Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Issue 1, 2012

Research Article

ENHANCEMENT OF DISSOLUTION FOR IMPROVING BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUG THROUGH ORAL MUCOSA

UTPAL NANDI AND TAPAN K PAL*

Bioequivalence Study Centre, Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700032, India.
Email: proftkpal@gmail.com

Received: 12 Feb 2011, Revised and Accepted: 18 May 2011

ABSTRACT

The aim of the present was to enhance the solubility and dissolution rate of a model drug, atorvastatin calcium (AVT) under the frame of improved bioavailability. Solid dispersion of AVT was prepared by using PVP K-30, PEG6000 and lactose as carrier in different ratio through solvent evaporation method. Then, best formulation of solid dispersed AVT was evaluated and went for development and evaluation of fast dissolving tablet (FDT) of it by using different superdisintegrants. Final tablet formulation was optimized on the basis of drug content analysis, disintegration study and *in vitro* dissolution study. Analysis of AVT in different study samples were done by a developed high performance liquid chromatographic method. Differential scanning calorimetry was performed to identify the physicochemical interaction between drug, carrier and other formulation constituents. Results showed that significantly better dissolution rate of solid dispersed AVT with PEG6000 in the ratio of 1:5 than its physical mixture. Final formulation of FDT containing solid dispersed AVT revealed that successfully improvement of solubility as well as dissolution of AVT in a very quick time. This study could be very much helpful for better bioavailability of poorly water soluble drug avoiding first pass metabolism.

Keywords: Solid dispersion; Fast dissolving tablet; Poorly water soluble drug; Solubility; Dissolution.

INTRODUCTION

Approximately 40% drugs have poor water solubility and the oral delivery of such drugs are frequently associated with implications of low bioavailability, high intra and inter subject variability, and lack of dose proportionality because their dissolution step is rate limiting due to poor water solubility.[1] Solid dispersion of drug helps to reduce the particle size of drug due to molecular dispersion.[2] It improves wettability as well as porosity of drug due to presence of water soluble carrier. Poorly water soluble crystalline drug presents as amorphous form in the product of solid dispersion of drug which aids to increase bioavailability of drug following improvement of solubility of the drug.[3-7]

Fast dissolving tablet (FDT) is placed in the mouth, allowed to disperse or dissolve in the saliva and then swallowed in normal way. From oral mucosa, drug is directly absorbed into the systemic circulation obviates first pass hepatic metabolism. Therefore, better bioavailability is obtained for poorly water soluble drug with high first pass metabolism. Drug that can be absorbed equally well through the gastro-intestinal tract, bioavailability can still be significantly reduced by site specific changes. Presystemic clearance may lead to poor absorption of drug into systemic circulation. So, FDT has an advantage for drugs which have presystemic clearance. FDT is also suitable for delivery of irritant drugs without producing any problem because maximum amount of drug is absorbed from oral cavity.[8-12]

Atorvastatin calcium (AVT), a hypolipidemic drug was chosen as model drug as it is sparingly soluble in water. But only 15-30% of oral dose is bioavailable due to its extensive presystemic metabolism (The major metabolites much less active than parent compound). Moreover, it has pH dependent solubility as well as least soluble in acidic pH and its solubility is increased on increase in pH. As it is least ionizable at pH 4.5 to 6, it is mostly in neutral form at salivary pH and facilitates absorption from oral cavity.[13-14]

In the present study, we developed and evaluated FDT containing solid dispersion of model drug under the frame of improved of solubility to achieve better bioavailability of the drug.

MATERIALS AND METHODS

Chemicals

Atorvastatin calcium was a gift sample from Kusum Healthcare Pvt. Ltd. (Mumbai). PVP K-30 was purchased from S. D. Fine Chemicals Ltd. (Mumbai). MCC, Cross povidone, Sodium starch glycolate, Mannitol, Cross carmellose sodium, PEG6000, Colloidal silicon dioxide, Talcum powder, Magnesium stearate and Lactose were provided by Stadmed Private Ltd. (Kolkata). All other chemicals used in the present study were of AR Grade.

Development of high performance liquid chromatography (HPLC) method for analysis of AVT

At first a method for quantitation of AVT was developed and optimized. Then, to obtain a standard curve, 20 mg of AVT was weighed accurately and a stock solution of 20µg/ml was prepared in methanol which is then diluted with mobile phase to 1, 2, 5, 8, 10, and 15 µg/ml. These solutions were analyzed by the developed HPLC method and obtained standard curve for estimation of AVT.

Preparation and evaluation of solid dispersions

Preparation of physical mixture

Physical mixture (PM) of AVT was prepared by mixing accurately weighed amounts of AVT with each carrier's viz. PVP K-30, PEG 6000 and talc in proportion of 1:1, 1:5 and 1:8 by geometric dilution method with the help of a spatula for 10 minutes.

