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Research Article

Novel Application of Mixed Solvency Concept to Develop and Formulate Dry Powder Injection for Reconstitution of a Poorly Water Soluble Drug, Amlodipine Besylate and their Evaluations

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Abstract

In the recent generation of pharmaceutical research, it has been observed that many newly designed and discovered drug products have less water solubility. Thus, leading to difficulties in several developmental, manufacturing and administrative processes. Furthermore, the clinical trials of these drugs have witnessed a great failure due to their poor pharmacokinetics. The lineup of our research work was promotion of mixed solvency concept by formulating the dry powder injection for reconstitution of poorly water-soluble drug amlodipine besylate by decreasing the solubilisers concentration in small proportion for expected synergistic enhancement of drug solubility in water. Solubilisers used are sodium benzoate, sodium caprylate, PVPK-25, sodium citrate, niacinamide, poloxamer 407, sodium acetate, L-arginine, benzoic acid, β -cyclodextrin and lysine hydrochloride to developed the dry powder injection for reconstitution of amlodipine besylate. The reconstitution time of amlodipine besylate injections were found 58 sec, 36 sec and 1 min 10 sec in selected blends. This drug is slightly soluble in water, and it comes in various forms, including tablets and other oral dosage forms. However, no amlodipine besylate dry powder injection or ready-made injections are currently available in the market. Dry powder injection for reconstitution of amlodipine besylate was formulated successfully and mixed solvency concept has been successfully employed.

Keywords: Mixed solvency concept, Amlodipine besylate, Dry powder injection for reconstitution, Solubilisers, Solubility.

INTRODUCTION

One of the difficult tasks that become a problem in the formulation development of a drug with low aqueous solubility is solubility enhancement. The low water solubility of drugs frequently presents substantial challenges in developing formulations with sufficiently high bioavailability, prohibiting effective drug usage. Dr. R.K. Maheshwari "mixed solvency concept" in 2009. Mixed solvency concept could be applied as a tool to overcome the solubility challenges in present research. It has several advantages over the other methods of solubilisation. Advantages of mixed solvency are many which include - It being a safe and ecofriendly method, reduces the risk for use

of toxic and harmful organic solvents. Also, it offers the expected enhancement in drug solubility and therefore enhanced achievable drug load. The reduction in individual concentration of each solid solubiliser resulting in reduction in individual toxic effects. It does not need chemical modification of hydrophobic drugs as in cases of complexation or derivatization or related toxicity. It is applicable in many pharmaceutical areas such as development of formulation, analysis of drug by UV spectra or TLC analysis or extraction of drug in Pharmacognosy field etc. A vast number of poorly soluble drugs have had their formulations developed using the mixed solvency approach. Followings are the formulations made by using mixed solvency concept.¹⁻⁴¹

Formulations made by using mixed solvency concept

Oily injection, Aqueous injection, Dry powder injection

Syrup(in solution form), Topical solutions

Solid dispersion, Lquisolid system, Liquid oral, Gel based forms

Fast dissolving oral films, Vaginal films, Microsphere, Niosomes, SEDDS

MATERIALS AND METHODS

Amlodipine besylate drug was obtained as a gift sample from MCW Healthcare Private Limited, Indore. Milli-Q water was used in this study. Other chemicals used were of analytical grade.

• UV SPECTROPHOTOMETRIC ANALYSIS OF DRUG, AMLODIPINE BESYLATE

In a volumetric flask with a capacity of 500 ml, 50 mg of amlodipine besylate (accurately weighed) and 400 ml of

milli-Q water (Type 1 ultrapure water) were taken. The flask was then shaken thoroughly to dissolve the drug. The volume was then made up to 500 ml with Milli-Q water to form a stock solution with a concentration of 100 µg/ml. To obtain a dilution of 20 µg/ml concentration, a 10 ml stock solution was diluted up to 50 ml. The resultant solution was scanned on a Shimadzu-1700 UV spectrophotometer between 200 and 400 nm against Milli-Q water. Figure 1 illustrates the spectrum.

