ISSN: 0975-5772

Md.Khairul Alam et al / Journal of Pharmaceutical Science and Technology Vol. 3 (6), 2011,613-627

STUDY OF DISSOLUTION IMPROVEMENT OF VARIOUS POORLY WATER SOLUBLE DRUGS BY SOLID DISPERSION MIXING WITH HPMC 6CPS AND PEG 6000

Md. Khairul Alam[1]*, Reza-ul Jalil[2], Nazia Zaman[1], Md. SM Ashraful Islam[3]

Department of Pharmacy, The University of Asia Pacific, Dhaka, Bangladesh.

[1] Department of Pharmacy, The University of Asia Pacific

[2] Professor, Department of Pharmaceutical Technology, University of Dhaka

[3] Assistant Professor, Department of Pharmacy, The University of Asia Pacific

Abstract

The aim of this work was to improve solubility of some poorly water soluble drugs (Atorvastatin, Carbamazepine, Etoricoxib, Fenofibrate, Furosemide, Glipizide, Ibuprofen and Spironolactone) by making solid dispersions. HPMC 6cps and PEG 6000 were used to improve the solubility. Dissolution studies were performed by preparing solid dispersions by solvent method. After studying all the results it can be said that PEG 6000 is a good vehicle to enhance the solubility of poorly water soluble drugs. Among drugs, Atorvastatin, Carbamazepine, Furosemide and Ibuprofen responded very well against PEG 600. For these drugs the release from the formulation reached around 50% only after 5 minutes. The release of these four drugs after 5 minutes were found 56.70%, 45.57%, 52.83% and 79.49% respectively. Where release from pure drugs after same time period were 40.18%, 32.70%, 8.95% and 36.59% for the respective drugs. Again for drugs with HPMC 6cps only and with HPMC 6cps and PEG 6000 Atorvastatin, Carbamazepine, Furosemide and Ibuprofen responded very well.

Keywords

Improve water solubility, Solid dispersion, Dissolution improvement.

1. INTRODUCTION

In order to ensure the optimum therapeutic effect of a drug it is necessary to prepare the proper dosage form. The enhancement of the drug dosage form formulation is connected with the application of new auxiliary substances or with new technological possibilities. Discovering a way to increase the solubility of poorly soluble drugs in order to improve their pharmaceutical and biological availability still remains one of the major technological problems. There are numerous ways of enhancing this process, of which the solid dispersion technique is more and more widely used and constantly improved[1]. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[2]. Generally, there are only two methods of preparing solid dispersions: fusion and solvent evaporation process. Atorvastatin[12,13], Carbamazepine[5,8,9], Etoricoxib[16,17], Fenofibrate[5,14,15], Furosemide[5,10,11], Glipizide[5,20,21], Ibuprofen[5,18,19] and Spironolactone[5,6,7] are some poor water soluble drugs which are included in the study and made solid dispersions with HPMC 6cps and PEG 6000 by solvent evaporation method.

2. MATERIALS AND METHODS

2.1 MATERIALS USED

Table 2.1: List of drugs used

Drug	Source
Atorvastatin	Dr. Reddy's Laboratories, India
Carbamazepine	Sun Pharma, India
Etoricoxib	Cipla Ltd., India
Fenofibrate	Ranbaxy Laboratories, India
Furosemide	Ipca Laboratories, India
Glipizide	Aurobido Pharma, India
Ibuprofen	Dr. Reddy's Laboratories, India
Spironolactone	Aurobido Pharma, India

Table 2.2: List of solvents used

Solvent	**Source**
Methanol	Merck, Germany
Acetone	Merck, Germany

Table 2.3: List of polymers used

Polymer	**Source**
HPMC 6 cps	Shin-etsu, Japan
PEG 6000	Loba Chemie, India

Table 2.4: List of buffering agents used

Buffering	**Source**
Potassium di-hydrogen ortho-phosphate	Merck Ltd, India
Sodium chloride	Merck Ltd, India

Table 2.5: List of acids and bases used

Buffering	**Source**
Hydrochloric acid	Merck, Germany
Sodium hydroxide	Merck Ltd, India

Table 2.6: List of equipments used

Equipments	**Source**
USP Type-II Dissolution Apparatus	Veego, India
UV-VIS Spectrophotometer (UV -1700 Pharma Spec)	Shimadzu Corporation, Japan.
Sonicator (Power Sonic 505)	Hwashin Technology CO., Seoul, Korea.
pH Meter (pH 211 Microprocessor pH Meter)	Hanna Instruments, Romania
Vortex Mixer (VM-2000)	Digisystem Laboratory Instruments INC. Taiwan
Electronic Balance (AUX 220)	Shimadzu Corporation, Japan.
Hand Drier	Miyako, Japan

2.2. PREPARATION OF SOLID DISPERSION BY SOLVENT EVAPORATION METHOD

The solvent based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule and followed by removal of solvent by evaporation resulting in formation of a solid dispersion[25]. Mixing at the molecular level is preferred, because this leads to optimal formulation and dissolution properties.

First of all 700 mg of each of the drugs were weighed and taken in vials and then polymers were added to it after proper weighing. Then the drug-polymer powders are mixed well physically and to these drug-polymer physical mixtures, solvent was added. Methanol was used as solvent for all the drugs except spironolactone; where acetone was used in stead of methanol, as solubility of this drug in methanol was not up to mark.

Solvent was added starting from a minimum amount and each time 0.5 ml of solvent was added to the existing content; i.e. 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml, 3 ml and so on if necessary. After adding each fraction of the solvent sonication was performed in sonicator to avoid excess addition of solvent. Solvent was being added until uniform and clear dispersion was achieved.

As the boiling point of the solvent is low, it was easily evaporated by keeping the vials below dryer. After evaporation of the solvent vials were kept in desiccator for 48 hours. Finally formulations were withdrawn from vial, crushed in mortar and pestle and passed through 150 micron sieve. The samples were then ready for dissolution testing.