Preparation by solvent evaporation method

The required amount of AVT(10mg) and carrier in 1:1, 1:2 & 1:3 ratio (Table 1) were dissolved in sufficient volume of methanol with continuous stirring. The solvent from the solution was removed at 45°C with continuous stirring to obtain dry mass. Dried mass was pulverized passed through 44 mesh sieve and stored in desiccator until used for further studies.

Drug content analysis of solid dispersed AVT

An accurately weighed quantity of solid dispersion equivalent to 10 mg of AVT was taken into a 10 ml volumetric flask and dissolved in methanol. Then solution was filtered and 50µl of it was injected into the HPLC system for drug content analysis.

In-vitro dissolution study solid dispersed AVT

Dissolution studies were performed in distilled water (pH 6.8) at (37 ± 0.5) ºC, using 6-station USP type II (basket) apparatus (TDT-50, Electrolab, Mumbai, India) with paddle rotating at 50 rpm. Solid products (solid dispersed product as well as physical mixtures) each containing 10 mg of AVT were subjected to dissolution following filling in colorless hard gelatin capsule by the hand filling method. At fixed time intervals, samples were withdrawn and filtered (pore size

0.22 µm). Volume of dissolution fluid was adjusted to 900 ml, by replacing each 5 ml aliquot withdrawn with 5 ml of distilled water, pH 6.8. Concentration of AVT in each sample was determined by HPLC using standard curve equation.

Table 1: Description and code of solid dispersion formulations

Formulation code	AVT (mg)	Carrier (mg)			Drug & Carrier Ratio
		PVP K-30	PEG6000	Lactose	
S-1	10	20	-	-	1 : 2
S-2	10	50	-	-	1 : 5
S-3	10	80	-	-	1 : 8
S-4	10	-	20	-	1 : 2
S-5	10	-	50	-	1 : 5
S-6	10	-	80	-	1 : 8
S-7	10	-	-	20	1 : 2
S-8	10	-	-	50	1 : 5
S-9	10	-	-	80	1 :8

Preparation and evaluation of FDT containing solid dispersed AVT

Preparation of FDT

Here we worked with best solid dispersed form of AVT. Compositions of different trial formulations(F-1 to F-9) which were prepared using different superdisintegrants, fillers ,glidants, lubricants, antiadhererants etc for solid dispersed AVT (equivalent to 10mg AVT), were summarized in Table 2. At first solid dispersed AVT, filler, sweetening agent, flavouring agent were blended in a planetary mixer for 5 minutes after passing all the materials through 60 mesh (250 µm) screen and mixed with magnesium stearate and talc or colloidal silicon dioxide for 2 minutes. Mixture of powder is weighed finally to adjust the final weight of individual tablet (150 mg) considering its loss during operational handling. The powder blend thus obtained was directly compressed into tablet to average hardness of 4 kg/sq.cm as on an 8 station rotary tablet machine (CIP Machineries Pvt. Ltd., Ahmedabad, India) with 8.93mm circular biconvex tooling at a rotational speed of 72 rpm.

Table 2: Description and code of FDT formulations of solid dispersed AVT

Ingredients	Formulation code								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Atorvastatin calcium	10	10	10	10	10	10	10	10	10
MCC	60	60	60	60	60	60	60	60	60
Cross povidone	4.5	7.5	7.5	-	-	-	-	-	7.5
Na-starch glycolate	-	-	-	6	12	6	-	-	-
Cross carmellose-sodium	-	-	7.5	-	-	7.5	3	7.5	-
Mg-stearate	2	2	2	2	2	2	2	2	-
Talc	2	2	2	2	2	2	2	2	-
Colloidal silicon dioxide	-	-	-	-	-	-	-	-	1.5
Orange flavour	1	1	1	1	1	1	1	1	1
Mannitol q.s to	150	150	150	150	150	150	150	150	150

Evaluation of FDT containing solid dispersed AVT

Physical property of FDT containing solid dispersed AVT

The tablets were characterized immediately after preparation. The weight variation of the tablets was evaluated on 20 tablets according to official method (IP, 1996) using an electronic balance (Sartorius GC 103). Friability was determined using 10 tablets in a Roche friabilator for 4 min at a speed of 25 rpm. For each formulation the hardness of 10 tablets was also evaluated using a Monsanto hardness tester (Campbell electronics, India). The thickness of the tablets was measured on 10 tablets with Vernier Calipers (Mitutoyo, Japan).

Assay of FDT containing solid dispersed AVT

Assay procedure was carried out by already developed HPLC method using test and reference solution. Test solution was prepared by using 20 tablets were weighed and powdered with the help of mortar and pestle. A quantity of powder equivalent to about 100 mg of AVT was weighed accurately and taken in a 100 ml volumetric flask, shaken with 70 ml of methanol for 15 minutes, diluted to 100 ml methanol and filtered. 0.1 ml of that solution was diluted to 10 ml with mobile phase so that final concentration of the test solution would be 10 µg/ml. In the other hand, reference solution was prepared at 1 mg/ml taking 10 mg reference standard of AVT in a 10 ml volumetric flask and dissolving it with 10 ml methanol. Reference working solution of 10 µg/ml was prepared diluting 0.1 ml stock solution to 10 ml with mobile phase.

