American Journal of Advanced Drug Delivery

www.ojadd.com

Original Article

Enhancement of Solubility and Bioavailability of Hydrochlorthiazide Using Solid Dispersion Technique

E. Sangeetha*, Vinay Umesh Rao, M. Sudhakar and S. Manisha

Department of Pharmaceutics, Malla Reddy College of Pharmacy, Secunderabad, Telangana, India

Date of Receipt- 19/11/2015
Date of Revision- 08/12/2015
Date of Acceptance- 22/12/2015

Address for Correspondence

Department of Pharmaceutics, Malla Reddy College of Pharmacy, Secunderabad, Telangana, India
E-mail: vinayrao68@gmail.com

ABSTRACT

Objective: The variable aqueous solubility of Hydrochlorthiazide (HCTZ) is the major factor limiting its oral bioavailability. The objective of the study is to enhance of the solubility of HCTZ by using solid dispersion technique.

Methods: The polymers used were PVP K30, PVP S630, HPMC & PEG 6000 and solid dispersions were prepared by solvent evaporation method in different ratios of 1:0.5, 1:1, 1:3, 1:5 respectively. The prepared solid dispersions were characterized by DSC and FTIR. The equilibrium solubility was determined in water to study the effect of polymers on solubility of HCTZ. *In vitro* dissolution studies were conducted in distilled water from solid dispersions equivalent to 12.5 mg of HCTZ. How the solid dispersions affect the permeation of the drug across membranes was evaluated by measuring the *In vitro* permeation of Drug PVP and Drug HPMC across cellophane membrane using the vertical Franz diffusion cell.

Results: Successful conversion of the crystalline Hydrochlorthiazide to amorphous solid dispersion was achieved at 1:1, 1:3 & 1:5 levels of drug to HPMC E 15 & drug to PVP and with PVP S630 it was achieved at 1:3 & 1:5 level. Amorphous conversion was not observed in case of PEG 6000 at any level. The solid dispersion prepared with HPMC E 15 & PVP K30 at 1:5 level showed a 98% and 66.3% drug release at 5min respectively. The enhancements in case of 1:5 Plasdone s630 and PEG 6000 were not significant. The results of equilibrium solubility studies indicates that the solvent evaporated solid dispersions of HPMC E 15 & PVP K30 were the best Permeation studies indicate that a 3 to 4 fold increase in the solubility of the drug results in 10 fold increase in permeation. Thus enhancement in solubility also results in enhancement in the permeation across artificial membranes.

Conclusion: The above study shows that solid dispersion of HCTZ

offers a simple and attractive solution to increasing the solubility of the poorly water soluble drug and thereby improve its oral bioavailability.

Keywords: Hydrochlorthiazide (HCTZ), Solid dispersions (SD), Permeation studies.

INTRODUCTION

The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.

Hydrochlorthiazide[1-2] is a diuretic drug belonging to the chemical class of benzoxazole derivative. It acts orally and the dosage used for treatment of congestive heart failure and hypertension ranges from 25 to 50 mg daily alone or combination with other antihypertensive drugs upto 100mg if necessary. HCTZ is a poorly water soluble drug which has a reported bioavailability of <65%.Therefore lots of efforts have been made to increase dissolution of drug. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion[3-6] (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method. The formulation of having low aqueous solubility using solid technology has been an active area of research since 1960. Among the various approaches to improve solubility, the SD technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous.

The aim of the present work was to improve the aqueous solubility of the drug by using solid dispersion technique. Ethanol was determined to be the solvent choice. The polymers used were PVP K30, PVP S630, HPMC & PEG 6000 and solid dispersions were prepared by solvent evaporation method in different ratios. The effect was evaluated by measuring the *In vitro* dissolution in water and permeation studies.

MATERIALS AND METHODS

Chemical and Reagents

HCTZ USP (EMCO Industries), HPMC E 15 CPS (Dow Chemical's), PVP K 30(Ashland specialty), Plasdone S630 (Ashland specialty), PEG 6000(Merck India), Ethanol (Merck India).All other reagents and chemicals used were of analytical reagent grade and were used as such without any further purification. Purified water USP was used where ever required.

EXPERIMENTAL

Solid dispersions were prepared by solvent evaporation technique[7]. The formulation composition details are given in table1.