Flow chart for the process of preparation of Solid Dispersion (Solvent Evaporation Method):

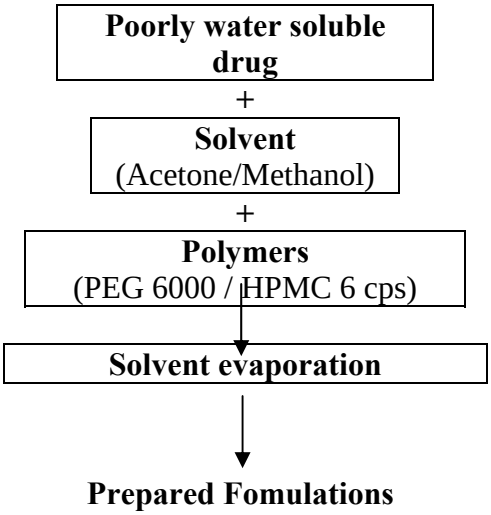


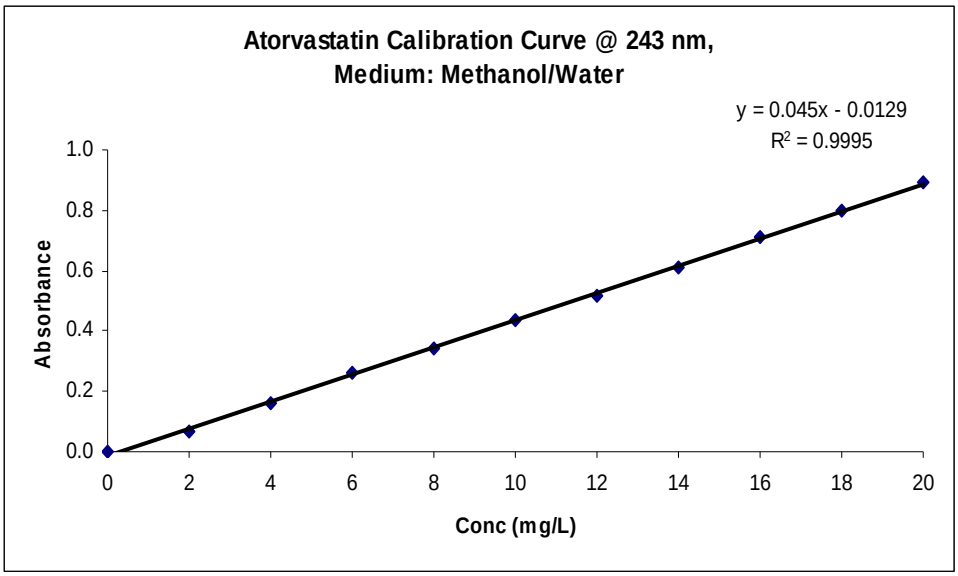
Table 2.8: Formulations of solid dispersions containing different drugs and polymer (and/or) carrier

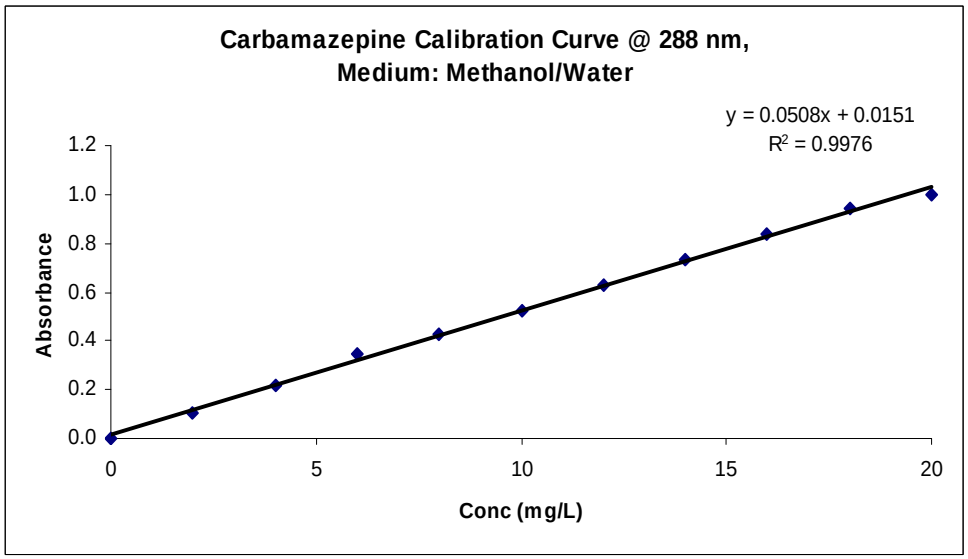
Codes	Drug	PEG 6000	HPMC 6cps
F11	700 mg	300 mg	0 gm
F12	700 mg	300 mg	0 gm
F13	700 mg	0 mg	1 gm

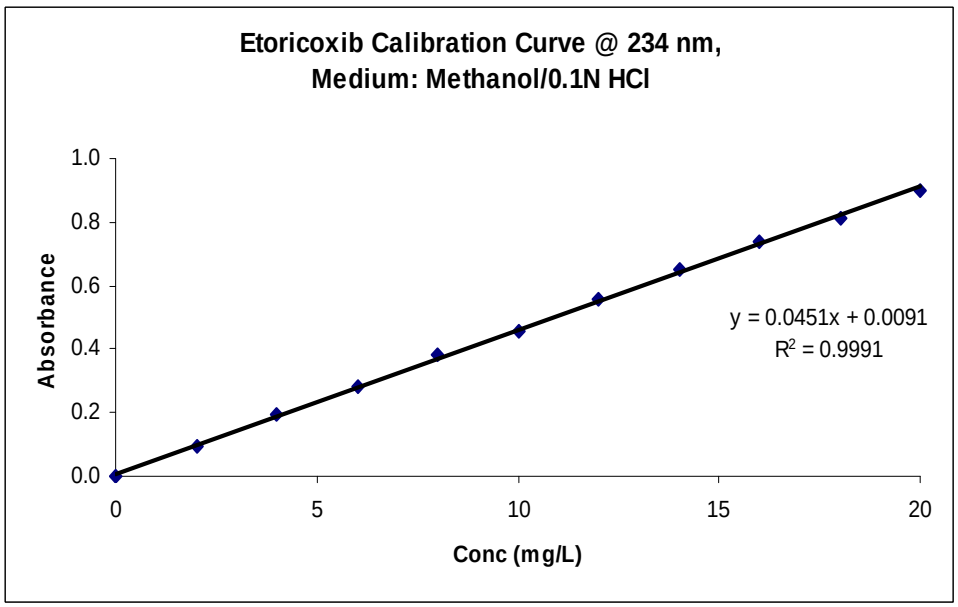
Table 2.9: Different drugs with their dissolution medium

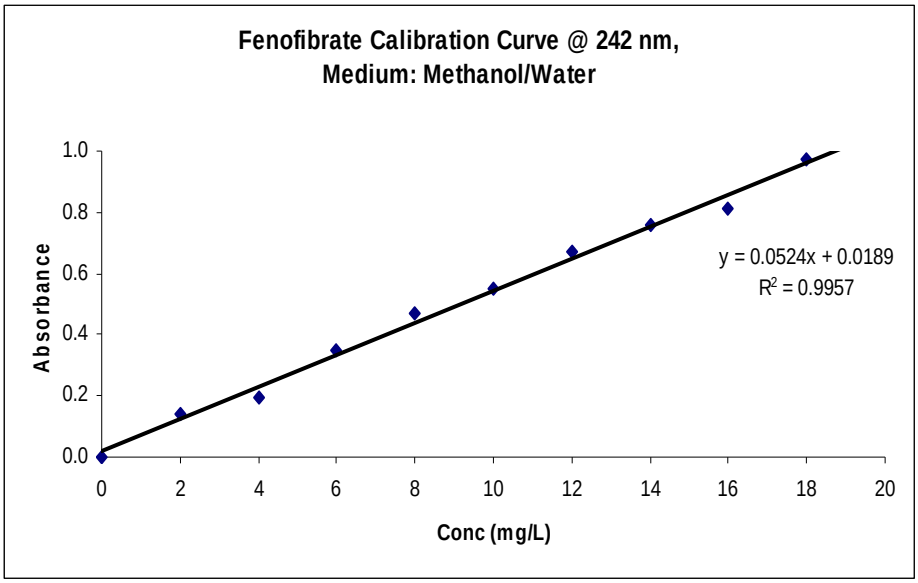
Drug	Dissolution medium
Atorvastatin	Distilled water
Carbamazepine	Distilled water
Etoricoxib	0.1 N Hydrochloric acid
Fenofibrate	Distilled water
Furosemide	Phosphate buffer (pH 5.8)
Glipizide	Simulated intestinal fluid without enzyme (pH 6.8)
Ibuprofen	Phosphate buffer (pH 7.2)
Spironolactone	0.1 N Hydrochloric acid