Disintegration study of FDT containing solid dispersed AVT

One of the important parameters in the development of fast dissolving tablet is disintegration time of tablet. Disintegration time of the tablet was measured individually on six tablets in distilled water of pH 6.8 at (37±0.5) ºC and following other parameters as described in Indian Pharmacopia using USP disintegration apparatus.

Dissolution study of FDT containing solid dispersed AVT

Drug release from 6 tablets of each formulation was determined using the USP II (paddle) apparatus (Electrolab, TDT 06P, USP XXIII) where water of pH 6.8 were used as dissolution media maintained at 37^0C (± 0.5^0C) at a paddle rotation speed of 100 rpm. 5 ml of aliquot were withdrawn at 5mins, 15min, 30min, 45min, and 60min with replacement of 5 ml fresh media. Samples were analyzed by developed HPLC method as described earlier.

Compatibility study of materials used in FDT containing solid dispersed AVT

Interactions in the solid state between the active ingredient(s) and excipients in pharmaceutical dosage forms can give rise to changes in the stability, solubility, dissolution rate and bioavailability of drugs. Unless incompatibility is evident, it is necessary to carry out a stability study that usually requires months or years. Thus, it is important to choose a method for evaluation of the solid state stability that gives fast and reliable information about the possible

interaction. A number of techniques can be used to indicate the drug/excipient interaction. DSC study is most convenient one of them. Differential Scanning Calorimetry (DSC) studies were carried out to find out if there was any interaction between AVT and other formulation constituents by DSC 821 (Parkin Elmer, Switzerland).

RESULT AND DISCUSSION

Chromatographic determination of AVT

Following chromatographic parameters for analysis of AVT were finalized and representative chromatogram of a dissolution sample showing separation of AVT at 1.767 min (Fig. 1):

Instrument	: Knauer Advanced Scientific Instruments, Germany,
Pump	: K-2501, UV Detector: K-501,
Mobile Phase	: Methanol: Water = 50: 50 (v/v)
Column	: Thermo BDS hypersil C 18, 250 X 4.6 mm, 5 µm particle size
Column	: 248 nm
Loop size	: 50 µl
Flow rate	: 1ml/min

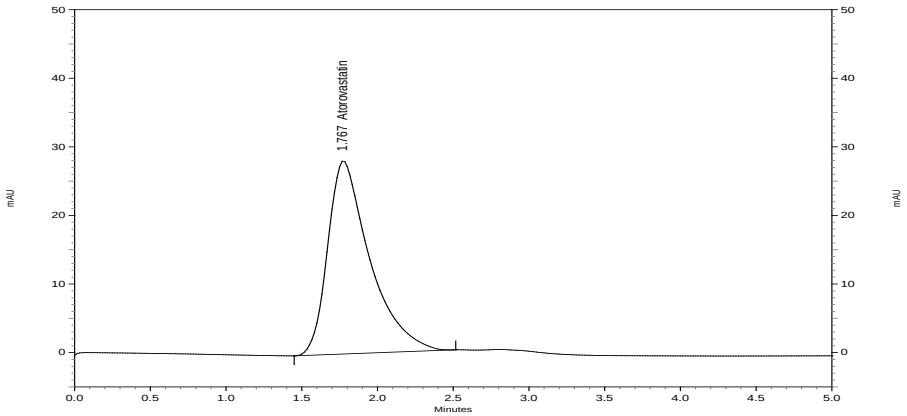

Fig. 1: Representative chromatogram showing separation of AVT at 1.767min.

Preparation of standard curve for AVT using HPLC method:

Standard samples for AVT were prepared as mentioned previously. The linear regression of the peak area of AVT versus concentration using weighted 1/concentration^2 was used to prepare the standard curve. Regression equation of the standard curve was then used to quantitate AVT in samples of drug content analysis as well as in vitro dissolution study. Standard curve of AVT was linear in the concentration range of 1 to 15 µg/ml with average correlation coefficient of 0.9936.

Evaluation of solid dispersion of AVT

Drug content analysis of solid dispersed AVT

Drug content of nine formulations (S-1 to S-9) were between the ranges of 75.29 to 99.47 %. Among all formulation S-5 contained the maximum amount of drug.