Figure 1: U.V. Spectra of amlodipine besylate in Milli-Q water

• MELTING POINT DETERMINATION

The open capillary technique was used to determine the drug's melting point. The melting range of the drug sample was measured using the Analog melting point test apparatus after it was packed in the capillary. The melting point range of the drug sample was 202-207 °C, similar to the literature value.

• PREPARATION OF CALIBRATION CURVE OF DRUG, AMLODIPINE BESYLATE IN WATER (MILLI-Q)

Fifty milligram of amlodipine besylate drug was weighed and transferred to a 10 ml volumetric flask. To dissolve the drug (amlodipine besylate), 30 percent sodium caprylate solution (approximately 8 ml) was added and volume made up to 10 ml to achieve the resulting 5000 µg/ml solution (stock solution). Appropriate dilutions were made from stock solution with Milli-Q water in concentration range of 20-100 µg/ml. Using a double beam UV visible spectrophotometer (Shimadzu 1700) at 368 nm against the reagent blanks respectively, the absorbance of the resulting drug solutions were observed. The data is recorded in table 1 and described graphically in fig 2.

Table 1: Absorbance data for calibration curve of amlodipine besylate in water (Milli-Q)

S.No.	Concentration (µg/ml)	Absorbance (mean ± S.D.) (n=3)
1	0	0
2	20	0.215 ± 0.0097
3	40	0.427 ± 0.0130
4	60	0.631 ± 0.0132
5	80	0.850 ± 0.0170
6	100	1.064 ± 0.0576

Figure 2: Calibration curve of amlodipine besylate in Milli-Q water at 368 nm

• APPROXIMATE SOLUBILITY DETERMINATION IN VARIOUS AQUEOUS SOLUTIONS OF SOLID SOLUBILISERS (MIXED BLENDS)

For approximate solubility determination of drug (amlodipine besylate) in Milli-Q water, 1 ml of blend was taken in 10 ml volumetric flask then 5 mg of drug amlodipine was added to it and this flask was shaken for about 15-20 minutes by vortex shaking (Remi cm 101 plus). If the drug was entirely dissolved and give a clear solution, again 5 mg of drug was added to the flask (volumetric) and the flask was shaken for about 15-20 minutes to get it dissolved. The same method was repeated until a turbid solution was obtained even after 15-20 minutes shaking. For each blend the same method was performed. The results of approximate solubility of amlodipine besylate are shown in Table 2.

Table 2: Results of approximate solubility studies of amlodipine besylate in various aqueous solutions of solubilisers.

S. No.	Blends	The composition of blends (w/v)	Approximate solubility (mg/ml)
1.	B-A	Sodium benzoate- 5% Sodium caprylate- 10% Lysine HCl- 5% PVP K-25- 5%	40
2.	B-B	Sodium benzoate- 5% Sodium caprylate- 5% Niacinamide- 2.5% β -cyclodextrin- 2.5% Sodium acetate- 5%	15
3.	B-C	Sodium benzoate- 5% Sodium acetate- 5% Sodium caprylate- 5% Poloxamer 407- 5% PVP K-25- 5%	30
4.	B-D	Sodium caprylate- 5% Sodium acetate- 5% Sodium benzoate- 5% PVP K-25- 5%	30
5.	B-E	Sodium caprylate- 5% Sodium citrate- 5% Niacinamide- 2.5% Lysine HCl- 2.5% Sodium benzoate- 5% PVP K-25- 5%	30
6.	B-F	L-Arginine- 5% Poloxamer 407- 5% Sodium citrate- 5%	15
7.	B-G	L-Arginine- 5% Poloxamer 407- 5% Sodium benzoate- 5% PVP K-25- 5%	35
8.	B-H	L-Arginine- 5% Sodium citrate- 5% Sodium benzoate- 5% Poloxamer 407- 5% Sodium acetate- 5%	25
9.	B-I	Sodium benzoate- 5% Poloxamer 407- 5% L-Arginine- 5% PVP K-25- 5% Benzoic acid- 5%	30