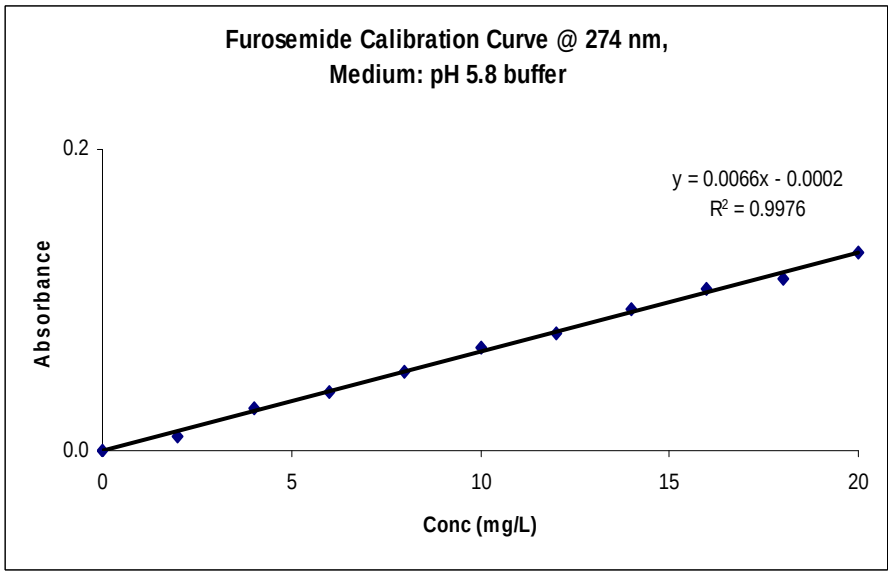
2.3. CALIBRATION CURVES OF DIFFERENT DRUGS

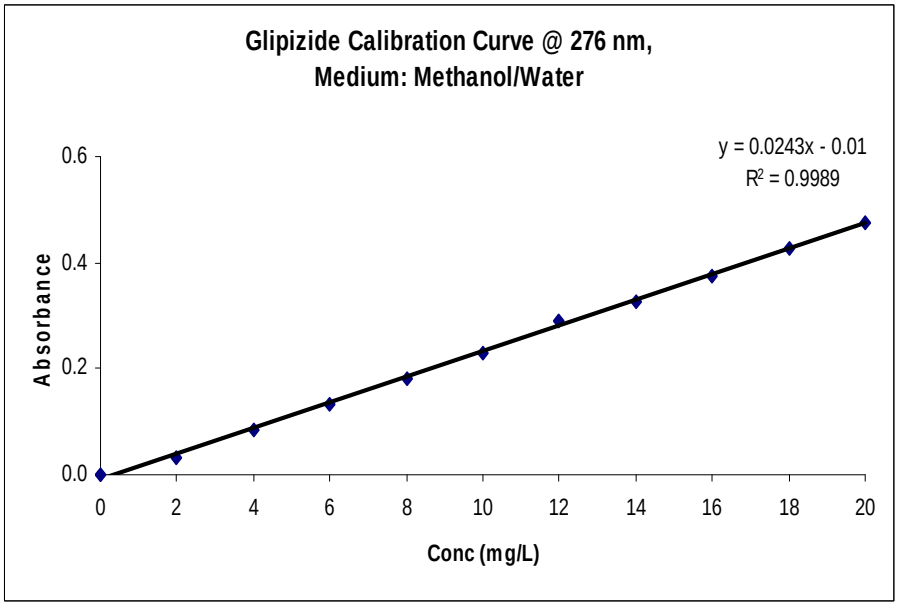


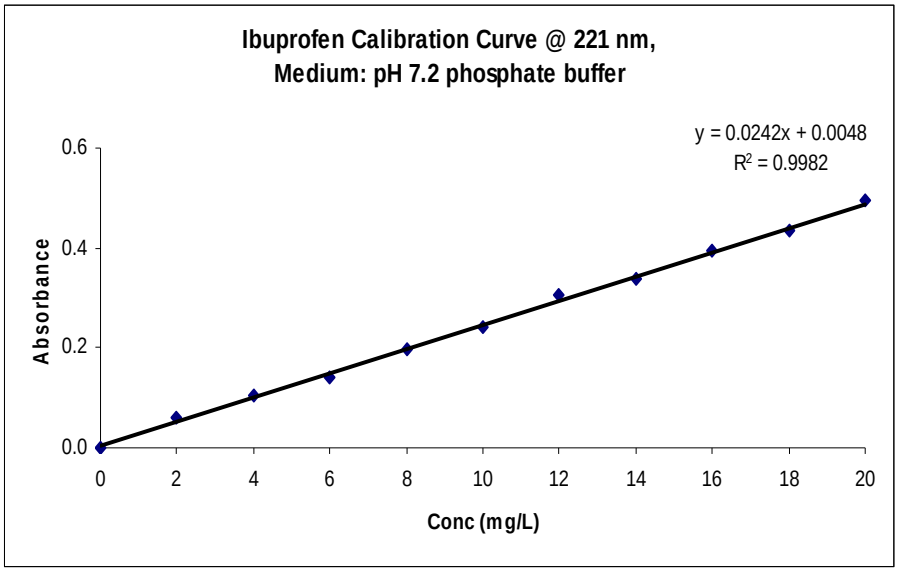


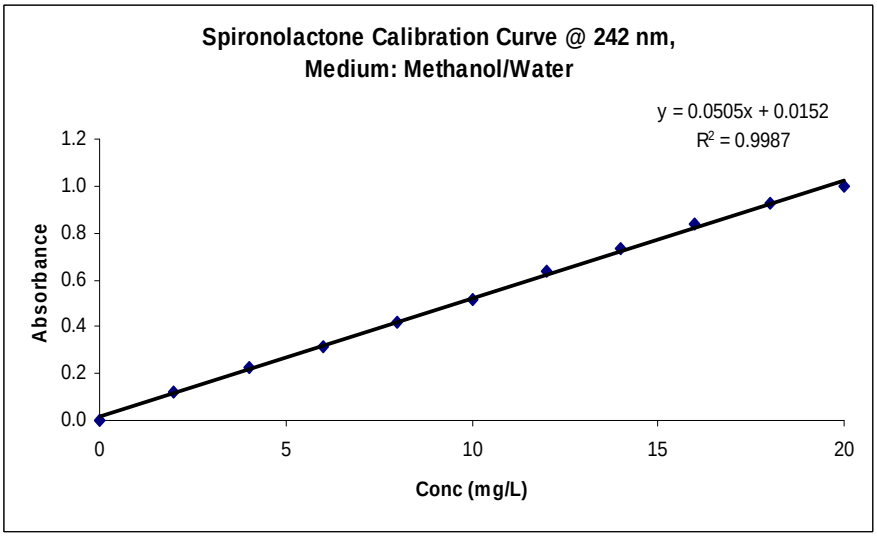



Fenofibrate Calibration Curve @ 242 nm,
Medium: Methanol/Water
Absorbance
Conc (mg/L)
y = 0.0524x + 0.0189
R2 = 0.9957
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
12
14
16
18
20


Furosemide Calibration Curve @ 274 nm,
Medium: pH 5.8 buffer
Absorbance
Conc (mg/L)
y = 0.0066x - 0.0002
R2 = 0.9976
0.0
0.2
0
5
10
15
20


Glipizide Calibration Curve @ 276 nm,
Medium: Methanol/Water
Absorbance
Conc (mg/L)
y = 0.0243x - 0.01
R2 = 0.9989
0.0
0.2
0.4
0.6
0
2
4
6
8
10
12
14
16
18
20





2.4. IN VITRO DISSOLUTION STUDY

In vitro dissolution study was performed in USP Type-II Dissolution Apparatus (Veego, India). The solid dispersion containing a fixed amount of drug was calculated and weighed by electric balance for dissolution. Dissolution medium was added in the baskets either 900 ml or 1000 ml depending on drug. The RPM for all the drugs were set 75. Temperature of the apparatus was set 37.5 ^{o}C.
Three formulations were taken in six baskets. Thus each formulation was taken in two baskets to perform duplicate to minimize the extent of error. Pure drug and drug solution (in methanol) were taken in next two baskets of the eight basket dissolution apparatus. The dissolution was performed for 1 hour. Two more baskets were needed for pure drug and the drug solution (in methanol). Thus dissolution of physical mixtures of two drugs was performed simultaneously in the eight basket dissolution tester.

After transferring the formulations into the baskets the dissolution apparatus was started. Stopwatch was maintained to monitor exact time interval. Samples from different baskets were withdrawn after 5, 10, 15, 20, 30, 40, 50 and 60 minutes. Each time 10 ml of sample was withdrawn by syringe filter and subsequently compensated by adding blank solution (dissolution medium).

Samples withdrawn were kept in test tubes which were already labeled according to the formula and time interval. The test tubes were covered by thin aluminium foil until UV-spectrometric readings were taken.

