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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET CONTAINING AMLODIPINE BESYLATE SOLID DISPERSION

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Abstract: The purpose of the present investigation was to increase the solubility and dissolution rate of amlodipine besylate by the preparation of its solid dispersion with cross povidone using solvent evaporation method. Drug polymer interactions were investigated using differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). Surface morphology of solid dispersion particle determined by SEM study. Dissolution rate of solid dispersion was determined in 0.01 N HCl at 75 rpm. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. The drug-to-carrier ratio was the controlling factor for dissolution improvement. FTIR spectra revealed no chemical incompatibility between the drug and cross povidone. As indicated from DSC data, amlodipine besylate was in the amorphous form, which explains the better dissolution rate of the drug from its solid dispersions. For the preparation of amlodipine besylate mouth dissolving tablets, solid dispersion in the ratio of 1:4 with cross povidone was used with various disintegrants. Mouth dissolving tablet was optimized by varying the concentration of various superdisintegrants. Concerning the optimization study, it revealed that crosspovidone in solid dispersion itself act as superdisintegrant and binder and an optimum concentration of a pregelatinized starch is required for obtaining rapidly disintegrating tablets. In conclusion, this investigation demonstrated the potential of experimental design in understanding the effect of the formulation variables on the quality of mouth dissolving tablets containing solid dispersion of a hydrophobic drug.
Key words: solid dispersion, crosspovidone, mouth dissolving tablet.

Introduction

Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions. There are 6 types of drug-carrier interactions in solid-state dispersions: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates, and compound or complex formation. Other factors such as increased wettability, solubilization of the drug by the carrier at the diffusion layer, and the reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. Among the carriers used in the formation of solid dispersions, cross polyvinyl pyrrolidone (PVP) is most commonly used. This polymer shows excellent water solubility and varies significantly in molecular weight, ranging from 10000 to 700000 Da. The molecular size of the polymer favors the formation of interstitial solid solutions. In recent years, the mouth dissolving tablet has attracted the interest of many researchers. Many elderly patients have difficulty in swallowing tablets, capsules, or powders. To alleviate this problem, these tablets are expected to dissolve or disintegrate in the oral cavity without drinking water. The disintegrated mass can slide down smoothly along the esophagus with the help of saliva, so even people who have swallowing or chewing difficulties can take it with ease. The basic approach used in the development of fast-dissolving tablets is the use of superdisintegrants.

Experimental

Determination of solubility:

The drug solubility was determine by adding excess amounts of amlodipine besylate in a beaker containing 10 ml of distilled water and incubated with continuous stirring at 25 ± 0.5ºC for 24 h to achieve equilibrium. The resultant solution was filtered through a 0.45 µm membrane filter and filtrate was analyzed by UV–spectrophotometer at 367nm after suitable dilution. The absorbance of solution was taken as aqueous solubility of the amlodipine besylate in terms of concentration (Table 1).

Preparation of Solid Dispersions and Physical Mixtures:

Solid dispersions of amlodipine besylate in cross povidone containing five different ratios (1:1, 1:2, 1:3, 1:4, and 1:5 w/w) were prepared by the solvent evaporation method. Amlodipine besylate and the polymer were dissolved in a 50ml of chloroform and dichloromethane (2:3). The solvent was stirred and removed by evaporation on magnetic stirrer at the temperature of 40°C. The resulting residue was dried for 2 h and stored overnight in a desiccator. After drying, the residue was ground in a mortar and sieved through mesh # 60. [1,2] The resultant solid dispersions were stored in desiccator until further investigation (Table 2). Physical mixtures were prepared by mixing the appropriate amounts of amlodipine besylate and cross povidone in a mortar. The resulting mixtures were sieved, collected, and stored in a closed container away from the light and humidity until use.

Characterization of solid dispersion:

Dissolution Studies:

The dissolution studies of optimized batches of solid dispersion SD_8 was performed in 500ml of 0.01 N HCl at 37ºC by the USP- II paddle apparatus at 75 rpm. In the present studies samples (equivalent to 2.5mg of drug) were dispersed in medium. Aliquots of 5 ml from the dissolution medium were withdrawn at different time interval and replenished by an equal volume of fresh dissolution medium. The samples were filtered through whatman filter paper and analyzed for amlodipine besylate contents by measuring its area under curve at 367 nm using Shimadzu 1700 UV/visible Spectrophotometer.