10	B-J	Sodium benzoate- 5% Sodium caprylate- 5% Niacinamide- 2.5% β -cyclodextrin- 2.5% Sodium acetate- 5%	15
11	B-K	Sodium benzoate- 5% Sodium caprylate- 10% Poloxamer 407- 5% Lysine HCl- 5%	25
12	B-L	Lysine HCl- 5% PVP K-25- 5% Sodium caprylate- 10%	35
13	B-M	Poloxamer 407- 10% Lysine HCl- 5% Sodium caprylate- 10%	25
14	B-N	β -cyclodextrin- 5% Poloxamer 407- 5% Lysine HCl- 5% Sodium caprylate- 10%	10
15	B-O	Sodium benzoate- 5% Sodium caprylate- 5% Sodium citrate- 5% L-Arginine- 10% Lysine HCl- 10% Poloxamer 407- 5%	30

•DETERMINATION OF EQUILLIBRIUM SOLUBILITY OF DRUG, AMLODIPINE BESYLATE IN MILLI-Q WATER.

In order to find out the equilibrium solubility of drug (amlodipine besylate) in Milli-Q water, excess amount of drug was weighed and added to the vial of capacity 20 ml with Milli-Q water and was capped and sealed with aluminum caps. The vial was shaken for 24 hours on the mechanical bath shaker (SciTech) and was kept untouched for 24 hours. Whatman filter paper (Grade no. 41) was used to filter the drug solution. Aliquot of filtrate was sufficiently diluted with Milli-Q water. The UV-Visible spectrophotometer (Shimadzu 1700) was used to analyze the solution. Then, equilibrium solubility of the drug, amlodipine besylate was calculated by using the calibration curve. The result is presented in Table 3.

Table 3: Equilibrium solubility of drug, Amlodipine besylate, in Milli-Q water

S.No.	Solvent	Solubility
1.	Milli-Q water	0.111 (w/v)

SELECTION OF BLENDS OF SOLUBILISERS FOR DRY POWDER INJECTION FOR RECONSTITUTION

Based on the results of the solubility tests, three blends with solubility of drug (amlodipine besylate) of greater than 15 mg/ml were chosen. Further blend selection was based on the solubility enhancement ratio. Blends B-A, B-D, and B-M were selected on the basis of desired solubility with fewer solubilisers. It was decided to make 10 mg/ml of amlodipine besylate injection using solubilisers. Tables 4, 5 and 6 illustrate the formulations proposed.

Table 4: Formulation DIF1 (Drug injection formulation-1)

S. No.	Ingredients	Formula for 10 mg /1ml	Formula for 50 ml batch
1	Sodium benzoate	50	2.5 gm
2	Sodium caprylate	100	5 gm
3	Lysine HCL	50	2.5 gm
4	PVP K-25	50	2.5 gm
5	Amlodipine besylate	10	0.5 gm

Table 5: Formulation DIF2 (Dry injection formulation-2)

S. No.	Ingredients	Formula for 10 mg /1ml	Formula for 50 ml batch
1	Sodium caprylate	50	2.5 gm
2	Sodium acetate	50	2.5 gm
3	Sodium benzoate	50	2.5 gm
4	PVP K-25	50	2.5 gm
5	Amlodipine besylate	10	0.5 gm

Table 6: Formulation DIF3 (Dry injection formulation-3)

S. No.	Ingredients	Formula for 10 mg /1ml	Formula for 50 ml batch
1	Poloxamer 407	100	5 gm
2	Lysine HCl	50	2.5 gm
3	Sodium caprylate	100	5 gm
4	Amlodipine besylate	10	0.5 gm

• FORMULATION OF DRY POWDER INJECTION FOR RECONSTITUTION

The dry powder injections for reconstitution were prepared in accordance with the formulation details provided in the preceding tables 4, 5 and 6. The process is provided below. All solubilisers were passed through sieve number 80 in order to individually reduce the particle size. All solubilisers and drug were weighed and blended with the aid of pestle and mortar using geometric dilution method. The combined mixture was again mixed manually using plastic bag and then the powder was passed through sieve no 80. The ready mixture was then put in 10 ml vials, then they were capped and sealed.