The dissolution samples were then analyzed spectrophotometrically by UV-VIS Spectrophotometer using the respective dissolution medium as the blank solution. The percent release of drugs from different formulations were calculated and then plotted in a graph against time in Microsoft excel worksheet.

Table 2.18: Formulation and dissolution medium for dissolution test.

	Drug	Drug Amount (mg)	Excepients		Dissolution Medium	RPM	λmax
			PEG 6000 (mg)	HPMC 6 cps (gm)			
F11	Spironolactone	700	300	0	0.1% HCl (1000 ml)	75	242.00
F12			300	1			
F13			0	1			
F21	Carbamazapine	700	300	0	Dist. Water (1000 ml)	75	288.00
F22			300	1			
F33			0	1			
F31	Furosemide	700	300	0	Phosphate Buffer pH 5.8 (900 ml)	75	274.00
F32			300	1			
F33			0	1			
F41	Atorvastatin	350	150	0	Dist. Water (1000 ml)	75	243.00
F42			150	0.5			
F43			0	0.5			
F51	Fenofibrate	700	300	0	Dist. Water (1000 ml)	75	288.00
F52			300	1			
F53			0	1			
F61	Etoricoxib	350	150	0	0.1 N HCl 0.2 (900 ml)	75	234.00
F62			150	0.5			
F63			0	0.5			
F71	Ibuprofen	700	300	0	Phosphate Buffer pH 7.2 (900 ml)	75	221.00
F72			300	1			
F73			0	1			
F81	Glipizide	350	150	0	Simulated Intestinal Fluid (900 ml)	75	276.00
F82			150	0.5			
F83			0	0.5			

3. RESULTS AND DISCUSSION

3.1. CALIBRATION CURVES OF DIFFERENT DRUGS

After studying all the calibration curves and their coefficient of determination (R^2) values of a linear regression it was found that all the drugs have got R^2 values nearer to one. It was a clear indication of the linearity and accuracy of the calibration curves; which subsequently ensured correct calculation of results from dissolution data of different formulations of the drugs.

Table 3.1 Coefficient of determination (R^2) values for different drugs

Drug	Coefficient of determination (R^2)
Atorvastatin	0.9995
Carbamazepine	0.9982
Etoricoxib	0.9991
Fenofibrate	0.99
Furosemide	0.9976
Glipizide	0.9989
Ibuprofen	0.9982
Spironolactone	0.9987

3.2. DISSOLUTION STUDY

The solvent evaporation method for preparing solid dispersion includes dissolving the drug and the carrier in a common organic solvent, followed by evaporating the solvent at elevated temperature, under vacuum, or by freeze-drying or spray-drying the mixture. For this purpose, methanol was used as a common solvent.

Upon studying the dissolution profiles of solid dispersions of different drugs prepared by solvent evaporation method it is clear that solid dispersions showed higher dissolution rates than pure drugs.

