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Research Article

FORMULATION AND EVALUATION OF FAST 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 PEG 4000, PVP K-30 using kneading process. Drug polymer interactions were investigated using differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FTIR). Surface morphology of solid dispersion particles was determined by SEM study. Dissolution rate of solid dispersion was determined in PBS 6.8. 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 PVP K-30, PEG 4000. 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 fast dissolving tablets, solid dispersion in the ratio of 1:2:2 with PVP K-30 and PEG 4000 was used with various superdisintegrants(croscarmellose sodium, microcrystalline cellulose and crospovidone). Dissolution profile of optimized mouth dissolving tablet was compared with the marketed formulation of amlodipine besylate(amdepin®) and the results obtained were better than the marketed formulation. Thus it justified the potential of solid dispersion technique in enhancing the bioavailability of drug.

Keywords: Solid dispersion, Amlodipine

INTRODUCTION

Amlodipine besylate is a drug that is used for treating high blood pressure, certain types of angina, and coronary heart failure. The drug works by slowing down the rate at which calcium moves to heart, blood vessel walls, allowing better blood flow. Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. It is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in urine. Its bioavailability is between 64-90%. Bioavailability can be enhanced by forming solid dispersions and hepatic metabolism can be overcome by forming fast dissolving tablets. Solid dispersion technique has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs. In solid dispersion the drugs are dispersed in a biologically inert matrix for the intention of enhancing oral bioavailability. A fast dissolving tablet system can be also employed as a dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed in form of liquid. Recently fast dissolving formulation is popular as Novel Drug Delivery systems because they are easy to administer and lead to better patient compliance.

MATERIAL AND METHOD

Materials

Amlodipine besylate was procured from Triveni chemicals Gujarat, India. PEG 4000, PVP K30, croscarmellose sodium, crospovidone, microcrystalline cellulose and magnesium stearate were procured from S.D. Fine Chemicals, Mumbai, India and all other chemicals / solvents used were of analytical grade.

Method

Preparation of solid dispersions

Solid dispersions of amlodipine besylate in PEG 4000, PVP K30 and PEG 4000:PVP K30 combination containing different ratios (composition given in table 2) were prepared by the kneading process. Weighed quantity of amlodipine besylate and polymers taken in a mortar and then mixture is kneaded with 1:1 methanol:water solution .The kneaded mixture is dried in an oven at 40^0C until it reaches uniform weight and then pulverized and screened through 100 mesh sieve and the final product is stored in a dessicator[1]. The development of solid dispersions as a practical viable method to enhance bioavailability of poorly water-soluble drugs overcome the limitation of other approaches such as salt formation, solubilization, cosolvency and particle size reduction[2]. An improvement in wetting of the drug is caused by the hydrophilic carrier[3].

Characterization of solid dispersion

Drug content

The content of amlodipine besylate in solid dispersions 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 239 nm (Table 3).

Dissolution studies

The dissolution studies of different batches of solid dispersion SD1, SD2, SD3, SD4, SD5, SD6 was performed in 900 ml of PBS pH 6.8 at 37ºC by the USP- II paddle apparatus. In the present studies samples (equivalent to 10 mg of drug) were dispersed in medium. Aliquots of 10 ml from the dissolution medium were withdrawn at different time intervals 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 λmax of 239 nm using Shimadzu 1700 UV/visible Spectrophotometer.

Fourier transform infrared spectroscopy

FTIR spectra were obtained on a FTIR spectrometer (Mettler-Toledo FTIR). 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 (DSC821e, Mettler Toledo). Sample was weighed and heated in hermetically sealed aluminium pans over a temperature range of 30 ^{0}C to 300 ^{0}C at a

constant rate of 5 ^{0}C /min under nitrogen purge (20 cm^3/min). A differential scanning calorimeter (DSC821e, Mettler Toledo) was used. The equipment was calibrated using indium and zinc. Samples were heated at 5 ^{0}C/min in aluminium pans under nitrogen atmosphere. The onsets of the melting points and enthalpies of fusion were calculated by the software (STAR^e SW 9.01, Mettler Toledo). The cell had a nitrogen purge flowing at approximately 20 cm3/min. The cell and sample were held isothermally at -79^{0}C for 30 min to purge the headspace and sample with nitrogen before heating. The cell and sample were then heated to 250^{0}C while monitoring heat flow. The DSC curve of PEG 4000, PVP K30, and solid dispersion was almost in similar pattern with an endothermic peak near 61^{0}C with heating enthalpy 179.77 J/g, 192.62 J/g and 63.47 J/g respectively. The DSC spectrum of the amlodipine besylate showed a sharp endothermic peak at 204.54^{0}C with heating enthalpy 75.52 J/g. 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[4].