In-vitro dissolution study of solid dispersed AVT

From Table 3 it was seen that dissolution of AVT was increased with increase in each PEG6000 and lactose up to 1:5 ratio of drug to PEG6000 or drug to lactose. Increment in the dissolution rate may be due to increase wettability by the carrier. At higher level (drug: carrier :: 1:8), the negative effect on dissolution appears that may be due to distortion of molecular dispersion structure, which leaves an insoluble base particle and increases accumulation of carrier molecule in the bulk, to cause a saturation, by which further solubility of AVT is retarded. It was also seen from Table 3 that dissolution rate of the drug moderately decreased with the increment in PVP K-30 proportion up to drug and PVP K-30 ratio of 1:5. Further increment of PVP K30 (drug: PVP K-30:: 1:8), gave marked decrease in dissolution. This may be due to formation of viscous boundary layer around the drug particles, leading to decrease in the dissolution rate. The PEG6000 solid dispersion in the drug and carrier ratio of 1:5 i.e. (S-5 in Fig. 2) showing maximum dissolution rate was converted to cost effective FDT, with improved dissolution. Comparison of solid dispersion of AVT with physical mixture of AVT (S-5(PM)) (Table 4) showed that increase in dissolution rate of AVT by solid dispersion with each carrier and maximum increment of dissolution rate in case of PEG6000 solid dispersion in the drug and carrier ratio of 1:5 (Fig. 3). Then we went for preparation of fast dissolving tablet where we used the best solid dispersed formulation of AVT i.e. S-5.

Table 3: Dissolution profiles of solid dispersed AVT formulations

Time	Cumulative % drug release*								
(min)	S-1	S-2	S-3	S-4	S-5	S-6	S-7	S-8	S-9
0	0	0	0	0	0	0	0	0	0
15	62.55 ± 0.216	45.86 ± 0.136	32.75 ± 0.211	64.93 ± 0.169	68.31 ± 0.102	45.46 ± 0.214	61.64 ± 0.314	65.32 ± 0.218	41.01 ± 0.326
30	73.76 ± 0.168	61.25 ± 0.120	41.01 ± 0.216	76.32 ± 0.157	80.82 ± 0.106.	56.94 ± 0.216	66.49 ± 0.169	78.2 ± 0.389	50.48 ± 0.369
45	76.13 ± 0.123	66.29 ± 0.321	48.81 ± 0.178	82.8 ± 0.199	88.99 ± 0.106	66.66 ± 0.209	73.49 ± 0.149	85.21 ± 0.258	57.56 ± 0.347
60	79.95 ± 0.214	72.48 ± 0.129	55.68 ± 0.147	83.21 ± 0.121	92.23 ± 0.101	73.24 ± 0.213	76.32 ± 0.198	87.11 ± 0.216	61.62 ± 0.269

*All values are expressed as mean (± SD), n = 3

Table 4: Dissolution profiles of physical mixture of AVT formulations

Time (Min)	Cumulative % drug release (PM)*								
	S-1 PM	S-2 PM	S-3 PM	S-4 PM	S-5 PM	S-6 PM	S-7 PM	S-8 PM	S-9 PM
0	0	0	0	0	0	0	0	0	0
15	11.08 ± 0.215	8.50 ± 0.254	32.75 ± 0.211	8.29 ± 0.256	9.59 ± 0.215	8.29 ± 0.215	8.97 ± 0.258	6.45 ± 0.215	9.86 ± 0.197
30	44.71 ± 0.369	41.71 ± 0.168	41.01 ± 0.312	45.83 ± 0.244	39.64 ± 0.121	40.82 ± 0.255	48.21 ± 0.321	39.58 ± 0.214	45.83 ± 0.478
45	50.33 ± 0.258	50.68 ± 0.187	48.81 ± 0.155	50.60 ± 0.147	41.54 ± 0.111	55.67 ± 0.269	51.61 ± 0.256	41.23 ± 0.111	49.79 ± 0.214
60	54.71 ± 0.298	53.018 ± 0.197	55.68 ± 0.169	51.86 ± 0.159	46.33 ± 0.129	59.62 ± 0.287	55.70 ± 0.197	50.37 ± 0.165	55.84 ± 0.159