Figure 3.1: Release pattern of different Atorvastatin solid dispersions

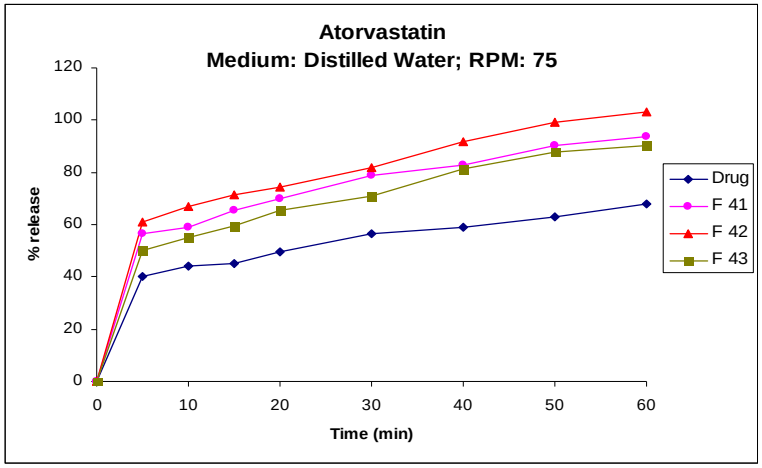


Figure 3.2: Release pattern of different Carbamazepine solid dispersions

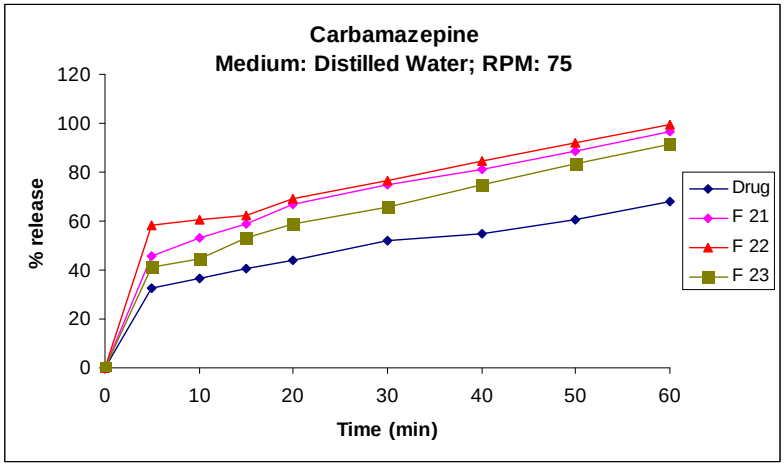


Figure 3.3: Release pattern of different Etoricoxib solid dispersions

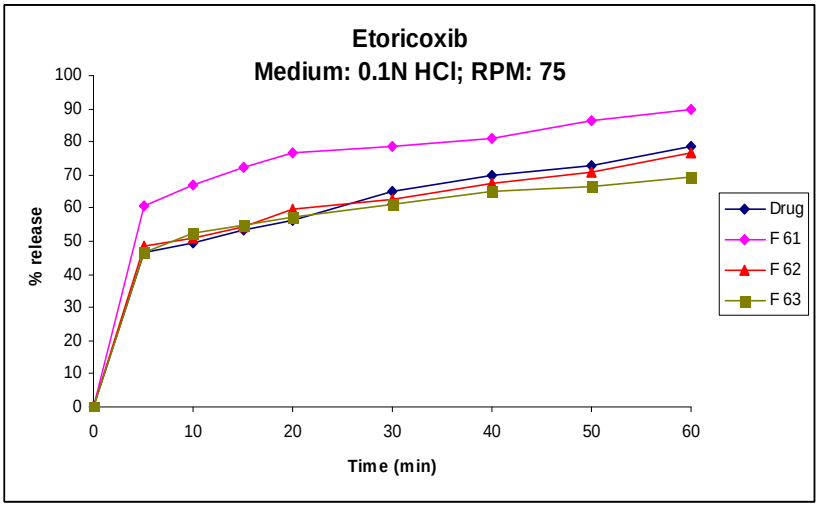


Figure 3.4: Release pattern of different Fenofibrate solid dispersions

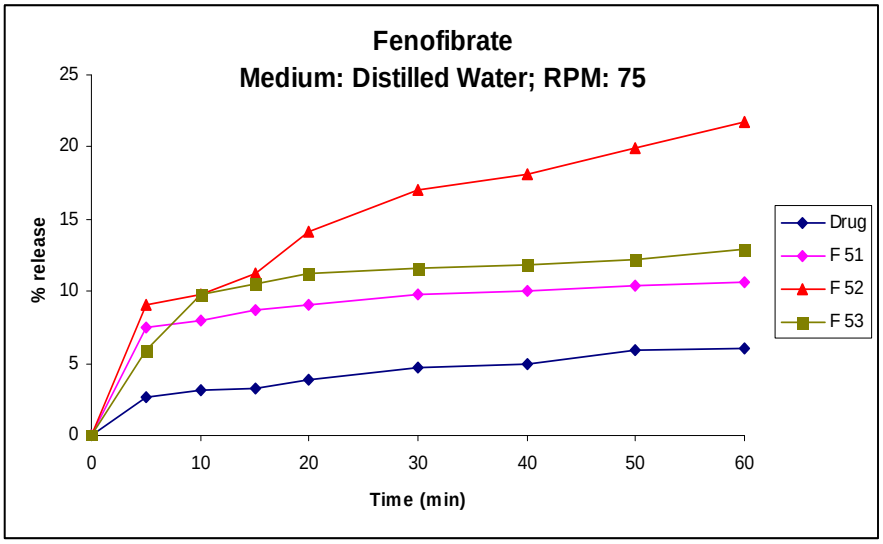


Figure 3.5: Release pattern of different Furosemide solid dispersions