Fourier Transform Infrared Spectroscopy:

FTIR spectra were obtained on a FTIR spectrometer (FTIR- Jasco-470 plus). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential Scanning Calorimetry:

The DSC thermograms were recorded on a DSC (DSC7, Perkin- Elmer). Sample was weighed and heated in hermetically sealed aluminium pans over a temperature range of 30°C to 300°C at a constant rate of 5 °C /min under nitrogen purge (20 cm^3/min).

A differential scanning calorimeter (DSC7, Perkin-Elmer) was used. The equipment was calibrated using indium and zinc. Samples were heated at 5 °C/min in aluminium pans under nitrogen atmosphere. The onsets of the melting points and enthalpies of fusion were calculated by the software (Pyris, Perkin-Elmer). The cell had a nitrogen purge flowing at approximately 20 cm^3/min. The cell and sample were held isothermally at -79° C for 30 min to purge the headspace and sample with nitrogen before heating. The cell and sample were then heated to 250 °C while monitoring heat flow. The DSC curve of crossPVP and solid dispersion was almost in similar pattern with an endothermic peak near 75°C with heating enthalpy 153.64 J/kg and 133.49 J/kg respectively. The DSC spectrum of the amlodipine besylate shows a sharp endothermic peak at 210°C with heating enthalpy 78.95J/kg. DSC spectra of solid dispersion does not exhibit the crystalline peak of amlodipine besylate from that conclusion drawn that in the solid dispersion amlodipine besylate was in an amorphous state in SD and there is no interaction between drug and polymer.

Scanning electron microscopy (SEM)

The surface morphology of optimized batches (SD_8) was determined by scanning electron microscopy (SEM, Leo 430, UK). The SEM photomicroscopy of pure polymer and solid dispersion are given in photgraph (1). It shows scanning electron microscope photographs of Cross Povidone and SD particles. The shape of SD particles is almost same as that of Cross Povidone .In the preparation process for the preparation of SD, both amlodipine besylate and crosspovidone completely dissolved in chloroform and dichloroform (2:3). In the solution form drug and polymer get completely mixed at the molecular level and when the solid dispersion passed through the same sieve as that of polymer it exhibit same size.

Drug Content:

The content of amlodipine besylate in crossPVP solid dispersion was estimated using Shimadzu 1700 spectrophotometer. An accurately weighed quantity of solid dispersion (equivalent to 10 mg of amlodipine besylate) was taken and dissolved in 10ml of methanol; from this solution 1ml of solution was diluted to 10ml and assayed for drug content at 367 nm (Table 3).

Preparation of Amlodipine Besylate Tablets:

S.No.	Ingredient	Quantity
1	Disintegrant	25 %
2	Sweetener	1%
3	Solid dispersion	14.2 mg
4	Glidant	4 %
5	Lubricant	1%
6	Diluent	q.s.

All the materials were passed through #60 sieve prior to mixing. The solid dispersion was properly mixed with Disintegrant, and then with the diluent mannitol. The mixture was mixed with aerosil, magnesium stearate. The material was then subjected to compression in 12 station rotary tablet machine (Minipress II MT, Rimek). **Shape:** Round, Flat, plain on both sides. **Size of punches:** 6.35 mm round, flat beveled edge, plain on both sides.

Evaluation of the Prepared Tablets

The tablet geometry was determined by a means of a micrometer (Baty Co, Ltd, Sussex, England), while the tablet breaking strength (hardness) and the tablet friability were determined using Pharma Test hardness tester and Pharma Test fribilator, respectively. The disintegration time was measured using a modified disintegration method. For this purpose, a Petri dish (10-cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the Petri dish and the time for the tablet to disintegrate completely into fine particles was noted. On the other hand, the wetting time was measured as follows: 5 circular tissue papers (10 cm diameter) to simulate the tongue conditions were placed in a Petri dish with a 10-cm diameter. Ten milliliters of water containing methylene blue, a water-soluble dye, was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.