All batches were evaluated for assay and uniformity of content. Each sample (approximately 2.5mg) was subjected to differential scanning calorimetry over a range of 50^0C to 300^oC. Samples were heated under nitrogen atmosphere.(Flow rate of N_2-

50ml/min). Equilibrium solubility studies (about 30 mg equivalent weight of SD) were carried out in purified water.

Each batch of SDs (at n=3) was subjected to dissolution in purified water using USP type I apparatus at 50rpm[8]. Samples were withdrawn at 5,10,15,30,45,60 and 75 minutes interval and analyzed for % drug dissolved using UV spectrophotometric method.

To find out the permeability of the solid dispersion of the HCTZ, *In vitro* permeation studies of solid dispersions (HPMC 1:5, PVP 1:5) and plain drug were carried out in pH 7.4 phosphate buffer. Samples were withdrawn at 1,2,3,4 and 5 hrs interval and analyzed for %drug permeated through artificial membrane using UV spectrophotometric method.

RESULTS AND DISCUSSION[11-19]

The content uniformity and assay values of solid dispersions were within a range of 96.5% to 98.3%.DSC thermograms of samples are shown in fig1, 2, 3 & 4.

Successful conversion of the crystalline HCTZ to amorphous solid dispersion was achieved at 1:1, 1:3, &1:5 levels of drug to HPMC E 15 & drug to PVP and with PVP S630 it was achieved at 1:3 &1:5 level. Amorphous conversion was not observed in case of PEG 6000 at any level. Comparative values of equilibrium solubility studies are shown in fig 5.

Equilibrium solubility data showed that there was no significant enhancement in aqueous solubility for PEG based at all ratios. In case of S 630 based SD, significant enhancement occurred only at 1:5 ratio (approximately 2 fold) at lower ratios the enhancement was not significant. In case of PVP, at 1:1 and 1:3 ratios the enhancement in permeability is four folds while at 1:5 ratio there is a nearly 5 fold enhancement in aqueous solubility.

In case of HPMC significant enhancement is observed at all ratios. Nearly 4 folds enhancement is observed up to 1:3 ratio and 6 to 6.5 folds enhancement is observed at 1:5 ratio. This may be due to the fact that in the DSC graphs no amorphous conversion of the drug is observed for PEG 6000 at any ratios. While in case of HPMC amorphous conversion is observed from 1:0.5 while in case of PVP it was observed from 1:1 ratio. On the other hand S-630 shows amorphous conversion from 1:3 level onwards.

The rank order correlation among the polymers is as follows:

HPMC (1:5)>PVP (1:5)>HPMC (1:0.5)>PVP (1:1)>HPMC (1:3)>PVP (1:3)>HPMC (1:1)

Hence HPMC (1:5) PVP (1:5) were selected as the best polymers and ratios for the further evaluation studies of solid dispersion of HCTZ.

In vitro dissolution data of solid dispersions was shown in the table 2 and comparison of drug release from 1:5 SDs at 5 min and 30 min were shown in fig 6.

The solid dispersion prepared with HPMC E 15 & PVP K30 at 1:5 level showed a 98% and 66.3% drug release at 5 min respectively. The enhancement in case of 1:5 Plasdone S630 and PEG 6000 were not significant.

The permeation studies were conducted to F4 and F8 formulations because from the results of dissolution data it is said that only 1:5 formulations were found to the best among all the rest formulations. The comparative values of drug permeated at 1hr and 5hr are shown in fig 7.

From this study it was clear that the permeation increased at about 10 folds with HPMC and 2.5 fold with PVP K 30 when compared to the plain drug.

CONCLUSION

DSC and FTIR studies results indicated that no interaction of drug with the carriers and conversion of crystalline form to amorphous form of drug results in improvement of solubility. SD technique was successfully employed to enhance the aqueous solubility of HCTZ. The enhanced solubility also leads to enhanced permeability across artificial membrane. Further *In vivo* studies to substantiate these findings are under progress in our laboratory.