Scanning electron microscopy (SEM)

The surface morphology of optimized solid dispersion(SD6), amlodipine besylate, PVP K-30 and PEG 4000 was determined by scanning electron microscopy(SEM, JSM 6100 JEOL, JAPAN). The shape of solid dispersion particles is almost same as that of PVP K30 and PEG4000. In the preparation process for the preparation of SD, amlodipine besylate, PEG 4000 and PVP K30 were completely dissolved in methanol and water (1:1). 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.

Preparation of amlodipine besylate tablets

All the materials were passed through sieve no.60 prior to mixing. The solid dispersion was properly mixed with croscarmellose sodium, crospovidone, microcrystalline cellulose seperately and then with the diluent mannitol. The mixture was mixed with Mg stearate, talc[5]. 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[6]. Composition of various tablet batches is shown below in Table 1.

Table 1: **Composition of amlodipine besylate tablets**

S. No.	Ingredients	Batch A(mg)	Batch B(mg)	Batch C(mg)
1.	Solid dispersion	50	50	50
2.	Croscarmellose sodium	46	-	-
3.	Microcrystalline cellulose	-	46	-
4.	Crospovidone	-	-	46
5.	Mannitol	100	100	100
6.	Mg stearate	2	2	2
7.	Talc	2	2	2

Evaluation of the prepared tablets

Uniformity of Weight

U.S.P procedure for uniformity of weight was followed, twenty tablets were randomly taken and their weight was determined individually and collectively on a digital weighing balance[7]. The average weight of one tablet was determined from the collective weight.

Tablet Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under storage conditions, transformation and handling before usage depends on its hardness. Hardness of the tablets was determined by using Monsanto Hardness Tester.

Table 2: Composition of different batches of Amlodipine besylate solid dispersions

S. No	Batch code	Polymer complex Ratio (PVP K-30:PEG 4000)	Amlodipine Besylate(mg)	PEG 4000(mg)	PVP K30 (mg)
1	SD1	1:1	10	10 -	
2	SD2	1:2	10	20	-
3	SD3	1:1	10	-	10
4	SD4	1:2	10	-	20
5	SD5	1:1:1	10	10	10
6	SD6	1:2:2	10	20	20

Table 3: Drug content in optimized batch of solid dispersion(SD6)

S. No.	Optimised batch	Mean drug content(%)
1	SD6	92.59

Table 4: Cumulative % drug release from different solid dispersion batches

S. No.	Time (min)	Cumulative % drug release from solid dispersions					
		SD1	SD2	SD3	SD4	SD5	SD6
1	0	0	0	0	0	0	0
2	5	39.57	43.24	47.29	52.19	55.93	57.8
3	10	55.43	61.39	68.27	71.25	74.83	78.95

4	15	61.28	68.91	73.45	79.54	83.47	90.28
5	20	65.24	73.25	78.43	84.83	88.56	95.28
6	25	70.23	78.13	83.24	87.29	91.24	97.59
7	30	71.25	80.45	87.29	91.64	95.43	99.90

Tablet friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1% [8].

% Friability = [(Initial weight- Final weight) / (Initial weight)] x 100

***In-vitro* disintegration test**

The test was carried out on 6 tablets using Tablet disintegration tester ED-20 (Electrolab, Mumbai, India) PBS pH6.8 at 37°C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Wetting time

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 mL of water-containing amaranth a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time [9].

Tablet Thickness

Tablet thickness can be measured using a simple procedure. 5 tablets were taken and their thickness was measured using Vernier callipers. The thickness was measured by placing tablet between two arms of the Vernier callipers (Mitutoyo).

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation [10].

$R = (W_a - W_b)/ W_a \times 100$

Where, W_a = Weight of tablet after water absorption

W_b = Weight of tablet before water absorption.