Results and Discussion

Solubility Measurement:

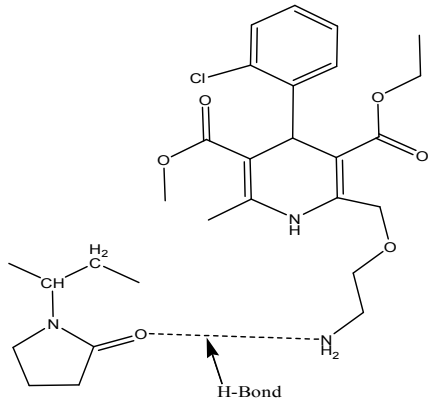
The solubility of amlodipine besylate in distilled water at 25°C was found to be 2626.26. The influence of cross povidone upon the solubility of amlodipine besylate is presented in Figure (1). The increase in solubility was linear with respect to the weight fraction of the carrier. At 1:4 (drug: crosspovidone) of crosspovidone the increase in solubility at 25°C was ~3-fold compared with pure drug. The increase in the solubility with increasing crosspovidone concentration indicates the solvent properties of crosspovidone for the drug. The increase in solubility in the presence of crosspovidone can probably be explained by increased wettability of amlodipine besylate. Indeed, amlodipine besylate causes a decrease of the interfacial tension between the drug and the dissolving solution.

Dissolution Studies:

The dissolution profile of physical mixture and solid dispersion was calculated and is shown in Table. The presence of cross povidone increases the dissolution of amlodipine besylate from the physical mixture and solid dispersions, which increases the dissolution rate (Figure: 2). The release profiles showed 2 different phases of drug release. An initial rapid release phase followed by a slower one. These results could be attributed to the general phenomenon of particle size reduction during the dissolution process medium by cross povidone.

Fourier Transform Infrared Spectroscopy:

The change in principle peaks of amlodipine besylate and excipients were found, which confirms the interactions between drug and excipients (Fig.5). The IR spectra of amlodipine Besylate, crosspovidone and solid dispersion are shown in Fig. (3,4,5) respectively. Amlodipine besylate shows absorption peaks at 3288, crosspovidone shows its absorption peaks at 1661 cm−1, which indicates C=O stretching solid dispersion formulation gave a spectrum that combined those of amlodipine Besylate and CrossPVP. In contrast, SD showed a new absorption pattern. Solid dispersion produced a spectrum that combined those of drug and SD. These changes in the SD correspond to interaction between amlodipine Besylate and PVP through FT-IR. Since CrossPVP has the same chemical structure as PVP these observations suggest an interaction between the amino group of amlodipine Besylate and the amide carbonyl group of CrossPVP.[3]



H-bond formation between amino group of amlodipine Besylate and the amide carbonyl group of CrossPVP

Differential Scanning Calorimetry:

A differential scanning calorimeter (DSC7, Perkin-Elmer) was used. The equipment was calibrated using indium and zinc. Samples were heated at 5 °C/min in aluminium pans under nitrogen atmosphere. The onset of the melting points and enthalpies of fusion were calculated by the software (Pyris, Perkin-Elmer). The cell had a nitrogen purge flowing at approximately 20 cm^3/min. The cell and sample were held isothermally at -79°C for 30 min to purge the headspace and sample with nitrogen before heating. The cell and sample were then heated to 250 °C while monitoring heat flow. The DSC curve of crossPVP and solid dispersion was almost in similar pattern with an endothermic peak near 75°C with heating enthalpy 153.64 J/kg and 133.49 J/kg respectively. The DSC spectrum of the amlodipine besylate shows a sharp endothermic peak at 210°C with heating enthalpy 78.95J/kg. DSC spectra of solid dispersion does not exhibit the crystalline peak of amlodipine besylate from that conclusion drawn that in the solid dispersion amlodipine besylate was in an amorphous state in SD and there is no interaction between drug and polymer.

Evaluation of Amlodipine Besylate mouth dissolving tablet:

Cross povidone is a polymer of polyvinylpyrrolidine which it self acts as a binder and cross povidone itself also a superdisintegrant. When cross povidone is used in tablet preparation with another superdisintegrant, the tablet disintegrates quickly upon contact with water.

In order to select the best superdisintegrant, preliminary trials were conducted as shown in Table. All the prepared tablets are characterized by a uniform thickness, diameter and weight. To select best superdisintegrant in combination with crosspovidone; pregelatinized, cross carmellose sodium and sodium starch glyccolate were used in their maximum limits. Based on the disintegration results in combination with crosspovidone in Table 5, the investigated superdisintegrants can be ranked according to their ability to swell in water as pregelatinized starch > croscarmellose > sodium starch glycolate. Wicking and capillary action are postulated to be major factors in the ability of these superdisintegrants to function. Pregelatinized starch facilitates wicking action of cross povidone in bringing about faster disintegration as compared to the other superdisintegrant used. As a result, the batch A11 containing both 25% pregelatinized starch exhibited faster disintegration and wetting. Hence, they were selected for further studies.