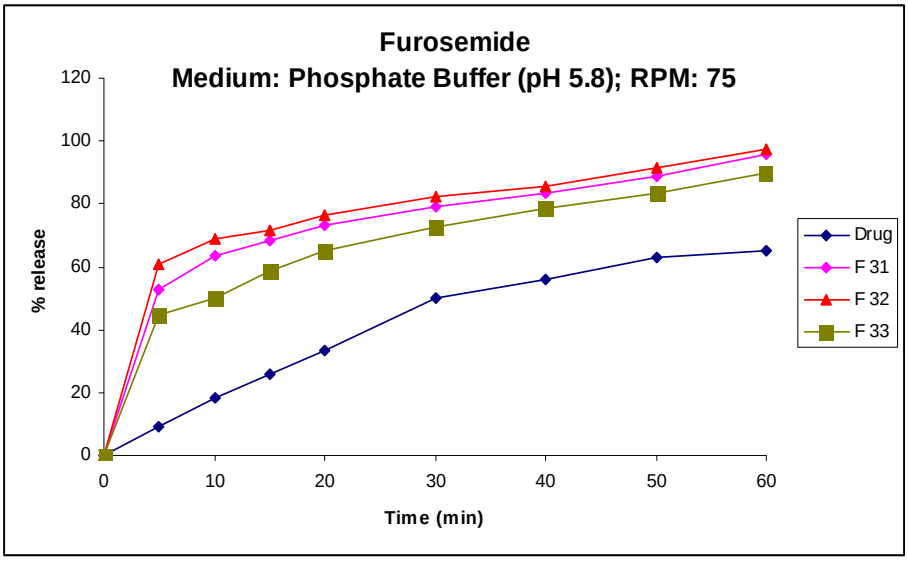


Figure 3.6: Release pattern of different Glipizide solid dispersions

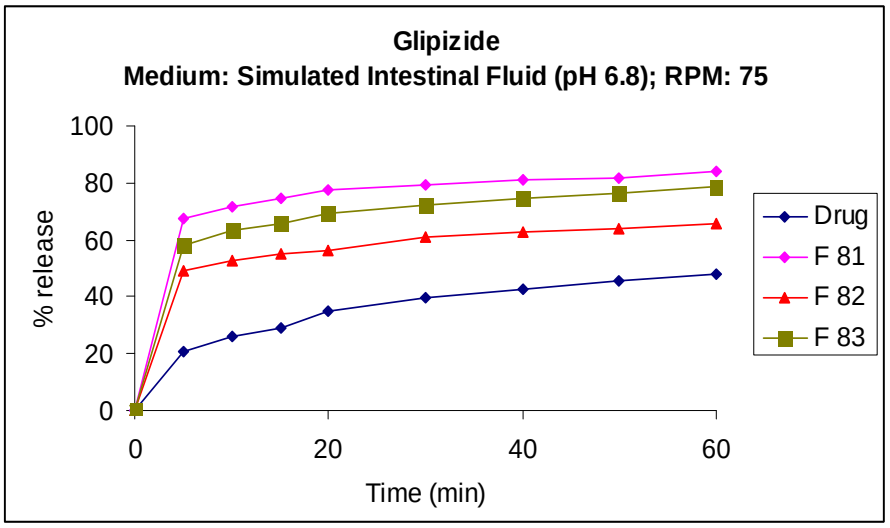


Figure 3.7: Release pattern of different Ibuprofen solid dispersions

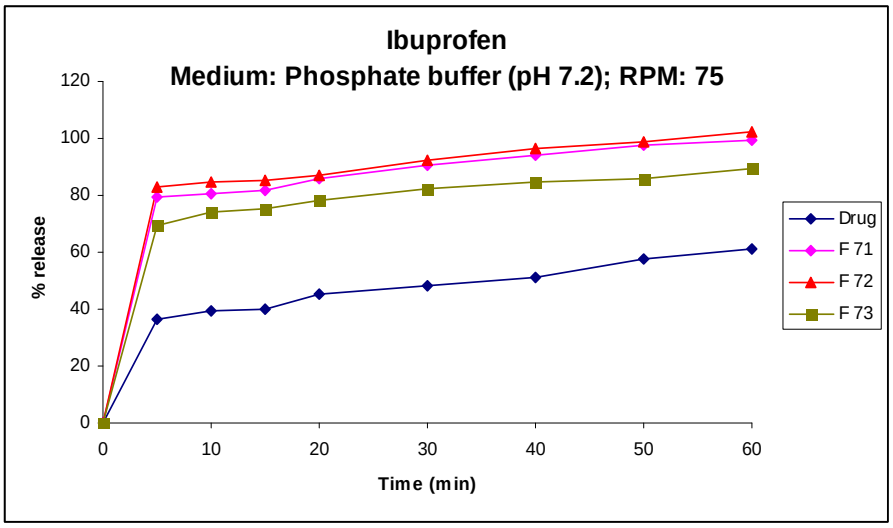


Figure 3.8: Release pattern of different Spironolactone solid dispersions

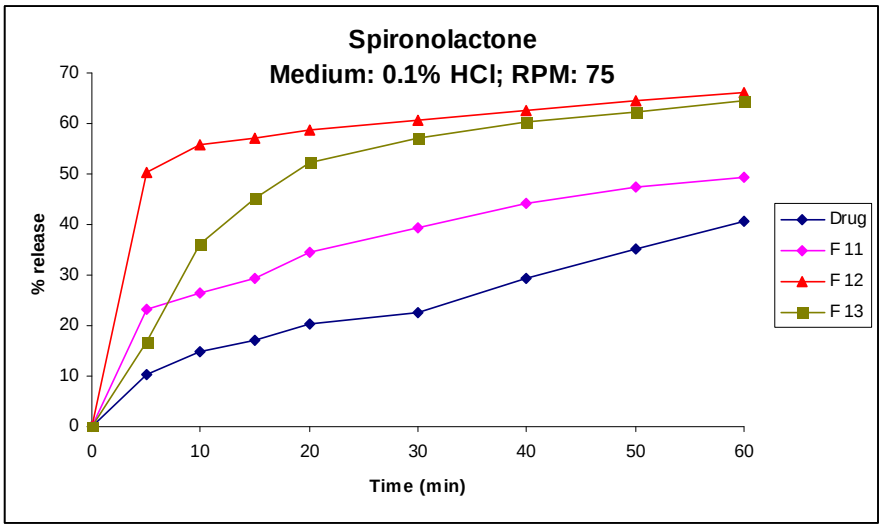


Figure 3.9: Comparison of release pattern of different drugs with PEG at different time.

