tight container for further studies. The above weighed 20 mg pure drug was used for dissolution rate study.

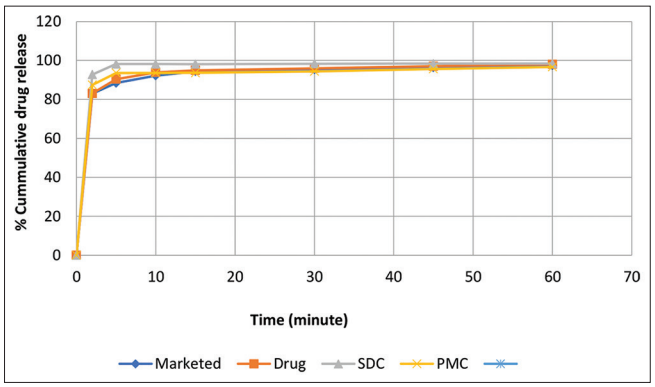

Figure 5: Comparative dissolution study in 0.1N HCl of marketed tablet (tablet powder), pure drug, SDC (1:4), PMC (1:4)

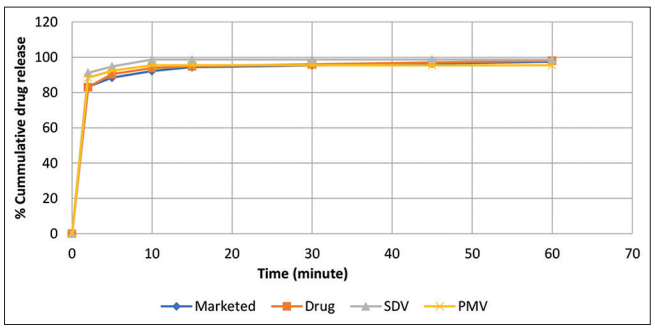

Figure 6: Comparative dissolution study in 0.1N HCl of marketed tablet (tablet powder), pure drug, SDV (1:3), PMV (1:3)

Table 11: Data for dissolution study of marketed tablet (tablet powder), solid dispersion (1:6), physical mixture (1:6), and pure drug in 0.1N HCl

Time (min)	% Cumulative drug release			
	Marketed tablet (tablet powder)	Pure drug	SDO (1:6)	PMO (1:6)
2	83.03	83.06	89.39	87.35
5	88.40	90.40	94.12	93.01
10	92.18	93.89	95.49	93.12
15	94.39	94.93	96.55	93.21
30	95.40	95.97	97.61	94.22
45	96.42	97.02	998.67	95.23
60	97.44	98.06	99.73	96.23

Table 12: Data for dissolution study of marketed tablet (tablet powder), solid dispersion (1:4), physical mixture (1:4), and pure drug in 0.1N HCl

Time (min)	% Cumulative drug release			
	Marketed tablet (tablet powder)	Pure drug	SDC (1:4)	PMC (1:4)
2	83.03	83.06	92.77	87.42
5	88.40	90.40	98.16	93.60
10	92.18	93.89	98.16	93.61
15	94.39	94.93	98.19	93.63
30	95.40	95.97	98.22	94.40
45	96.42	97.02	98.30	95.64
60	97.44	98.06	98.36	96.65

Table 13: Data for dissolution study of marketed tablet (tablet powder), solid dispersion (1:3), physical mixture (1:3), and pure drug in 0.1N HCl

Time (min)	% Cumulative drug release			
	Marketed tablet (Tablet powder)	Pure drug	SDV (1:3)	PMV (1:3)
2	83.03	83.06	91.19	88.39
5	88.40	90.40	94.73	92.33
10	92.18	93.89	98.70	95.47
15	94.39	94.93	98.71	95.49
30	95.40	95.97	98.72	95.43
45	96.42	97.02	98.73	95.36
60	97.44	98.06	98.73	95.43

- The condition and equipment used for the dissolution rate study were as follows: U.S.P. XXIV (Type II) dissolution test apparatus with 0.1N HCl as dissolution media, and the paddle rotation speed was kept at 100 rpm at 37 ± 0.5°C in 900 ml of media 0.1N HCl. After 2 min, 10 mL sample was withdrawn from dissolution media for analysis, and an equal quantity of 0.1 N HCl was replaced in dissolution medium. A similar procedure was performed again after different time intervals. Collected sample solutions were analyzed by measuring the absorbances at 368nm. After appropriate dilutions with 0.1N HCl.

Dissolution profile of solid dispersion and physical mixture

Solid dispersion and physical mixture of amlodipine besylate equivalent to 20 mg were tested in dissolution rate studies using U.S.P. XXIV (Type II) dissolution test apparatus with 0.1N HCl as dissolution media, and the paddle rotation speed was kept at 100 rpm at 37 ± 0.5°C in 900 ml of media. After 2 min, 10 ml sample was withdrawn from dissolution media for analysis, and an equal quantity of 0.1N HCl was replaced in dissolution medium. A similar procedure was performed again after different time intervals. Collected sample solutions were analyzed by measuring the absorbances at 368 nm after appropriate dilutions with 0.1N HCl solution. Calculations for the amount of drug release were done using respective regression equations and the results of the dissolution studies are shown in Tables 11-13.

SUMMARY AND CONCLUSION

The main objective of the present study is to explore the concept of mixed solvency to formulate the solid dispersion of model drug, amlodipine besylate and also to propose mixed solvency concept as a tool to overcome the situation of limiting resources to increase solubility of poorly soluble substances.[19-22]

As per mixed solvency concept, each and every substance present on earth has solubilizing power. A concentrated aqueous solution containing various water-soluble substances may act as good solvent for PWS drugs. Such concentrated solution may show synergistic or additive solubilizing action of for a particular solute. Conventional dosage forms such as capsules and tablets can be prepared from this solid dispersion by selecting suitable excipients. Solid dispersion formulation prepared from the mixed solvency concept is a promising tool for the enhancement of bioavailability of drug. Amlodipine besylate is a calcium channel blocker. The amlodipine besylate used for the preparation of solid dispersion was characterized and identified by UV spectrophotometric analysis and melting range determination. The observed values were in accordance with the reported values in the literatures. For pre-formulation studies, the solubility studies of the drug were done in different blends. Furthermore, calibration curves in water and 0.1N HCl were prepared. Interaction studies of drug-solubilizers have shown no interaction and incompatibility between drugs and solubilizers. Solubility of amlodipine besylate drug sample was reported in different blends. UV spectrophotometric study of drugs and solubilizers indicated no drug-solubilizer interference at 368 nm. Different blends

of solubilizers were prepared by varying their concentrations. Out of these prepared blends, blend V, blend O, and blend C were selected on the basis of the drug solubility at 80–90 □. Different solid dispersions were prepared with different drug and solubilizers ratios. One of three trail batches of solid dispersions were selected for comparative dissolution studies. The formulated solid dispersions were compared with marketed tablet (tablet powder) and pure drug. The drug content and drug release studies were assessed. Based on the above findings, it may be concluded that the solubility and release of a PWS drug can be enhanced using various solid solubilizers by the application of mixed solvency concept. The principle of mixed solvency was successfully employed in formulating the fast release solid dispersion, formulation of PWS drug amlodipine besylate. In this study, there was no involvement of organic solvents to prepare formulation of solid dispersions because higher costs and toxicity due to residual solvents are the major disadvantages of organic-solvents. The present study demonstrates the application of the principle of mixed solvency concept to solve the problems of the above-mentioned organic solvent-related disadvantages and also to increase the solubility of the drug with increased drug release. It concluded that toxic organic solvent can be replaced by safe and economic solid solubilizers (solid additives).

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