***In vitro* drug release:**

USFDA has suggested the USP 2 Paddle apparatus which is the most suitable and common choice for amlodipine besylate tablets, with a paddle speed of 75 rpm, dissolution media 500 ml of 0.01N HCl, sample withdrawing at 10,20,30,45,60 minutes commonly used. To know the accuracy in the dissolution profile of mouth dissolving tablet, we withdraw aliquots of 5ml at time period of 5,10,15,20,25,30,45,60 minutes and replenishment with equal volume of fresh media. Typically the dissolution of mouth dissolving tablet is very fast when using USP monograph conditions. UV is often required to analyze dissolution aliquots due to presence of UV absorbing components, such as excipients. Excipients to drug ratio may be higher since the formulation is designed to have good taste and mouth feel, decreasing the signal of the drug to background (excipients) in the UV/spectrophotometer technique at λ_{max} 237 nm for 0.01N HCl. So we measure the absorbance at λ_{max} 367 nm 0.01N HCl.

Table 1: Solubility of Amlodipine besylate in distilled water

S.No.	Drug	Saturated solubility(µg/ml)			Mean Saturated solubility±SD (µg/ml)
		S1	S2	S3	
1	Amlodipine besylate	2561.09	2668.62	2649.07	2626.26±57.27

Table 2: Solubility of solid dispersion of drug and crosspovidone

S. No.	Type of preparation and code	Drug excipient ratio	Saturated solubility(µg/ml)			Mean Saturated solubility± SD (µg/ml)
			S1	S2	S3	
1	Solid Dispersion (SD_6)	1:1	4017.59	4076.24	3998.04	4030.62±40.69
2	Solid Dispersion (SD_7)	1:2	4604.10	4682.30	4652.98	4646.46±39.50
3	Solid Dispersion (SD_8)	1:3	6168.13	6275.66	6226.78	6223.52±53.83
4	Solid Dispersion (SD_9)	1:4	6774.19	6793.74	6852.39	6806.77±40.69
5	Solid Dispersion (SD_{10})	1:5	6862.17	6832.84	6783.96	6826.32±39.50

Table 3: Drug Content in optimized batches of solid dispersion

S.No.	Optimized batches	Mean Drug content (%)
1	SD_8	92.87±0.19

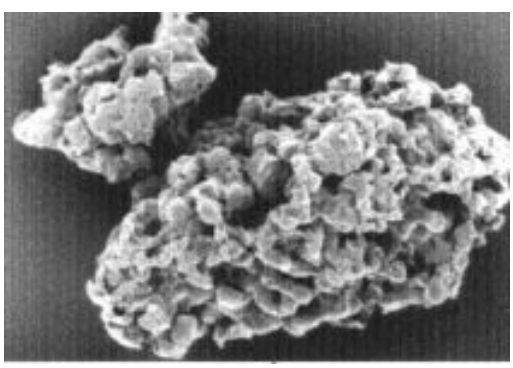
Table 4: Dissolution profile of solid dispersion

S. No.	Time (min)	Cumulative % drug release from optimized batches			
		SD_{8A}	SD_{8B}	SD_{8C}	Mean±SD
1	0	0	0	0	0
2	5	53.88	54.8	55.6	54.76±0.86
3	10	72.52	72.92	73.28	72.90±0.38
4	15	92.72	91.92	92.72	92.45±0.46
5	20	97.76	97.36	97.76	97.62±0.23
6	25	98.72	98.36	98.92	98.66±0.28
7	30	99.2	99.08	99.28	99.18±0.10

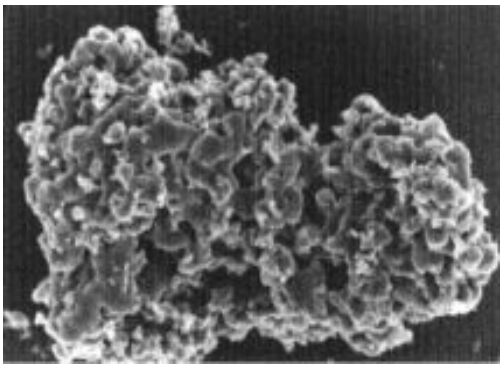
Table 5: Selection of optimized batch:

S.No.	Ingredient		A5	A6	A7	A8	A9	A10	A11
1	Disintegrant	Sta-R_X 1500	15%	-	-	10%	15%	20%	**25%**
2		Primogel®	-	12%	-	-	-	-	**-**
3		Ac-Di-Sol®	-	-	8%	-	-	-	**-**
5	Sweetener	Aspartame	1%	1%	1%	1%	1%	1%	1%
6	Lubricant	Magnesium stearate	1%	1%	1%	1%	1%	1%	**1%**
7	Anti adherent	Talc	1%	1%	1%	1%	1%	1%	**1%**
8	Glidant	Aerosil	4%	4%	4%	4%	4%	4%	**4%**
9	Solid Dispersion (cross povidone)	Amlodipine besylate(2.5mg)	14.2 mg	14.2 mg	14.2 mg	14.2 mg	14.2 mg	14.2 mg	**14.2 mg**
10	Diluent	Mannitol up to	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	**100 mg**
Evaluation parameter of tablet batches									
1.	Bulk Density (gm/cm^3)		0.632	0.631	0.620	0.645	0.632	0.624	0.620
2.	Compressibility Index (%)		6.025	6.054	6.036	6.09	6.025	6.023	6.029
3.	Angle of Repose (O)		23.1	22.5	24.3	24.3	23.1	21.9	**20.6**
4.	Weight (g)		102.3 ±0.31	104.3 ±0.61	99.96 ±0.26	99.02 ±0.12	102.3 ±0.31	99.96 ±0.17	**99.96 ±0.25**
5.	Thickness (mm)		1	1	1	1	1	1	**1**
6.	Diameter (mm)		6.35	6.35	6.35	6.35	6.35	6.35	**6.35**
7.	Crushing strength (kg/cm^2)		3.0 ±0.25	3.5 ±.2	3.5 ±.5	3.0 ±0.1	3.0 ±0.25	3.0 ±0.2	**3.0 ±0.3**
8.	Friability (%)		0.18	0.17	0.18	0.21	0.18	0.17	**0.15**
9.	Wetting time (sec.)		43	45	43	51	43	24	**21**
10.	Disintegration time (Sec.)		48	53	51	57	48	28	**26**
11.	% Drug content		101.21 ±.19	99.94 ±.14	101.11± 0.33	100.46± .09	100.14± .16	101.04± 0.21	100.13± 0.04

Photograph (1): Scanning electron microscope photographs of Cross Povidone and SD particles