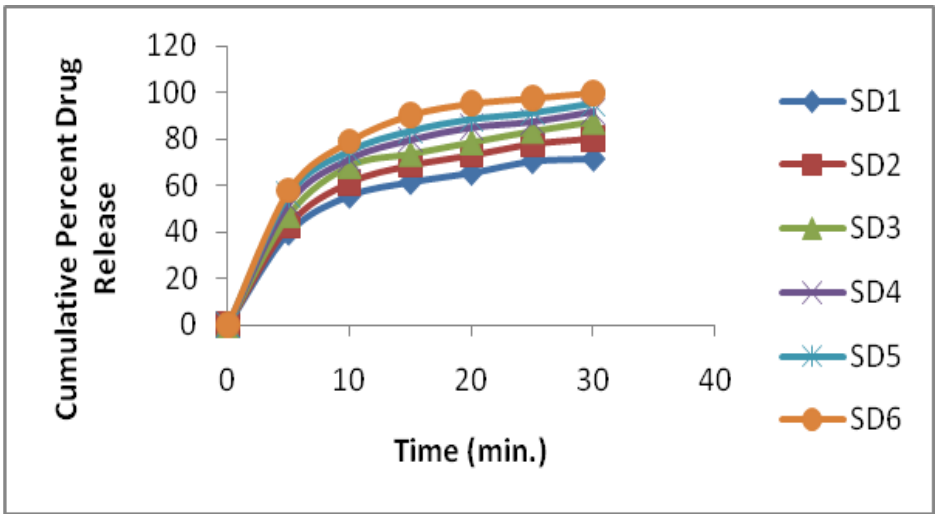

Fig. 1: Cumulative % drug release of different batches of solid dispersion vs time

Table 5: Evaluation parameters of formulated batches A, B, C and marketed amlodipine besylate tablet (Amdepin)

S.No.	Evaluation parameter	Batch A	Batch B	Batch C	Amdepin
1.	Weight Variation	2.1±0.12	1.8±0.09	1.5±0.10	1.0±0.07
2.	Hardness(Kg/cm^2)	3.2±0.08	3.3±0.05	3.5±0.12	3.7±0.15
3.	Friability	0.72±0.09	0.73±0.15	0.74±0.13	0.71±0.20
4.	Thickness(mm)	3.03±0.19	3.05±0.20	3.09±0.12	3.01±0.10
5.	Wetting time(sec.)	12±0.3	11±0.23	10±0.09	13±0.10
6.	Water absorption ratio	80.96±0.31	81.17±0.23	82.64±0.15	80.35±0.32
7.	Disintegration Time (sec.)	12±0.12	11±0.08	10±0.10	13±0.09

Table 6: Comparison of Cumulative % drug release of formulated tablet batches and marketed amlodipine besylate tablet (Amdepin)

S. No.	Time (min)	Cumulative % drug release from Tablets using different superdisintegrants and marketed formulation (Amdepin)			
		Croscarmellose sodium (A)	Microcrystalline cellulose (B)	Crosspovidone (C)	Amdepin
1	0	0	0	0	0
2	5	57.23	53.15	47.35	41.26
3	10	76.15	67.24	60.14	52.34

4	15	81.25	72.34	65.21	57.25
5	20	85.31	76.39	70.32	61.25
6	25	89.34	81.35	75.23	67.35
7	30	94.21	86.53	80.12	[71.35

Table 7: Effect of Storage Condition on Dissolution Studies of Amlodipine besylate Tablets

Storage Conditions	Batch	Cumulative Percent Drug Released in 30 min.		
		Initial	3 months	6 months
40^0C/75%RH	A	92.09	92.11	92.15
	B	93.10	93.12	93.15
	C	94.05	94.10	94.12

***In-vitro* dissolution study**

The release rate of Amlodipine Besylate from fast dissolving tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus (paddle method). The dissolution test was performed using 900 ml of PBS pH 6.8, at 37± 0.5 ^{0}C. A sample(5 ml) of the solution was withdrawn from the dissolution apparatus at regular intervals for 10 min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45ì membrane filter. Absorbance of these solutions was measured at 239 nm using a Shimadzu-1700 UV spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve [11].

Statistical analysis

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in zero order kinetic model between cumulative amount of drug released vs time.

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be described by zero order kinetics.

$$\mathbf{Q_1 = Q_0 + K_0 t}$$

Where Q_1 is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in solution and K_0 is the zero-order rate constant and t is the time in h. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept at the origin of the axis.

RESULTS AND DISCUSSION

Dissolution studies

The dissolution profile of solid dispersions was calculated and is shown in Table 4 and Fig 1. The presence of PVP K-30 and PEG 4000 increases the dissolution of amlodipine besylate from the solid dispersions, which increases the dissolution rate.