*All values are expressed as mean (± SD), n = 3

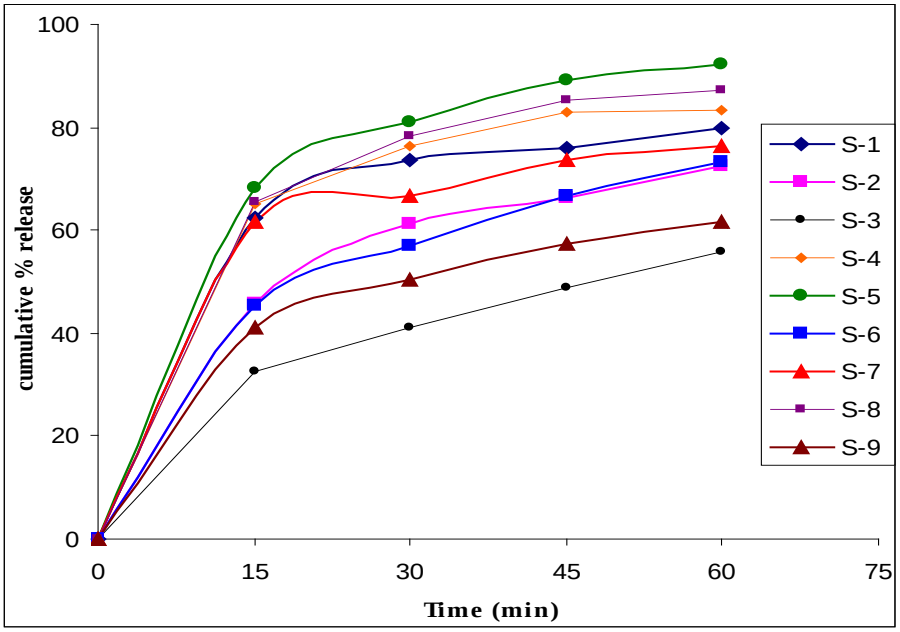

Fig. 2: Dissolution profiles of solid dispersed AVT

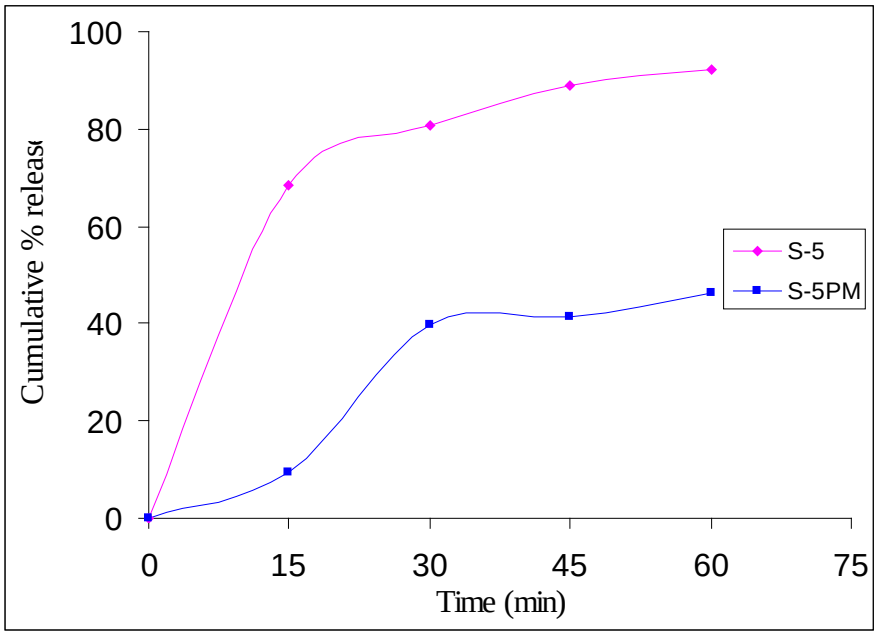

Fig. 3: Dissolution profiles of solid dispersed AVT (S-5) and physical mixture of AVT (S-5PM)

Physical properties and drug content of fast dissolving tablet containing solid dispersed AVT

Assayed amount of drug in various formulations varied between 98.21% and 99.52%. Among all F-1, F-2, F-4 and F-9 were having greater than 99% drug content. Tablets weights varied between 150.51 and 151.04 mg, thickness between 4.49 and 4.57 mm, hardness around 4.0 kg/sq. cm, and friability ranged between 0.39% and 0.57%. Thus, all the physical parameters of the matrices were practically within acceptable limit.

Disintegration study of FDT containing solid dispersed AVT

In the present study, all the tablets disintegrated in less than 27.53 sec fulfilling the official requirements (less than 3 min) for fast dissolving tablets. F-9 formulation took 7.53sec to disintegrate completely. Fig. 4 depicted the disintegration behavior of the tablets. It was observed that the disintegration time of the tablets decreased with increase in the level of cross povidone. In case of tablets containing cross carmellose sodium, increasing level of cross carmellose sodium had almost no effect on the disintegration time of the tablets. However, disintegration time decreased with increase in the level of sodium starch glycolate. It indicates that sodium starch glycolate had a negative effect on the disintegration of tablets. At higher levels, formation of a viscous gel layer by sodium starch glycolate might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration of tablet contents. Thus these results suggest that the disintegration times can be decreased by using wicking type of disintegrants like cross povidone.