[Formulations DIF1- 260 mg per vial, DIF2- 210 mg per vial, and DIF3- 260 mg per vial were filled]. Each vial was containing 10 mg of amlodipine besylate.

• EVALUATION OF DRY POWDER INJECTION FOR RECONSTITUTION

The prepared formulations were subjected for various evaluation parameters.

A. DETERMINATION OF DRUG CONTENT OF DRY POWDER INJECTION FORMULATION

To assess the drug content, the 260 mg powder of DIF1 formulation (equivalent to 10 mg drug) was transferred to a 500 ml volumetric flask and about 400 ml Milli-Q water was added and then flask was shaken to solubilise it. After complete dissolution, the volume was made up to 500 ml with Milli-Q water and absorbance of this solution was noted at 368 nm. By using the calibration curve, drug content was determined. The same procedure was repeated with DIF2 (210 mg formulation powder equivalent to 10 mg drug) and DIF3 (260 mg formulation powder equivalent to 10 mg drug) and table 7 shows the outcomes.

Table 7: Drug content of reconstituted injection formulations

Formulation name	Amount of drug (mg)
DIF1	9.787
DIF2	9.925
DIF3	9.925

B. pH STUDY OF RECONSTITUTED INJECTION

The pH of the reconstituted injection was determined using a digital pH meter (Cyber Scan 510, Utech Instruments,

Singapore). Table 8 illustrates the observed results.

Table 8: pH values of reconstituted injection formulations

Formulation name	pH
DIF1	6.51
DIF2	6.72
DIF3	6.54

C. DETERMINATION OF RECONSTITUTION TIME

To determine the reconstitution time, Milli-Q water (1 ml) was used to dissolve the dry injectable formulation for all batches, and the time was recorded to obtain the clear solution. Table 9 shows the results of reconstitution time.

Table 9: Reconstitution times of various formulations

Formulation name	Reconstitution time
DIF1	58 sec
DIF2	36 sec
DIF3	1 min 10 sec

D. CLARITY TESTING OF RECONSTITUTED INJECTION

By visually examining the externally clean vial, the clarity examination of the reconstituted product was carried out and viewed against black and white background. Results of the clarity testing of the reconstituted developed injection formulation are shown in table 10.

Table 10: Results of clarity testing of various reconstituted injections

Formulation name	Clarity
DIF1	Clear
DIF2	Clear
DIF3	Clear

E. THIN LAYER CHROMATOGRAPHIC STUDIES

In order to know the interaction between drug and solubilisers, thin layer chromatography studies were performed. An aluminum support silica gel 60 matrix TLC plate was used. One percent methanolic solution of amlodipine besylate pure drug was prepared and the aqueous solution (1%) of amlodipine besylate in B-A, B-D and B-M were prepared and all were spotted with the aid of capillary tube. Then, the plates were left in air for sufficient

time to dry and then were transferred to a saturated jar with the solvent system containing 12.5 % w/v sodium caprylate and 7.5 % w/v sodium acetate solution (aqueous) as mobile phase.

The mobile phase was allowed to run for about 4.5 cm. Finally, the plates were allowed to air dry and were observed for visualization of spots by UV chamber. The respective R_f values were determined and recorded in table 11.

Table 11: R_f values of amlodipine besylate in TLC study

Solvent system	Adsorbent	R_f value			
		Drug	DIF1	DIF2	DIF3
Sodium caprylate (12.5%) + Sodium acetate (7.5%)	Silica Gel	0.76	0.70	0.73	0.66

Inference- As per the observation of TLC study, there is no significant change in R_f values of amlodipine besylate pure drug and the drug solubilised in blend solutions. From the results of TLC study, it can be concluded that there is no reaction of drug (amlodipine besylate) with solubilisers.