Fourier transform infrared spectroscopy

The change in principle peaks of amlodipine besylate and excipients were found. The IR spectra of Amlodipine besylate, PVP K-30, PEG 4000 and its solid dispersion with PVP K-30, PEG 4000 are presented in Fig.2, 3, 4, 5. Pure Amlodipine besylate spectra showed sharp characteristic peaks at 3300.20, 3158.50, 1651.08, and 1616.08 cm^{-1}. All the above characteristic peaks appears in the spectra of solid dispersion at same wavenumber indicating no modification or interaction between the drug and carrier .

Differential scanning calorimetry

Thermal behaviour of Amlodipine besylate, PVP K-30, PEG 4000 and solid dispersion of Amlodipine besylate with PVP K-30 and PEG 4000 are depicted in Fig.6, 7, 8, 9. The DSC curve of Amlodipine besylate profiles a sharp endothermic peak (Tpeak = 204.54°C) corresponding to its melting, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting was broadened and shifted toward lower temperature, with reduced intensity, in solid dispersion. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Moreover, the data also indicate there seems to be no interaction between the components of solid dispersion. No significant difference in DSC pattern of solid dispersion suggests that even the kneading process could not induce interaction at the molecular level and solid dispersion contains highly dispersed drug crystals in carrier.

Scanning electron microscopy (SEM)

Scanning electron micrographs of PVP K-30, PEG 4000 and SD are shown in Fig. 10, 11, 12. Amlodipine besylate was present in a crystalline form. PVP K-30, PEG 4000 were present in amorphous form. The surface morphology of SDs indicate that amlodipine besylate was adsorbed into the PVP K-30, PEG 4000 and homogeneously dispersed into the polymer. SEM picture images suggested that the individual surface properties of polymers and drug were lost during kneading and the formation of effective SD systems. These findings demonstrated that the drug was thoroughly mixed in the carriers with the negligible loss of little crystallinity [12].

Selection of best batch

Selection of best batch was done on the basis of result obtained from *in vitro* release studies. Batch SD6 was selected from solid dispersion batches of PVP K-30 and PEG 4000. Selection of this batch was done because batch SD6 was releasing 99.90% of drug after 30 mins . These characteristics of polymer complex are prerequisites for the development of fast dissolving tablet. After selection of best batch SD6 fast dissolving tablet was formed using crospovidone, croscarmellose sodium and microcrystalline cellulose as superdisintegrants and tablets were evaluated for various parameters and *in vitro* release studies was done to compare the release profile of formulated Amlodipine besylate tablets with marketed formulation Amdepin.

Evaluation of Amlodipine Besylate mouth dissolving tablet

Table 5 shows that the formulated and marketed tablets exhibited low weight variation that varies between 1.0 to 2.1 from different batches. The wetting time of the tablets was also considerably low between 10-12. The porous structure is responsible for faster water uptake; hence it facilitates wicking action of disintegrants in bringing about faster disintegration. Tablets with lower friability (0.5%) may not break during handling on machines. The results shown in Table 5 reveal that presence of croscarmellose sodium(A), microcrystalline cellulose(B) and crospovidone(C) superdisintegrants in tablets resulted in faster disintegration. The low value of wetting time and disintegration time indicate that the porosity of formulated tablets would be greater than marketed tablets. The thickness of tablets varies from 3.01 to 3.09 mm.

In vitro drug release

In vitro release studies were conducted as per USP procedure using phosphate buffer pH 6.8 as dissolution medium. The *in vitro* profiles of amlodipine besylate from formulated and marketed tablets are given in Table 6 and Fig.13. Drug release profile was found to be far much better in case of formulated tablets rather than the marketed tablet of amlodipine besylate (Amdepin®).

Stability studies

Formulated tablet batches A, B, C showed no significant variation in dissolution profile under the test period at different conditions. All the test results were found to be in limits. Hence the formulations were stable under stated storage conditions. The results are shown in Table 7.