ACKNOWLEDGEMENT

The authors were thankful to Malla Reddy College of Pharmacy, Hyderabad for providing the facilities of this research work

Declaration

This research work entitled **"**ENHANCEMENT OF SOLUBILITY AND BIOAVAILABILITY OF HYDROCHLOR-THIAZIDE USING SOLID DISPERSION TECHNIQUE**"** is an original one and carried out by us in Malla Reddy College of Pharmacy, Hyderabad.

REFERENCES

1. "Hydrochlorothiazide". *The American Society of Health-System Pharmacists*. Retrieved 3 April 2011.
2. Beermann B, Groschinsky-Grind M, Rosén A. (1976). "Absorption, metabolism, and excretion of hydrochlorothiazide". *Clin Pharmacol Ther* **19** (5 (Pt 1)): 531–7
3. W. L. Chiou, and S. Riegelman, "Pharmaceutical applications of solid dispersion systems," J. Pharm. Sci., vol. 60, no. 9, 1971, pp. 1281-1302, doi: 10.1002/jps.2600600902
4. C. Leunner, and J. Dressman, "Improving drug solubility for oral delivery using solid di3.spersions," Eur. J. Pharm. Biopharm., vol. 50, no.1, July 2000, pp. 47-60.
5. Sethia, "Solid dispersions-revival with greater possibilities and applications in oral drug delivery," Crit. Rev. Ther. Drug Carrier Syst., vol. 20, issues 2-3, 2003, pp. 215-247.
6. T. Vasconcelos, B. Sarmento, and P. Costa, "Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs," Drug Discov. Today, vol. 12 issues 23-24, 2007, pp. 1068-1075, doi:10.1016/j.drudis.2007.09.005.
7. L. S. Taylor, and G. Zografi, "Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions," Pharm. Res., vol. 14, no. 12, 1997, pp. 1691-1698, doi: 10.1023/A:1012167410376.
8. S. Gahoi, G. K. Jain, M. Singhal, M. Anwar, F. J. Ahmad, and R. K. Khar, "Influence of novel dispersed fusion technique on dissolution and properties of pharmaceutical solid dispersion," Int. J. Pharm. Sci. Rev. Res., vol. 8, issue 2, Article-028, May-June 2011, pp. 170-175.
9. Guidance for Industry, Immediate Release Solid Oral Dosage Forms: Scale Up and Post Approval Changes, November 1995, CDER/FDA.
10. N. S. Seth, "Formulation and evaluation of solid dispersion of olanzepine,"Int. J. Pharm. Sci. Res., vol. 2, issue 3, 2011, pp. 691-697.
11. Akbuga J., Gursoy A., and Kendi E. (1988). The preparation and stability of fast release furosemide-PVP solid dispersion. *Drug Dev. Ind. Pharm.,* 14: 1439–1464.
12. Usui F., Maeda K., Kusai A., Ikeda M., Nishimura K. and Yamamoto K. (1998). Dissolution improvement of RS-8359 by the solid dispersion prepared by the

solvent method. Int. J. Pharm. 170: 247-256.
13. Iskandarsyah, Fudholi A. and Riswaka S. (1999). The effect of two cellulose derivatives as solid dispersion carriers on physical properties and dissolution rate of dexamethasone tablets. Maj. Farm. Indones. 10: 1-8.
14. Duarte JD, Cooper-DeHoff RM (June 2010). "Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics". *Expert Rev Cardiovasc Ther* **8** (6): 793–802. doi:10.1586/erc.10.27. PMC 2904515. PMID 20528637.
15. Londhe V. and Nagarsenker M. (1999). Comparision between Hydroxypropyl-cyclodextrin and polyvinyl pyrrolidine as carriers for carbamazepine solid dispersions. *Indian J. Pharm. Sci.* 61:237-240.
16. Chowdary K.P.and Ramesh K.V. (1995). Microencapsulation of solid dispersions of nifedipine-novel approach for controlling drug release. *Indian Drugs*.32: 477-483.
17. K. Dua, K. Pabreja, and M. V. Ramana, "Preparation, characterization and *In vitro* evaluation of aceclofenac solid dispersions," ARS Pharmaceutica, vol. 51, no. 1, 2010, pp. 57-76.
18. Chaitanya P, Jyothi penta, "Ezetimibe solid dispersions: Formulation, Development and evaluation" *American journal of advanced drug delivery*. vol 2 no 1 (2014)
19. *In vivo-In vitro* evaluation of solid dispersion containing Ibuprofen, *American journal of advanced drug delivery*. vol 1. no 1 (2013).