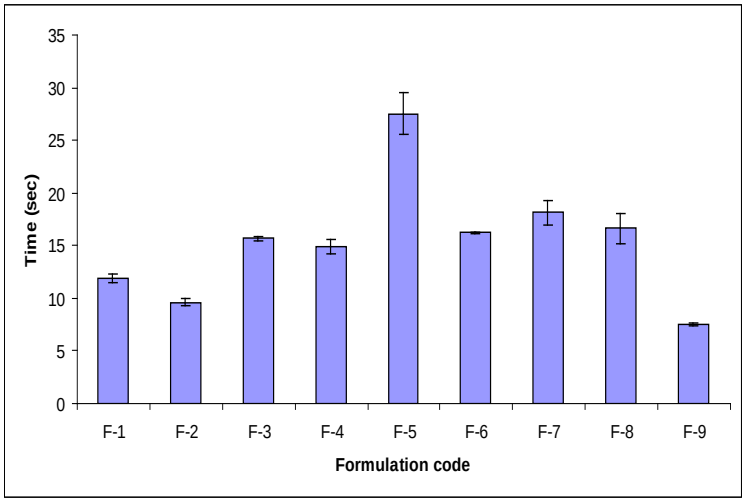

Fig. 4: Study of disintegration time of FDT containing solid dispersed AVT

In vitro dissolution study of FDT containing solid dispersed AVT

From *in vitro* dissolution study of FDT containing solid dispersion of AVT with PEG6000 in the 1:5 ratio of drug to PEG6000. Dissolution data shown that only two formulations (F-2, F-9) gave over 50% of drug release within 5 minutes and only one formulation gave maximum drug release of 89.90% in 60 min. So, F-9 is the best formulation among these formulations (Fig. 5). Tablets were prepared with the physical mixtures of AVT and PEG6000 in the proportion of 1:5 and keeping other composition of F-9 was fixed. Then we compared F-9 & F-9(PM) in respect to the cumulative percentage release of AVT. There was only 7.98% drug release from F-9(PM). So, there was improvement of dissolution of AVT (Fig. 6).

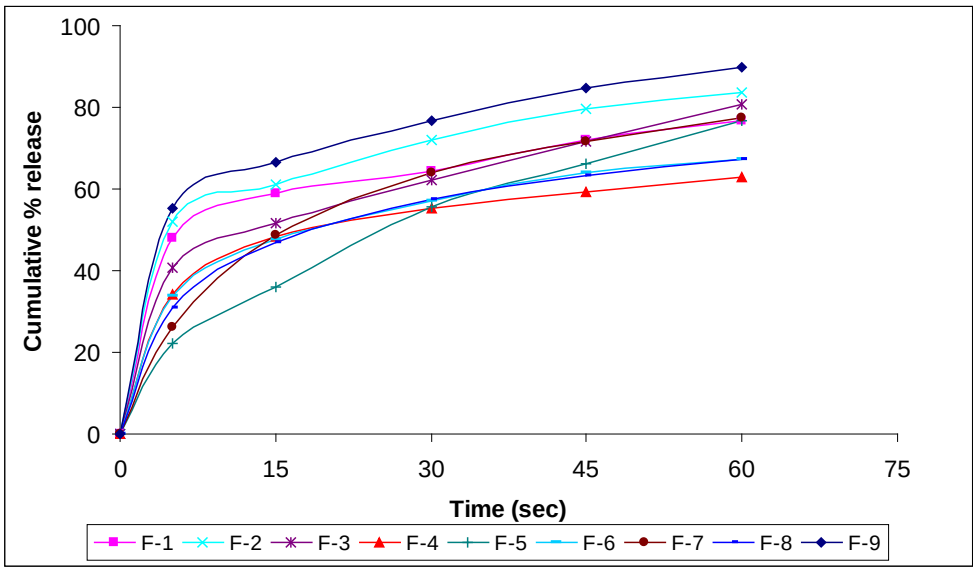

Fig. 5: Dissolution profiles of FDT containing solid dispersed AVT

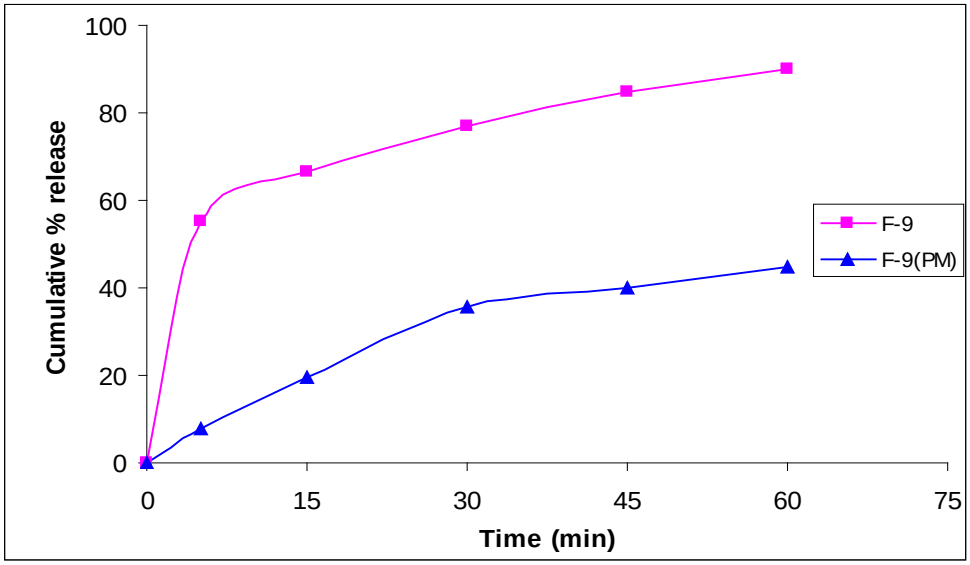

Fig.6: Dissolution profiles of FDT formulations containing solid dispersed AVT {F-9} and AVT {F-9 (PM)}