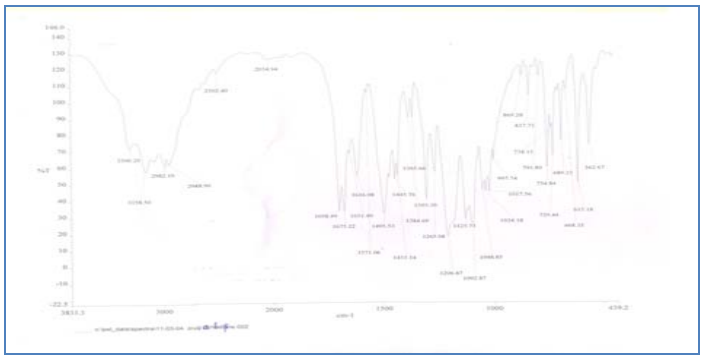

Fig. 2: FTIR of amlodipine besylate

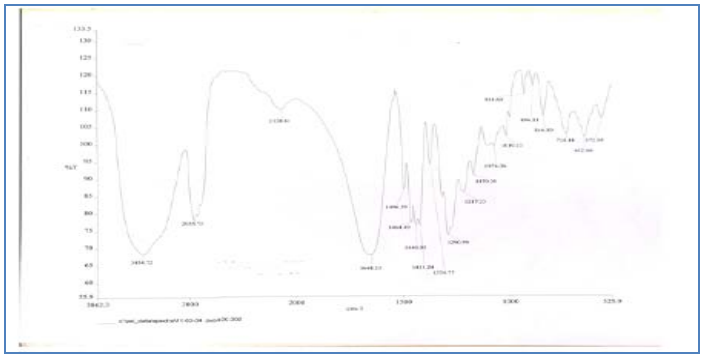

Fig. 3: FTIR of PVP K-30

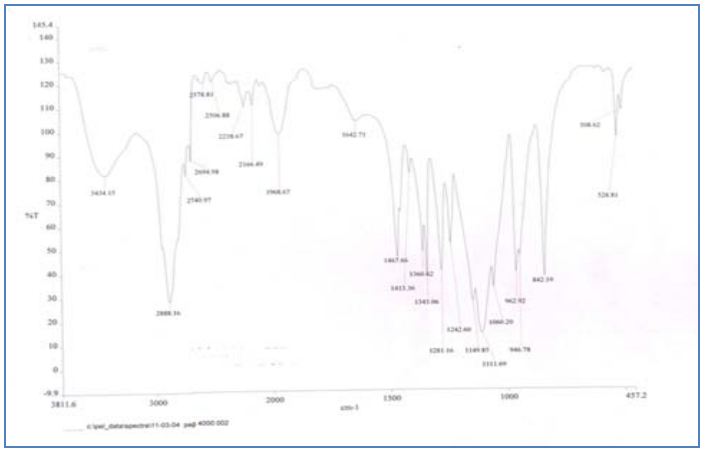

Fig. 4: FTIR of PEG 4000

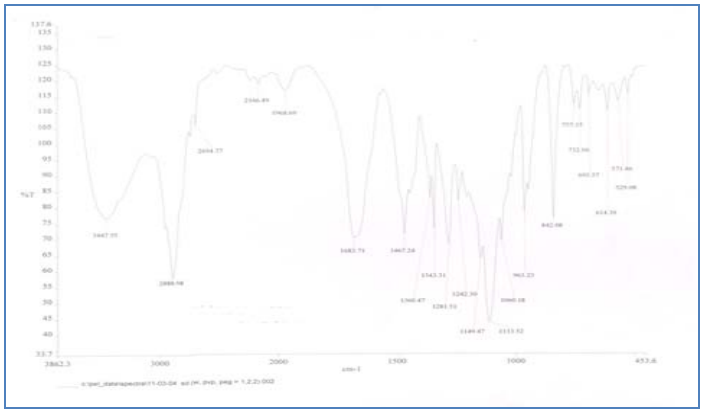

Fig. 5: FTIR of solid dispersion(SD6)