Table 1. SD Formulation Chart

	HPMC				PVP				PLASDONE S 630				PEG 6000			
Ratios	**1:0.5**	**1:1**	**1:3**	**1:5**	**1:05**	**1:1**	**1:3**	**1:5**	**1:0.5**	**1:1**	**1:3**	**1:5**	**1:0.5**	**1:1**	**1:3**	**1:5**
Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Drug (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Polymer (mg)	50	100	300	500	50	100	300	500	50	100	300	500	50	100	300	500

Table 2. *In vitro* Dissolution data of SDs

Time (min)	MEAN %DRUG RELEASE FROM SDs				
	Plain Drug	HPMC 1:5	PVP (1:5)	Plasdone S630(1:5)	PEG6000 (1:5)
0	0	0	0	0	0
5	57.1	98.05	66.33	51.4	41.9
10	66.33	99	67.3	69.21	49.9
15	78.8	100	73.15	74.5	51.2
30	79.02	100	86.04	80.2	50.3
45	78.7	100	95.94	80.5	50.6
60	78.4	100	98.7	80.8	50.1
75	78.6	100	99.08	83	50

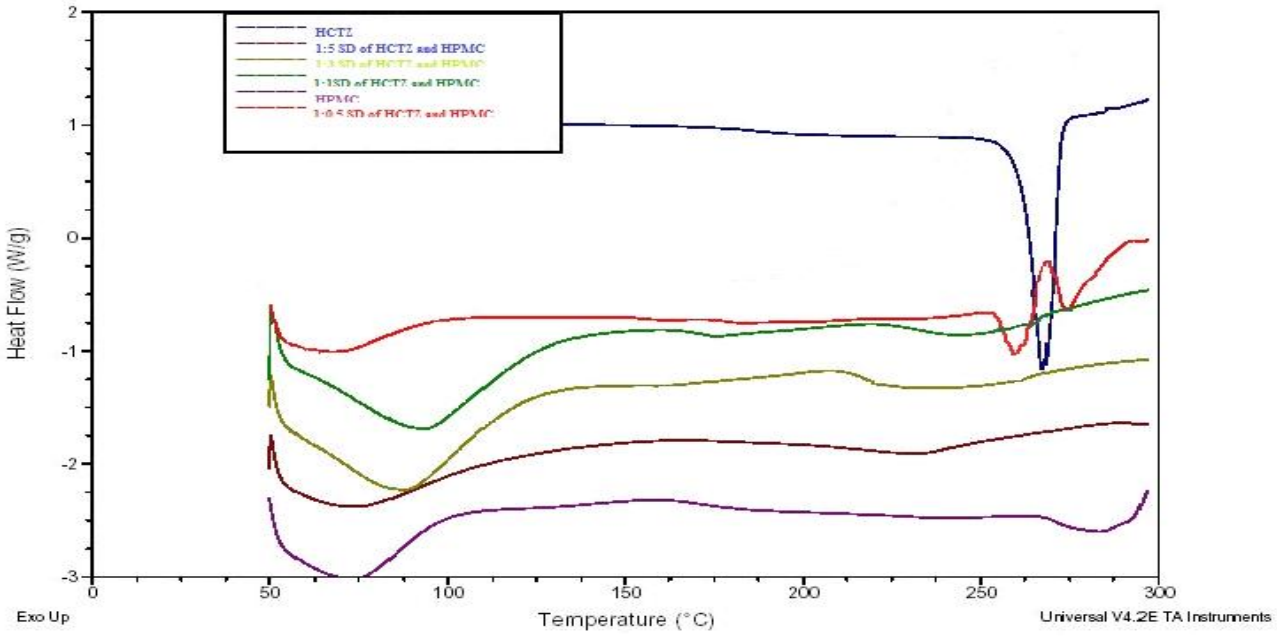

Figure 1. DSC Thermogram of HCTZ SD with HPMC E 15 Cps

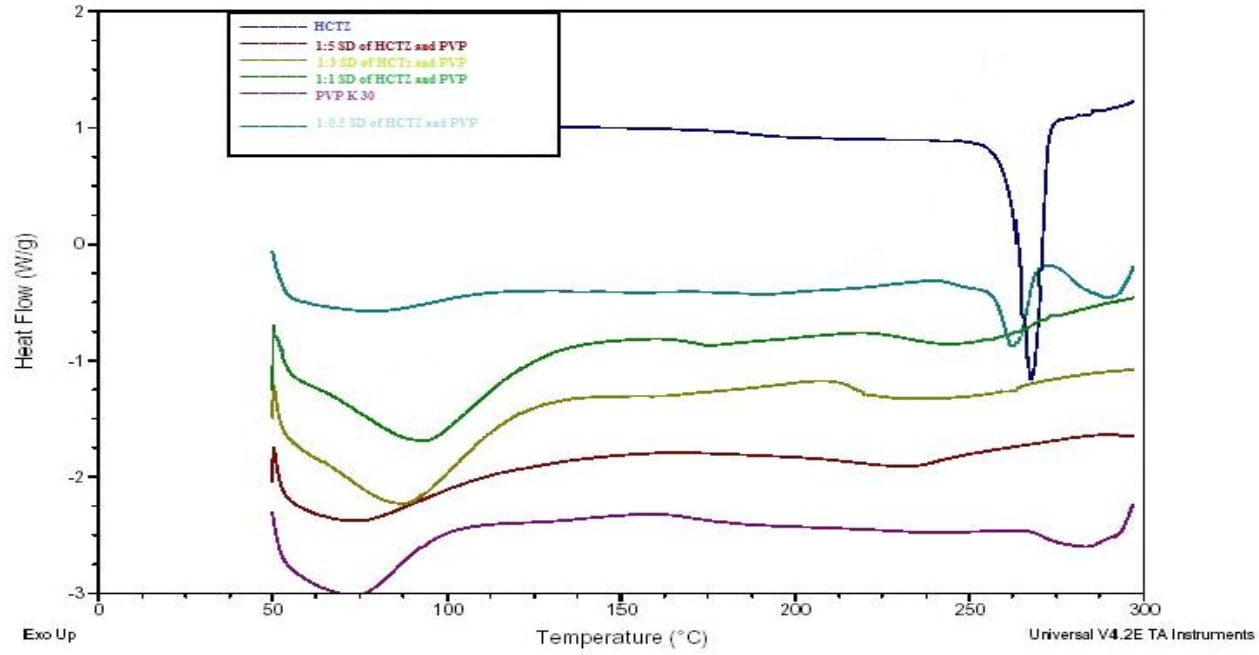