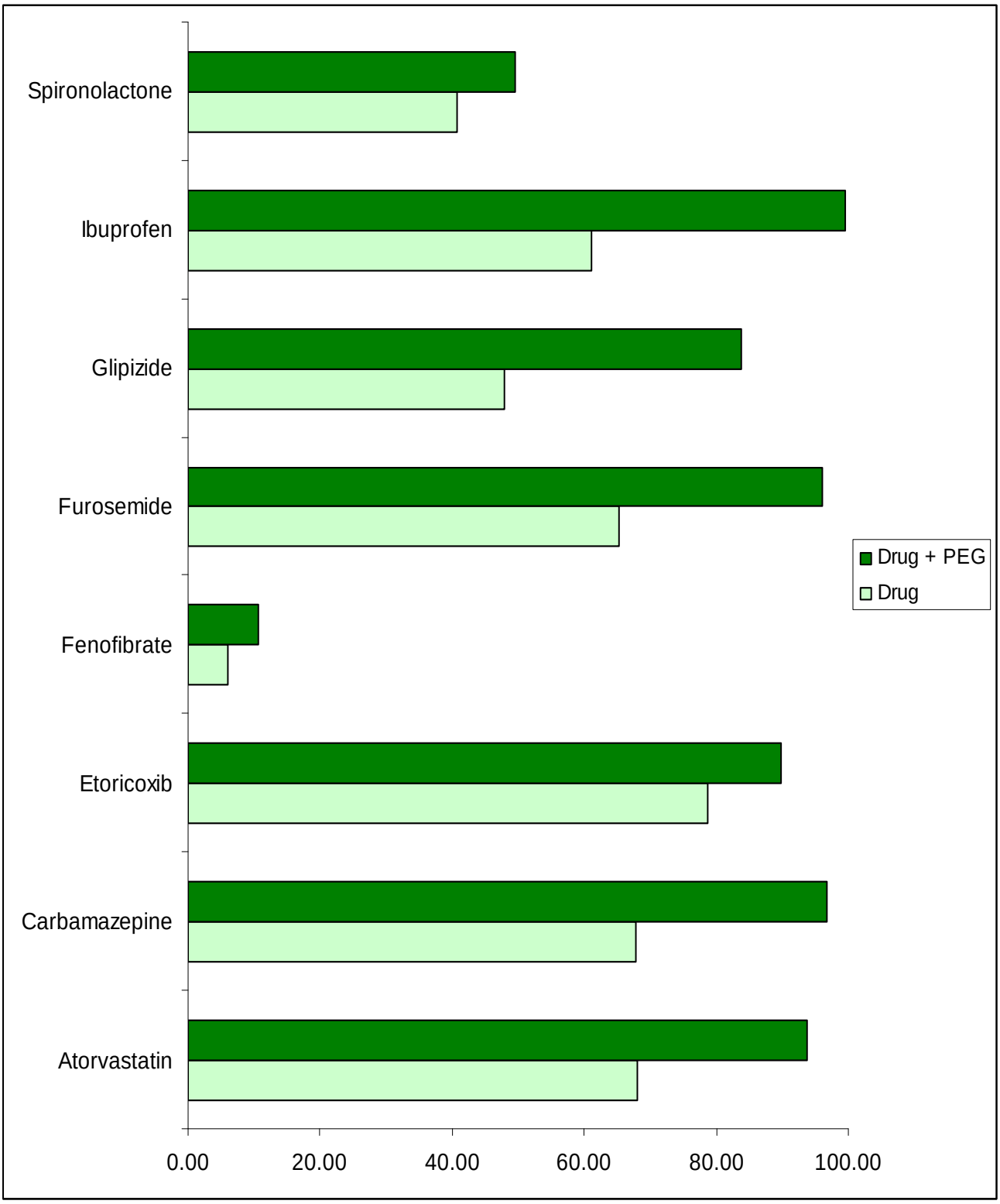


Figure 3.10: Comparison of release pattern of different drugs with PEG and HPMC at different time.

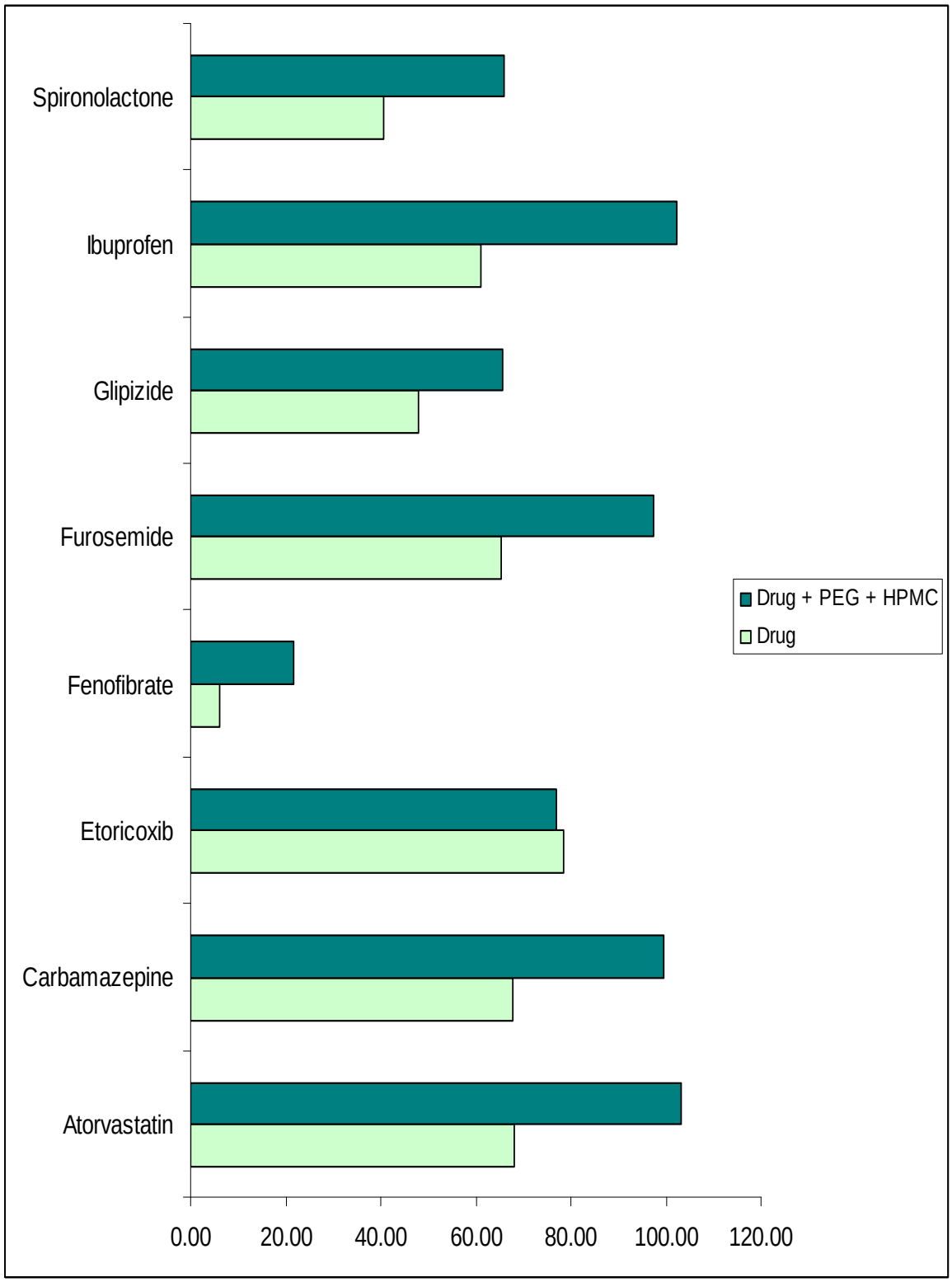
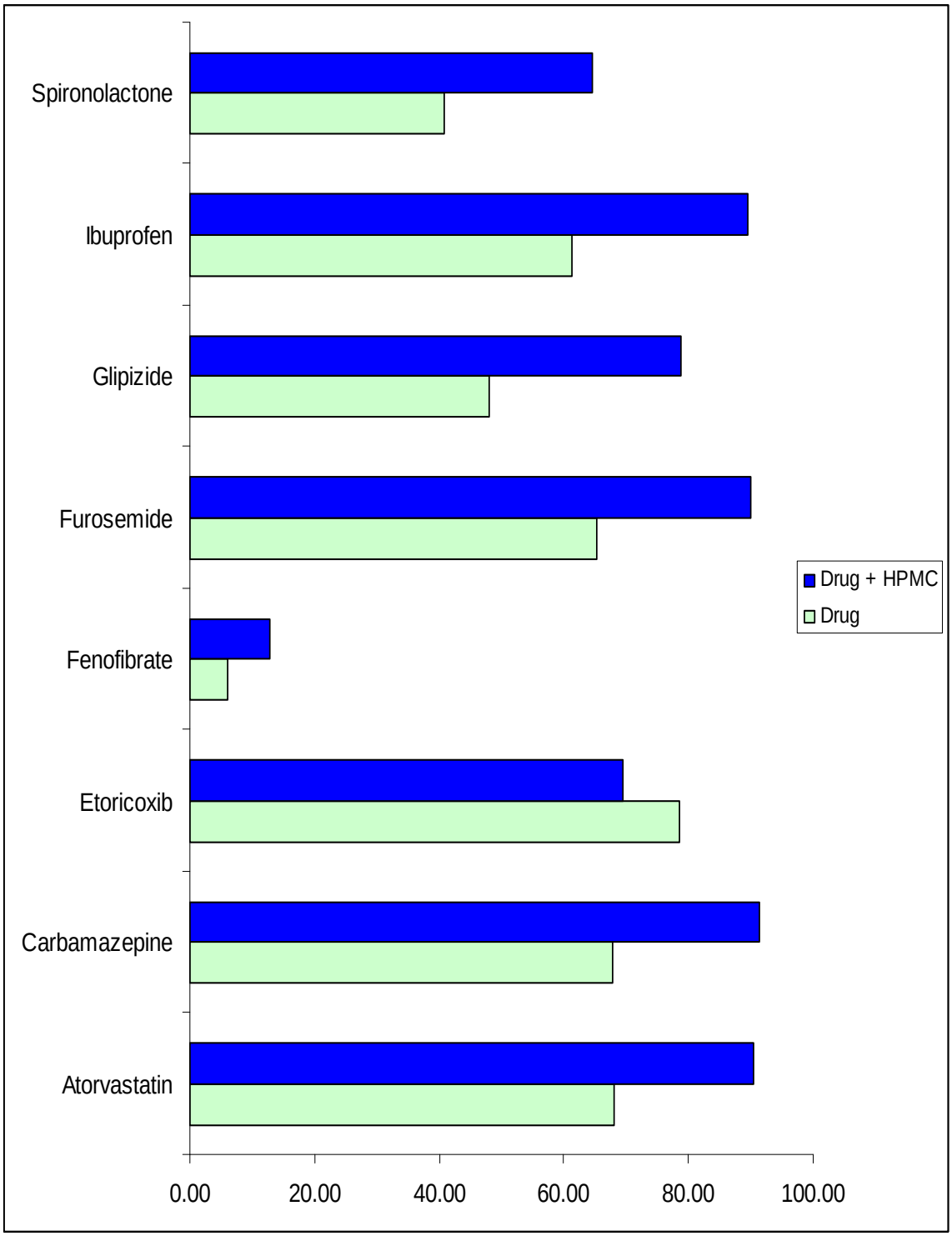