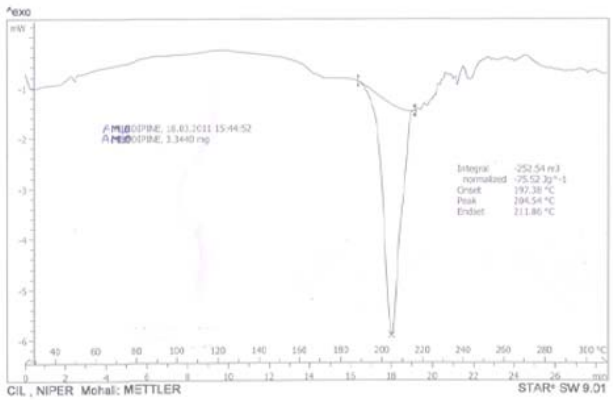

Fig. 6: DSC of amlodipine besylate

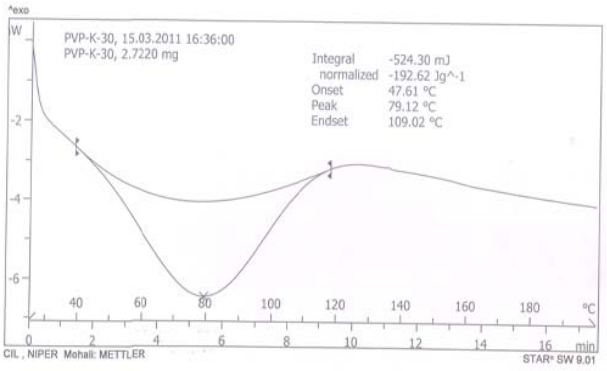

Fig. 7: DSC of PVP K-30

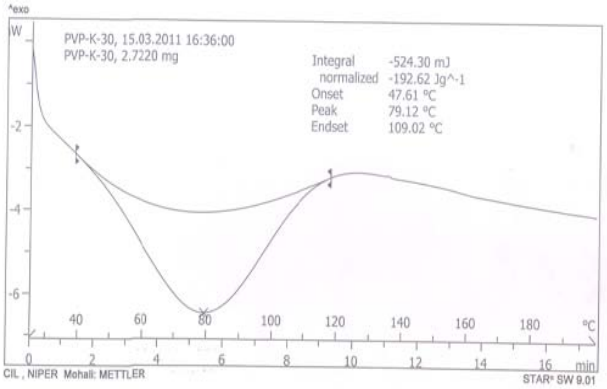

Fig. 8: DSC of PEG 4000

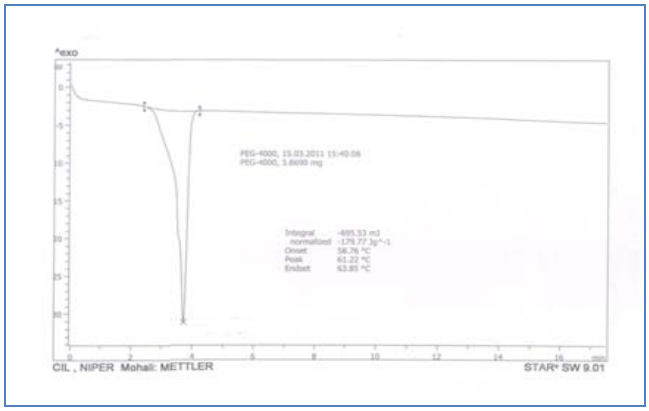

Fig. 9: DSC of solid dispersion (SD6)