Cross povidone



Solid dispersion

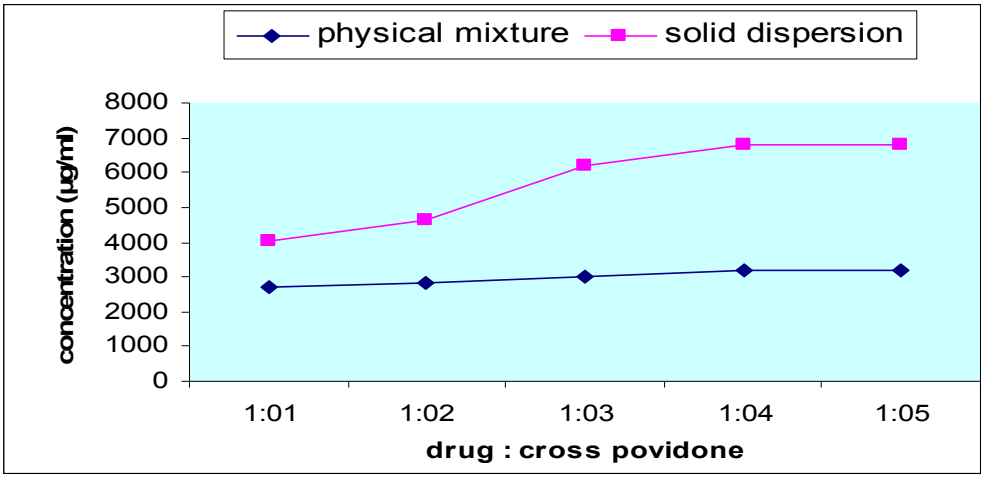


Figure: 1 Solubility Measurement

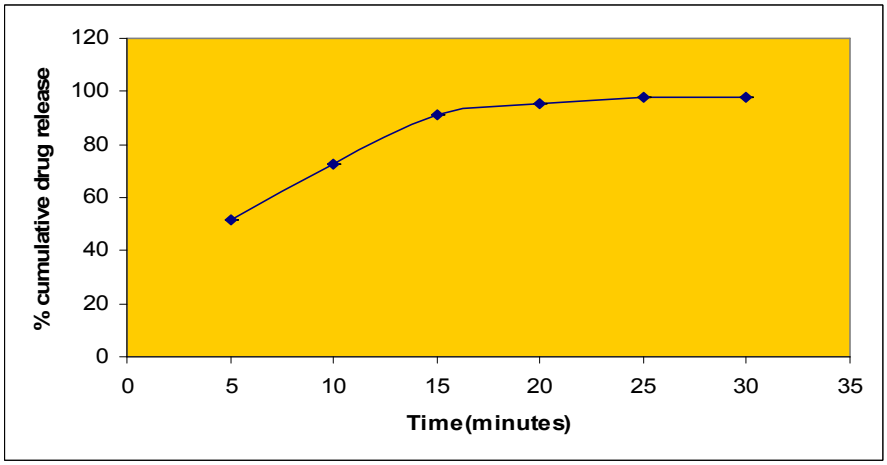


Figure: 2 Dissolution profile of solid dispersion

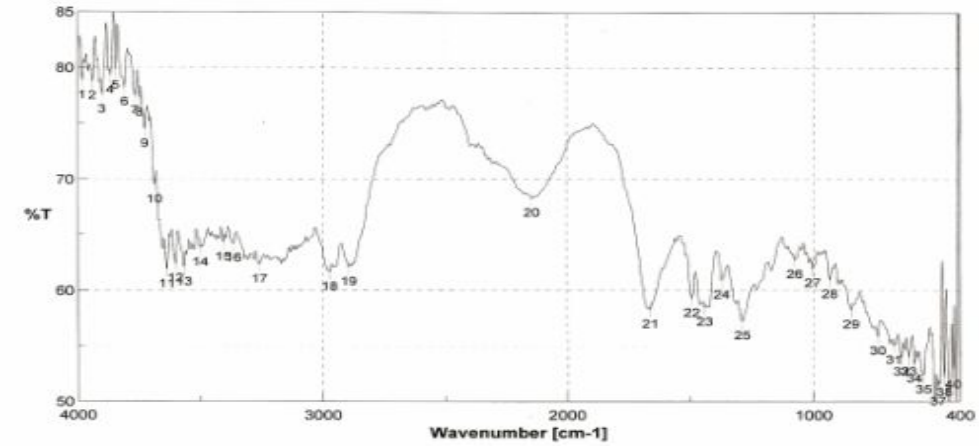


Figure: 3 IR-spectra of amlodipine besylate

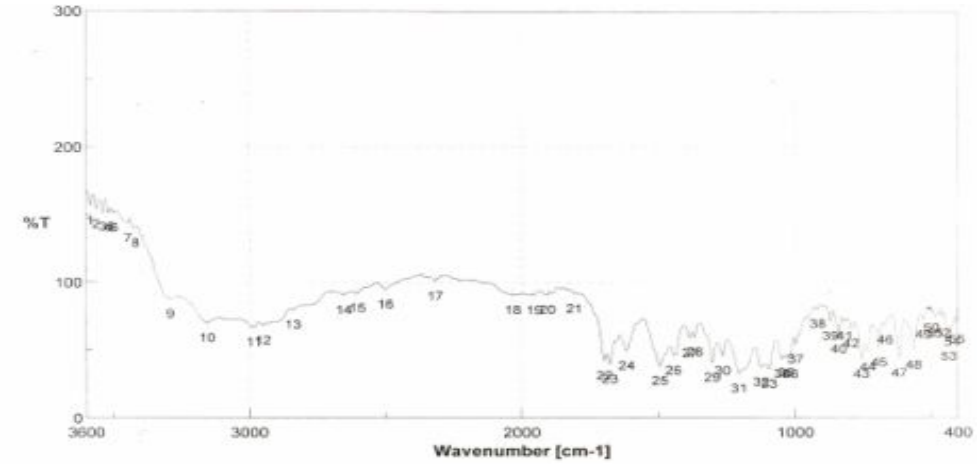