Series of dilutions were done by diluting reconstituted injection of amlodipine besylate (formulation DIF1, DIF2, and DIF3) with different diluents, normal saline (0.9% Sodium chloride) and 5% dextrose solution. The diluted products were observed for any precipitation up to 24 hours. The observations were recorded in Table 12, 13 and 14.

F. DILUTION STUDY OF RECONSTITUTED INJECTION

Table 12: Dilution profile of reconstituted solution of formulation DIF1

Dilution	Time (hrs.)											
	Normal saline solution						5% dextrose solution					
	1	2	4	6	8	24	1	2	4	6	8	24
1:1	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:5	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:10	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:20	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:30	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:40	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:50	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:100	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:500	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑

↑= NO Precipitation, ↓= Precipitation

Table 13: Dilution profile of reconstituted solution of formulation DIF2

Dilution	Time (hrs.)											
	Normal saline solution						5% dextrose solution					
	1	2	4	6	8	24	1	2	4	6	8	24
1:1	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:5	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:10	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:20	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:30	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:40	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:50	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:100	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:500	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑

↑= NO Precipitation, ↓= Precipitation

Table 14: Dilution profile of reconstituted solution of formulation DIF3

Dilution	Time (hrs.)											
	Normal saline solution						5% dextrose solution					
	1	2	4	6	8	24	1	2	4	6	8	24
1:1	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:5	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:10	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:20	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:30	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:40	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:50	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:100	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
1:500	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑

↑= NO Precipitation, ↓= Precipitation

RESULTS AND DISCUSSION

The primary goal of this research work was to facilitate the innovative use of the mixed solvency principle in the formulation of dry powder injection of drugs which are poorly soluble in water, as well as to reduce the harmful effects of solubilisers by minimizing individual solubilisers concentrations those solubilisers used for solubility enhancement.

The drug, amlodipine besylate was chosen for this research work because it is poorly water soluble. To prepare the parenteral preparation (dry powder injection for reconstitution of amlodipine besylate), solubility tests were performed utilizing a variety of physiologically suitable solubilisers.

A sample of the bulk drug (amlodipine besylate) was obtained and characterized using UV, DSC, and melting point studies. The outcomes of the experiments were consistent with those described in official compendia, hence the sample obtained was employed for further research.

In the current study, the amlodipine besylate drug sample was subjected to various characterization parameters. The melting range of the drug was calculated using the open capillary method and found to be 202-207 °C. UV spectrophotometric analysis showed the peak at 368 nm. The characterization result of the drug sample obtained confirmed that it was amlodipine besylate, hence it was used for further research.

The calibration curve of the drug, amlodipine besylate in Milli-Q water was developed during the preformulation studies. The absorbances at 368 nm of solution or pure drug and drug with solubilisers are nearly same therefore no interference was shown by the excipients in the UV visible estimation of drug amlodipine besylate at 368 nm.

Various aqueous solutions of mixed blend solubilisers (sodium benzoate, sodium caprylate, sodium acetate, sodium citrate, β -cyclo dextrin, lysine HCl, poloxamer 407, L-arginine and niacinamide) were used to study the solubility of amlodipine besylate. The approximate solubility of drug in blend-A was 4 percent, in blend-D was 3 percent and in blend-M was 2.5 percent. Over the course of a month, drug-excipient interactions were

studied, and no incompatibility between the drug and the chosen excipients was observed.

Based on the desired solubility, the above three mixed blends were chosen for batch formation for dry powder injection for reconstitution. For development and formulation of dry powder injection for reconstitution of amlodipine besylate, mixed blends containing only solid solubilisers were selected which are based on the solubility studies, these are B-A, B-D and B-M. Formulations were made by geometric dilution method with the help of mortar and pestle and then mixing in plastic bag manually, passed through a sieve no 80 to reduce the particle size. All the developed formulations (DIF1, DIF2 and DIF3) were then subjected to various evaluations; pH of reconstituted injections was found to be physiologically compatible, reconstitution time was found to be 58 sec, 36 sec and 1 min 10 sec respectively. all the developed injection formulations were clear after reconstitution. Prepared formulations did not show any precipitation during dilution studies in different dilution ratios.

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