Compatibility study of materials used in FDT containing solid dispersed AVT

If there was any interactions in the final composition of FDT were deduced from DSC by changes in the thermal events, such as elimination of an endotherm or exotherm peak, or appearance of a new peak. However, very mild broadening of peaks leading to changes in peak temperature occurs simply due to mixing of the components without indicating any significant interaction. As all thermal features more or less remain the same, compatibility could be expected (Fig. 7 to Fig. 10).

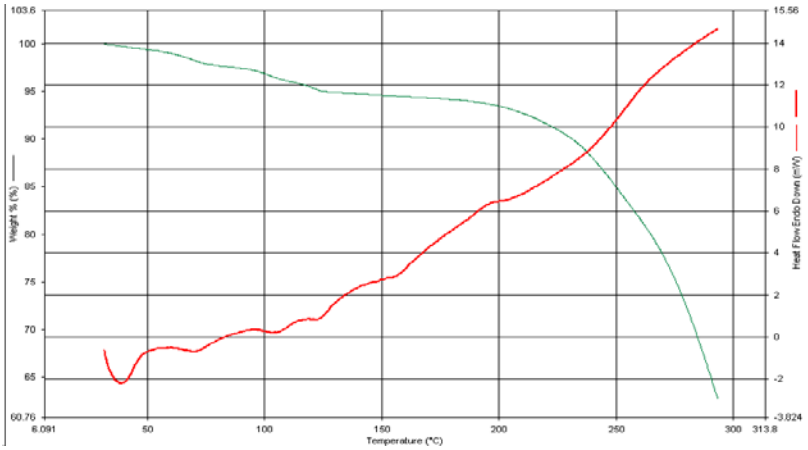

Fig. 7: Thermogram of AVT

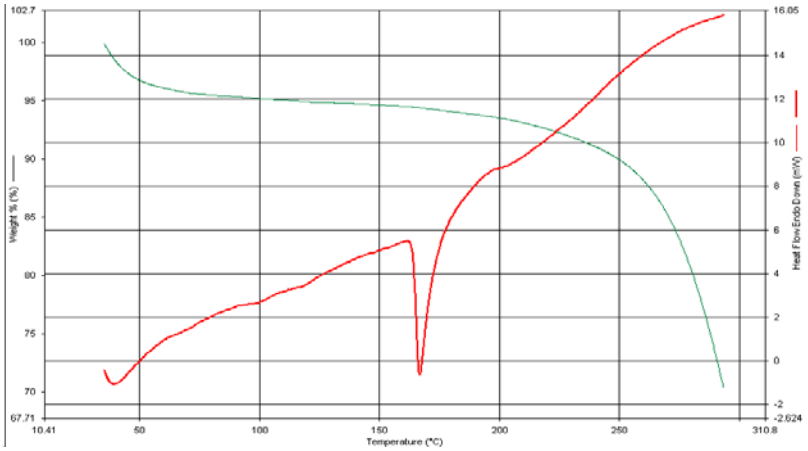

Fig. 8: Thermogram of mannitol

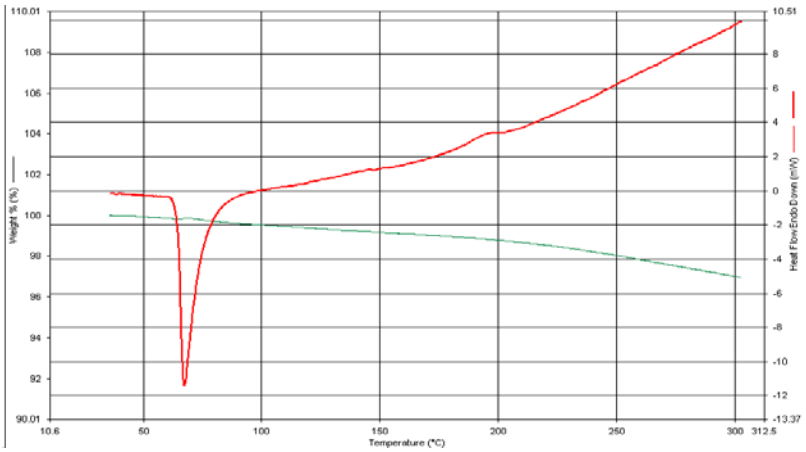

Fig. 9: Thermogram of PEG6000

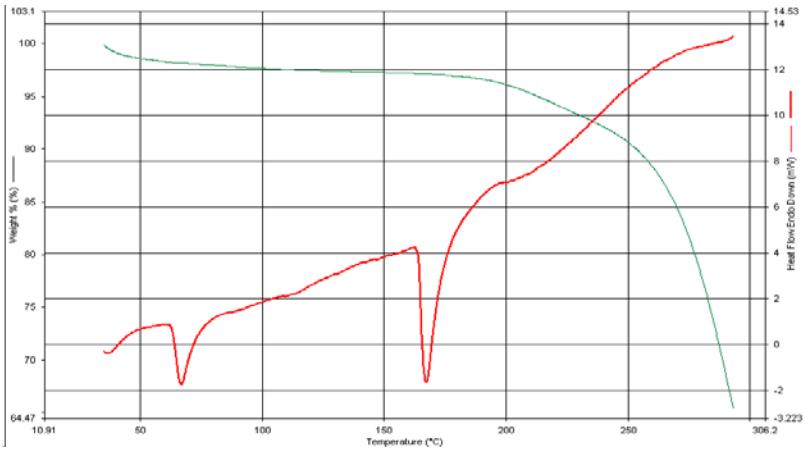

Fig. 10: Thermogram of physical mixture of final formulation of FDT containing solid dispersion of AVT with PEG6000

CONCLUSION

It can be concluded that the poorly water soluble drugs like AVT is having the problem of less bioavailability. Solid dispersion technique adopted in this investigation has been found to increase the dissolution rate following improved solubility of AVT by reducing particle size which facilitates improved absorption through buccal mucosa. Further studies are required to establish a correlation between pharmacokinetic and pharmacodynamic responses of the drug when administered in the form of fast dissolving tablet. Again, it is also necessary to carry out further studies in animals and human being before this formulation could be commercially exploited.

ACKNOWLEDGEMENTS

We are very much thankful to the University Grants Commission (UGC), New Delhi, India for providing the necessary fund for this research. We are very grateful to the M/s Kusum Healthcare Private Limited, Mumbai, India for getting atorvastatin calcium as a gift sample. We are also grateful to the Department of Science and Technology (DST), New Delhi, India for providing the necessary instrumental facilities.

REFERENCES

1. Quan D, Xu G, Wu X. Studies on preparation and absolute bioavailability of a self-emulsifying system containing puerarin. Chem Pharm Bull 2007; 55: 800-803.