Figure: 4 IR-spectra of cross povidone

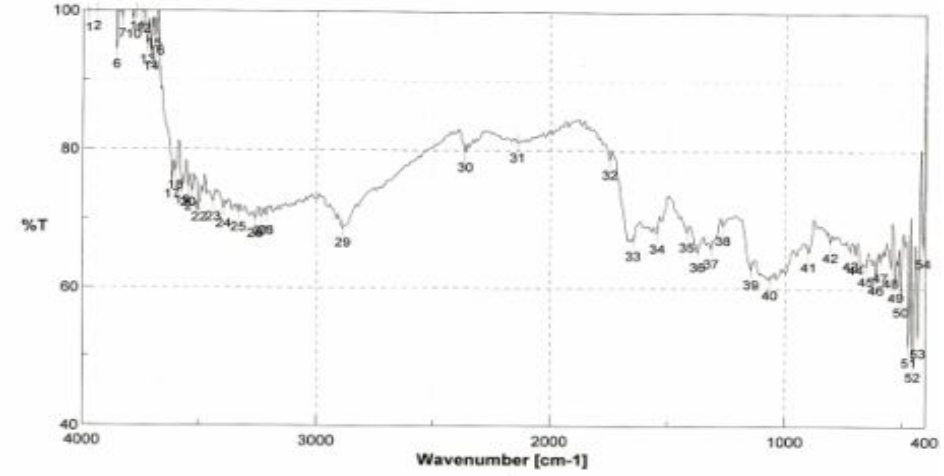


Figure: 5 IR-spectra of solid dispersion formulation with cross povidone

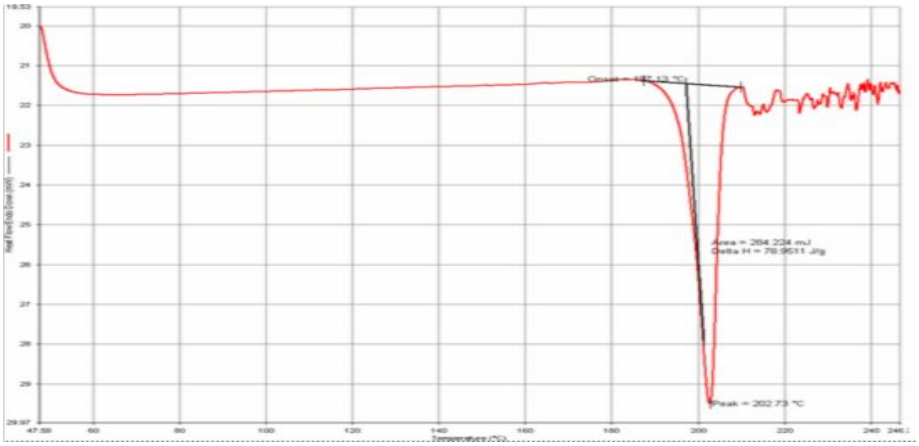


Figure: 6 DSC spectra of amlodipine besylate

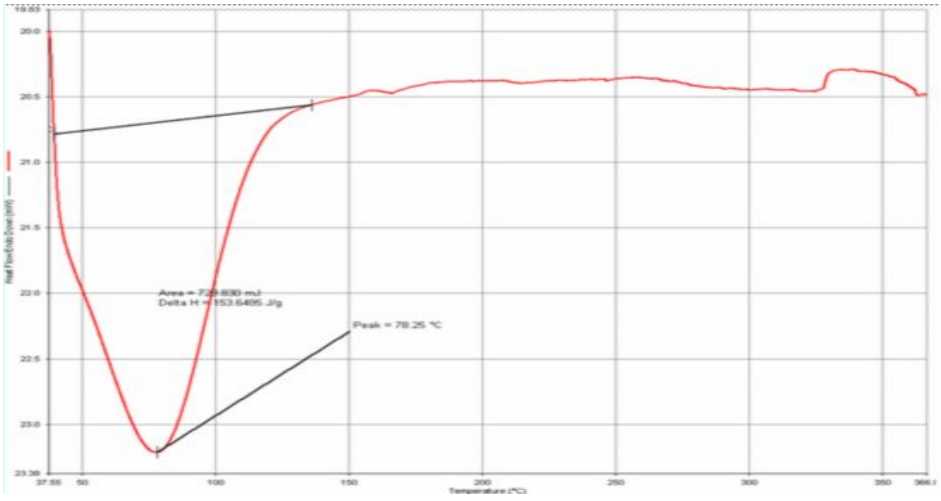


Figure: 7 DSC spectra of cross povidone