Figure 2. DSC Thermogram of HCTZ SD with PVP K 30

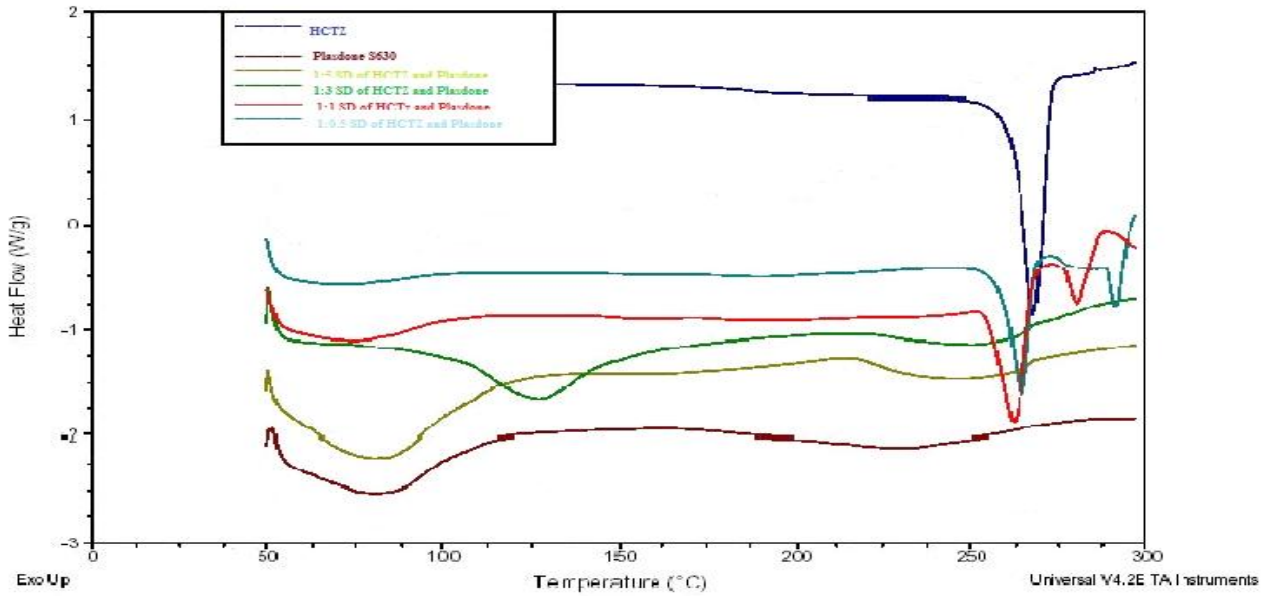

Figure 3. DSC Thermogram of HCTZ SD with Plasdone S630

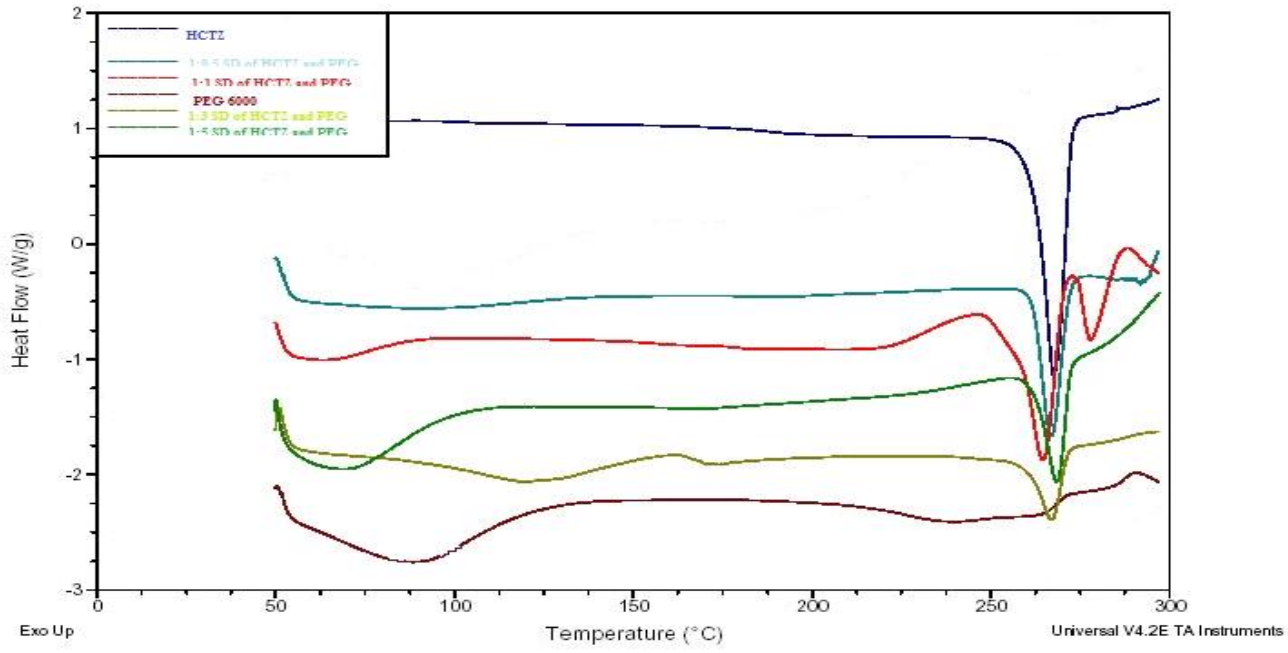

Figure 4. DSC Thermogram of HCTZ SD with PEG 6000

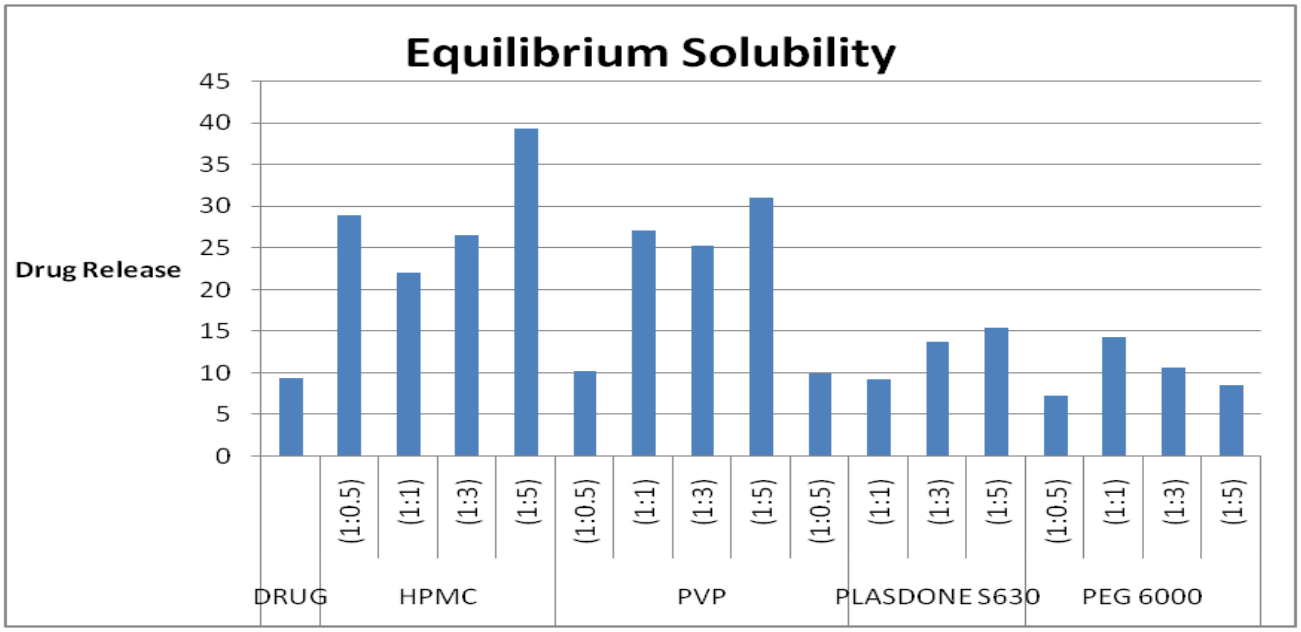