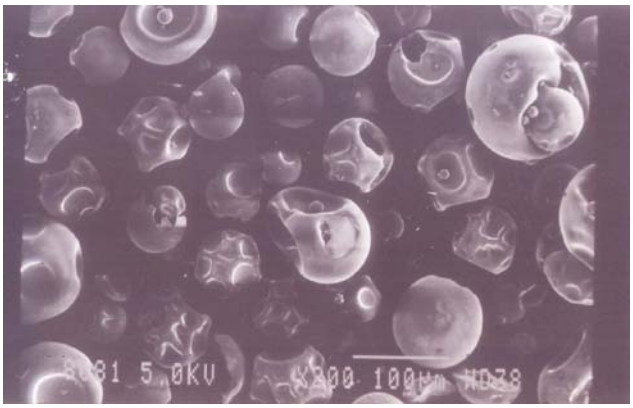

Fig. 10: SEM of PVP K-30

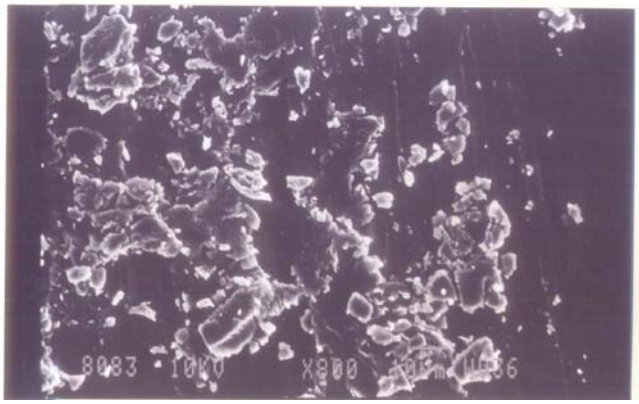

Fig. 11: SEM of PEG 4000

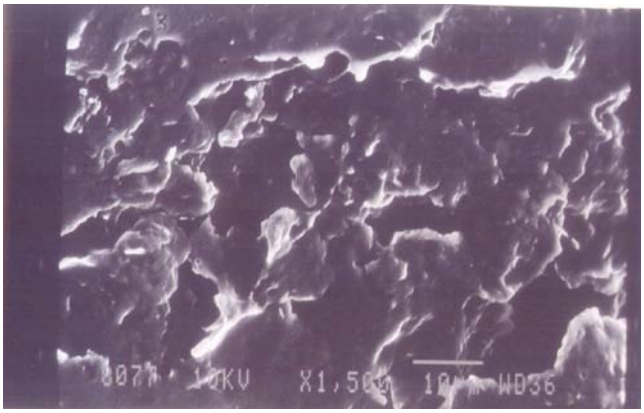

Fig. 12: SEM of solid dispersion (SD6)

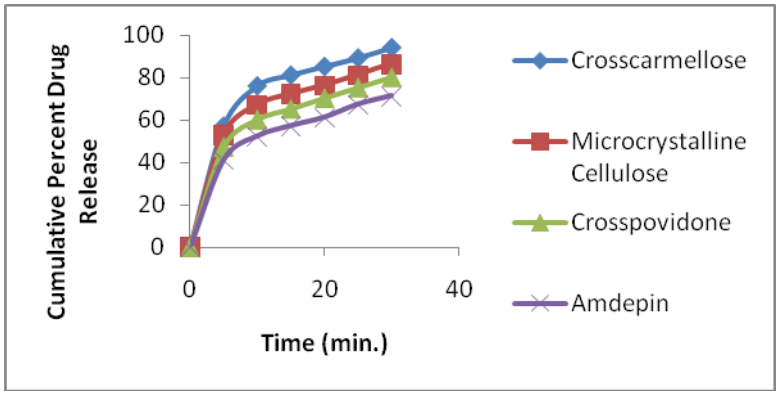

Fig. 13: Comparison of Cumulative % drug release of formulated tablet batches and marketed amlodipine besylate tablet (Amdepin®)

CONCLUSION

Based on the observation and results it is concluded that the formulation can be effectively used.

REFERENCES

1. Shah J, Vasanti S, Anroop B, Vyas H. Enhancement of dissolution rate of valdecoxib by solid dispersions technique with PVP K 30 and PEG 4000: preparation and in vitro evaluation. J Incl Phenom Macrocycl Chem. 2009; 63:69-75.
2. Kalia A, Poddar M. Solid dispersions: An approach towards enhancing dissolution rate. Int J Pharm Pharm Sci. 2011; 3(4):9-19.
3. Gupta MM, Patel MG, Patel NS, Kedawat M. Enhancement of dissolution rate of ibuprofen by preparing solid dispersion using different methods. Int J Pharm Pharm Sci. 2011; 3(3):204-206.
4. Golcu A, Yucesoy C. Colorimetric determination of amlodipine besylate in tablets. J Sci Eng. 2006; 9(2):52-55.
5. Herbert Lieberman A, Lachman, Schwartz JB. Pharmaceutical dosage forms tablets. Vol. 3. 2nd ed. p. 500-501.
6. Parakh SR, Gothoskar AV. A review of mouth dissolving tablet technologies. Pharm Tech. 2003; 27(11):92-98.
7. Indian Pharmacopoeia. Ministery of health and family welfare. Govt. of India. The Controller of publications: New Delhi; 1996.
8. Sivakranth M, Abdul S Altaf, Rajasekhar S. Formulation and evaluation of oral fast dissolving tablets of sildenafil citrate. Int J Pharm Pharm Sci. 2011; 3(2):112-121.
9. Sunanda H, Bi YX, Yonezawa Y, Danjo K. Preparation,evaluation and optimization of rapidly disintegrating tablets. Powder Tech. 2002; 122:188-198.
10. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. Eur J Pharm Sci. 2002; 15 :295-305.
11. The United States Pharmacopoeia 30/NF 25. Asian edition. The official compendia of standard United States Pharmacopoeial Convection Inc: Rockville; 2007. p. 277.
12. Lalitha Y, Lakshmi PK. Enhancement of dissolution of nifedipine by surface solid dispersion technique. Int J Pharm Pharm Sci. 2011; 3(3):41-46.