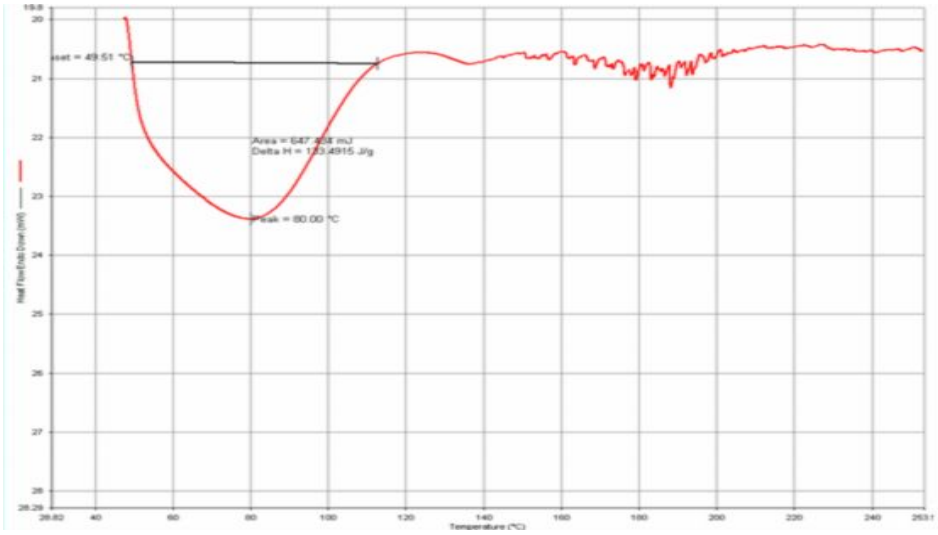


Figure: 8 DSC spectra of solid dispersion

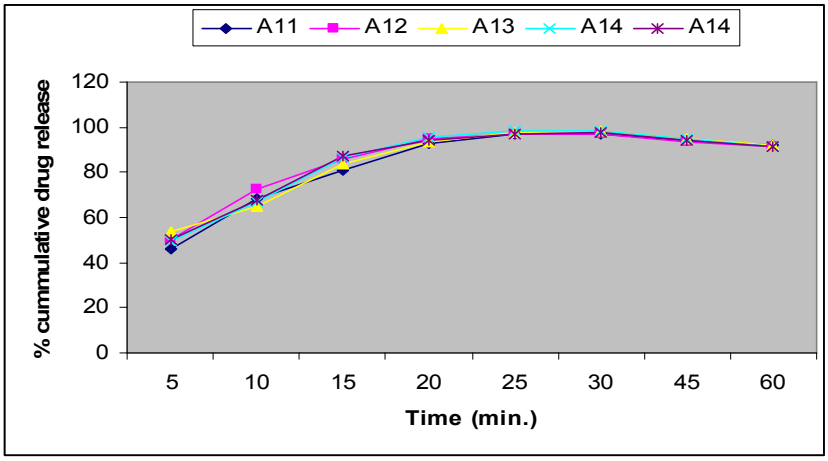


Figure: 9 Drug release profile of laboratory tablet

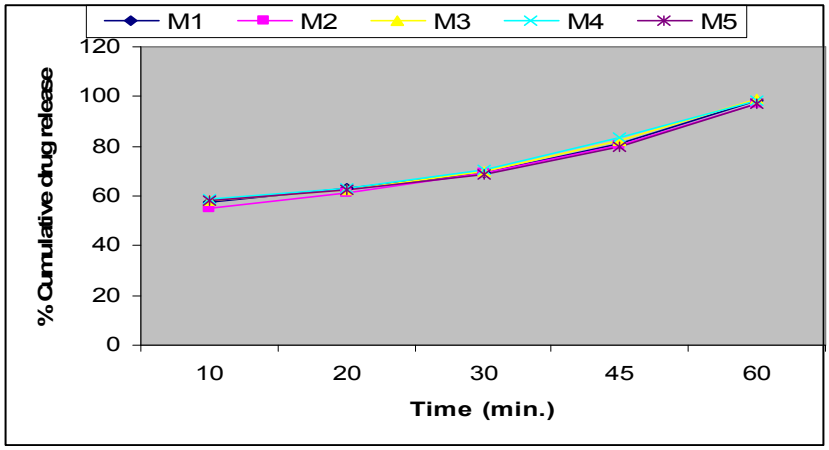


Figure: 10 Drug release profile of laboratory tablet

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