Figure 3.11: Comparison of release pattern of different drugs with HPMC at different time.



3.3. DISCUSSION

After studying all the results it can be said that PEG 6000 is a good vehicle to enhance the solubility of poorly water soluble drugs.

Dissolution studies were performed by preparing solid dispersions (solvent method).

Among these drugs, Atorvastatin, Carbamazepine, Furosemide and Ibuprofen [Figure 3.9] responded very well against PEG 600. For these drugs the release from the formulation reaches around 50% only after 5 minutes. The release of these four drugs after 5 minutes were found

56.70%, 45.57%, 52.83% and 79.49% respectively. Where release from pure drugs after same time period were 40.18%, 32.70%, 8.95% and 36.59% for the respective drugs.
Again for drugs with HPMC 6cps only [Figure 3.10] and with HPMC 6cps and PEG 6000 [Figure 3.11] Atorvastatin, Carbamazepine, Furosemide and Ibuprofen responded very well.
After studying dissolution profiles of solid dispersions prepared by solvent evaporation method [Figure 3.1 – 3.8] it can be concluded that except Fenofibrate, solid dispersions caused greater dissolution of drugs which are mainly poorly water soluble in nature.
After studying all the eight drugs, it was found that solid dispersion increased the dissolution to significant extent and it was almost 100% after 60 minutes for most of the drugs. Several mechanisms may be possible to the enhanced release of these drugs in the solid dispersion formulation with the water soluble polymer PEG 6000 and HPMC 6cps. The reduction of crystallinity of drug resulting in improved release may be a reason. In the dry state, drug particles were in close contact or adhered to the polymer particles as a result of mixing. When the mixture comes in contact with water, the polymer particles might have hydrated rapidly into the polymer solution, solubilizing the adjacent drug particles and subsequently releasing the drug into the medium.
After this study, PEG came out as a good device to increase the solubility of poorly soluble drugs. Solid dispersions prepared by both PEG and HPMC were found to exhibit best dissolution results for most of the drugs [Figure 3.10]. These polymers complimented each other to give rapid dissolution and better formulation. Among these drugs Fenofibrate [Figure 3.4] did not responded well with any of the combinations.
This study should be continued to the larger extent with more drugs and polymers to find out the suitable and perfect solid dispersion for individual drug.

4. CONCLUSION

It has been found that solid dispersions prepared by solvent evaporation method caused greater dissolution of drugs with poor water solubility. The combination of PEG and HPMC worked best in this study. Solid dispersion only by solvent evaporation method is examined here. But fusion and fusion-solvent method was not studied. These methods should also be studied for better understanding. Further study in this field is still required to establish this solid dispersion system so that in future it can be used effectively in commercial basis.

REFERENCES

1. **Margarit, M.V., Rodriguez, I.C., Cereso, A.**, *Physical characteristics and dissolution kinetics of solid dispersions of ketoprofen and polyethylene glycol 6000*. Int. J. Pharm. 108, 101–107. 1994.
2. http://dissertations.ub.rug.nl/FILES/faculties/science/2006/d.j.van.drooge/c1.pdf
3. Pharmaceutical solid dispersion technology, Muhammad J. Habib, 2001
4. http://www.fysikaalinenfarmasia.fi/symposium09/Mooter_FFY_solid_dispersion_formulation_strategy_poorly_soluble_compounds.pdf
5. British Pharmacopoeia 2010
6. http://en.wikipedia.org/wiki/Spironolactone
7. http://www.rxlist.com/aldactone-drug.htm
8. http://en.wikipedia.org/wiki/Carbamazepine
9. http://www.rxlist.com/tegretol-drug.htm
10. http://en.wikipedia.org/wiki/Furosemide
11. http://www.rxlist.com/lasix-drug.htm
12. http://en.wikipedia.org/wiki/Atorvastatin
13. http://www.rxlist.com/lipitor-drug.htm
14. http://en.wikipedia.org/wiki/Fenofibrate

15. http://www.rxlist.com/antara-drug.htm
16. http://en.wikipedia.org/wiki/Etoricoxib
17. http://www.mims.com/Page.aspx?menuid=mng&name=etoricoxib&brief=false#Actions
18. http://en.wikipedia.org/wiki/Ibuprofen
19. http://www.rxlist.com/ibuprofen-drug.htm
20. http://en.wikipedia.org/wiki/Glipizide
21. http://www.rxlist.com/glucotrol-drug.htm
22. http://en.wikipedia.org/wiki/Acetone
23. Handbook of pharmaceutical excipients by Rowe, Paul J Sheskey and Siân C Owen, 5th edition, 2006.
24. http://en.wikipedia.org/wiki/Methanol
25. **Chiou, W.L., Riegelman, S.**, *Pharmaceutical applications of solid dispersion systems.* J. Pharm. Sci. 60, 1281–1302. 1971.