Figure 5. Drug dissolution profile in equilibrium solubility analysis

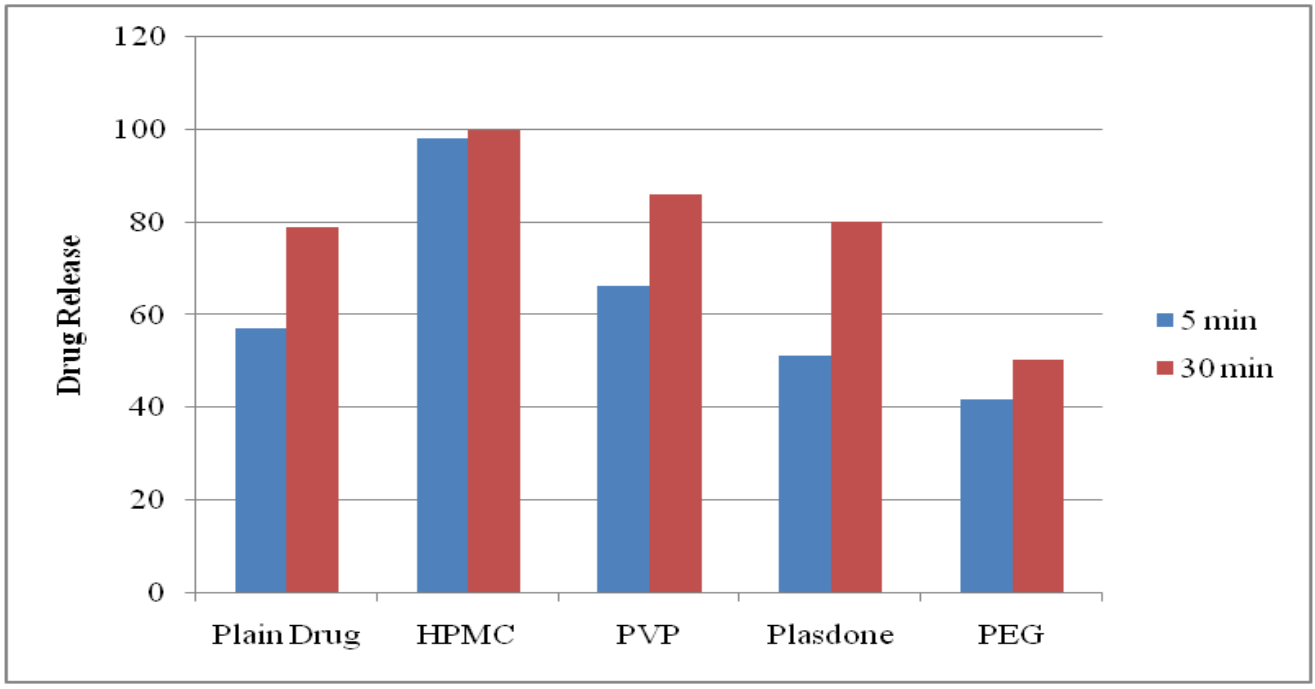

Figure 6. Comparision of drug release from 1:5 sds at 5 min and 30 min

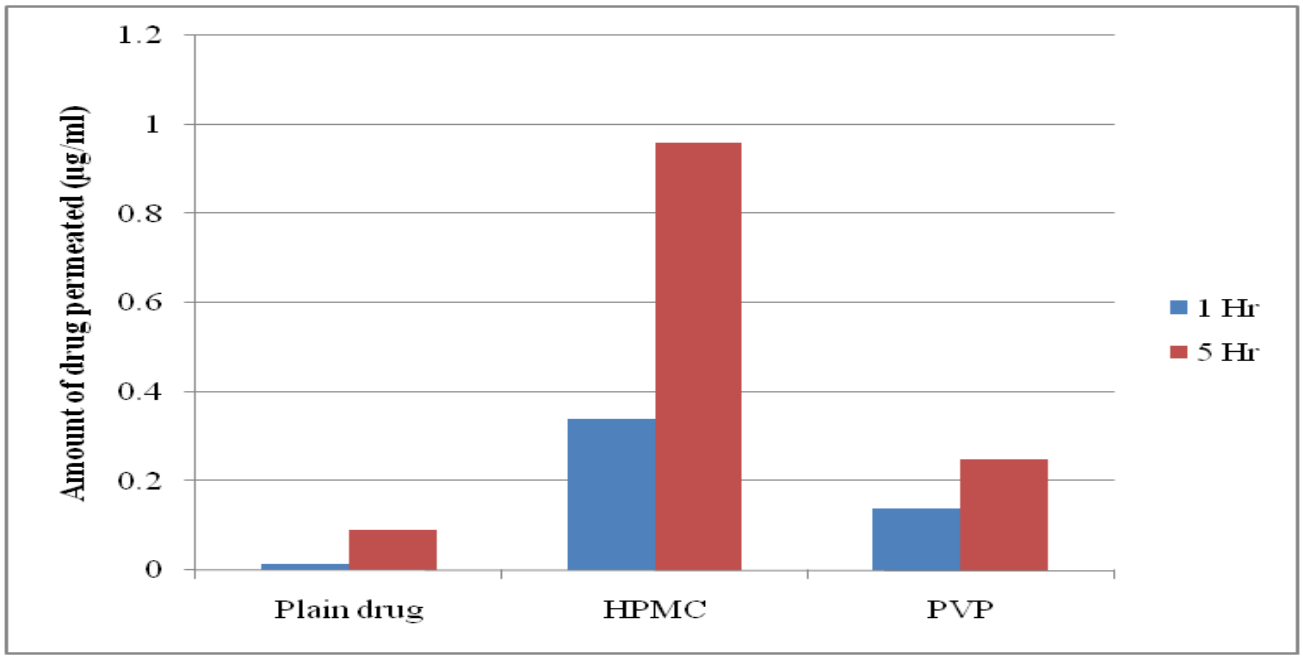

Figure 7. Comparision of drug permeation through membrane at 1 hr and 5 hr