2. Vasconcelos T. Solid dispersions as stratigy to improve oral bioavailability of poorly water soluble drugs. Drug Discov Today 2007; 12: 1068-1075.
3. Babu GV, Kumar NR, Himasankar K, Seshasayana A, Murthy KV. Nimesulide-modified gum karaya solid mixtures: preparation, characterization and formulation development. Drug Dev Ind Pharm 2003; 29: 855-864.
4. Murali Mohan Babu GV, Prasad CHDS, Ramana Murthy KV. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water soluble drug nimodipine. Int J Pharm 2002; 234:1-17.
5. Modi A and Tayade P. Enhancement of Dissolution Profile by Solid Dispersion (Kneading) Technique. AAPS PharmSciTech 2006; 7: 68.
6. Mandal D, Ojha PK, Nandy BC, Ghosh LK. Effects of carriers on solid dispersions of simvastatin: Physicochemical characterization and dissolution studies. Der Pharmacia Littre. 2010; 2:47-56.
7. Aejaz A, Azmail K, Sanaullah S, Mohsin AA.Studies on aceclofenac solid dispersion in corporated gels: development, characterizatio n and in vitro evaluation. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2 (Suppl 1):111-115.
8. Patel MM and Patel DM. Fast dissolving Valdecoxib tablets containing solid dispersion of Valdecoxib. International Journal of Pharmaceutical Sciences 2006; 68: 222-226.
9. Patel DM and Patel MM. Optimization of fast dissolving etoricoxib tablets prepared by sublimation technique. International Journal of Pharmaceutical Sciences 2008; 70:71-76.
10. Newa M, Bhandari KH, Kim J, Yoo B. Preparation and Evaluation of Fast Dissolving Ibuprofen-Polyethylene Glycol 6000 Solid Dispersions. Drug delivery 2008; 15:355 – 364.
11. Seager H. Drug-delivery products and the Zydis Fast Dissolving Dosage Form. J Pharm Pharmacol 1998; 50: 375-382.

12. Squier CA, Nanny D. Measurement of blood flow in the oral mucosa and skin of the rhesus monkey using radiolabelled microspheres. Arch Oral Biol 1985; 30: 313-8.
13. Kadu PJ, Kushare SS, Thacker DD, Gattani SG. Enhancement of oral bioavailability of atorvastatin calcium by self-emulsifying drug delivery systems (SEDDS). Pharmaceutical Development and Technology 2011; 16: 65-74
14. Shen HR, Li ZD, Zhong MK. Preparation and evaluation of self-microemulsifying drug delivery systems containing atorvastatin. Yao Xue Xue Bao 2005; 40: 982–7.