Research Article

Solubility and dissolution rate enhancement of nevirapine solid dispersions using skimmed milk powder

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ABSTRACT

This research was aimed in enhancing solubility and rate of dissolution of nevirapine by employing solid dispersions. Saturation solubility studies and pH solubility profile were determined for nevirapine. Nevirapine solid dispersions with skimmed milk powder were prepared using techniques like solvent evaporation, physical mixing and microwave method. The obtained solid dispersions were tested for *in vitro* dissolution data and were characterized by FTIR analysis. Twelve different formulations of nevirapine with skimmed milk were prepared using solvent evaporation, physical mixing and microwave techniques. FTIR studies indicated absence of interactions between excipients and drug used. Nevirapine exhibited 16.2 % dissolution in 45 minutes, while dissolution rate of solid dispersion of nevirapine: skimmed milk powder (1:7) prepared by solvent evaporation showed 87.66 % drug release. Dissolution rate of nevirapine could be enhanced by preparation of solid dispersions with skimmed milk.

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INTRODUCTION

Most of the drug candidates in discovery exhibit low aqueous solubility that results in low bioavailability. For absorption into the body, the drug needs to be solubilized in the gastric fluids. Higher doses of such drugs are required to achieve therapeutic levels in plasma on oral administration. Dissolution of drugs is rate limiting step in most cases and this increasing absorption and hence oral bioavailability of such drug molecules by formulation design approach proves promising. Hence formulating suitable products for enhanced solubility and bioavailability is necessary. [1-3]

Solubility issues are a major drawback especially for drugs belonging to BCS class II and IV. To overcome this, various formulation techniques that improve solubility and/or dissolution of such drugs are essential. Among these, solid dispersions (SD) are effective and simple for solubility enhancement. [4-5] Solid dispersions can be prepared by dispersing drug molecularly in hydrophilic carrier. Difficulties in scale-up techniques and physical stability problems limit the number of marketed products of solid dispersions. [6-8]

The objective here was to prepare SD by solvent evaporation, microwave method and physical mixing to enhance rate of dissolution of nevirapine.

METHODS

Solubility studies of Nevirapine:

Solubility studies were performed in 0.1N HCl, pH 6.8 phosphate buffer and distilled water.

Preparation of solid dispersions (SD):

Solid dispersions with skimmed milk powder (SMP) were prepared using following methods:

Physical mixtures (PM)

Required amount of nevirapine and SMP in % w/w ratios of 1:1, 1:3, 1:5, 1:7 and 1:9 were taken together in a mortar and pestle and ground to obtain a homogenous mixture. This was then sieved through 60 mesh sieve; powder was collected and stored in a container at room temperature.

Solvent Evaporation (SE)

Required amounts of Nevirapine and SMP 1:1, 1:3, 1:5, 1:7 and 1:9 % w/w ratios were added in methanol and stirred for formation of a clear solution. Removal of solvent was done by triturating to obtain a dry powder. It was later dried at 50 ^{0}C for 4hours in oven. The final product was ground into powder and sieved through sieve number 60. [9-11]

Microwave method (MW)

Microwave activated solid dispersions were obtained by microwave irradiation. Physical mixture of each sample was considered in a glass beaker and subjected to microwaves at 560W in a scientific microwave oven. Formed solid dispersions were then ground and sieved through 100 mesh sieve. [12]

Table 1: Formulation of solid dispersions

Formulation	Method	Drug: Polymer Ratio
F1	Solvent evaporation	1:1
F2		1:3
F3		1:5
F4		1:7
F5	Physical mixing	1:1
F6		1:3
F7		1:5
F8		1:7
F9	Microwave method	1:1
F10		1:3
F11		1:5
F12		1:7

Compatibility studies

FTIR analysis

FTIR studies were performed to detect interactions between the nevirapine and SMP by KBr pellet method. Spectral scans were performed at a range of 4000-400 cm^{-1}.

***In vitro* drug release**

Dissolution was conducted using type II dissolution apparatus (USP-XXIII Electrolab, Mumbai) containing 900 mL of pH 6.8 phosphate buffer at 37±0.5 ^{0}C temperature and agitation speed of 50 rpm. An accurately weighed quantity of solid dispersions was added in dissolution medium. At present points of time 5, 10, 15, 30 and 45 min, 5mL aliquots were withdrawn and analyzed spectrophotometrically after suitable dilutions. [13]

RESULTS

Solubility studies of Nevirapine:

The solubility of Nevirapine in distilled water was 0.012 mg/mL, 0.142mg/ml in pH 6.8 phosphate buffer and in 0.1N HCl it was 0.112mg/mL. The solubility has been increased by using SMP with different ratios.

Compatibility studies

FTIR analysis

FTIR data of Nevirapine was characterized by peak appearances at 3061.36cm^{-1} corresponding to N-H stretch, 2982.02cm^{-1} indicating C-H stretch, 1706.03cm^{-1} pertaining to C=O stretch and 1611.90 cm^{-1} related to C-N stretch. The SD showed peaks of nevirapine and SMP, indicating compatibility between nevirapine and SMP.

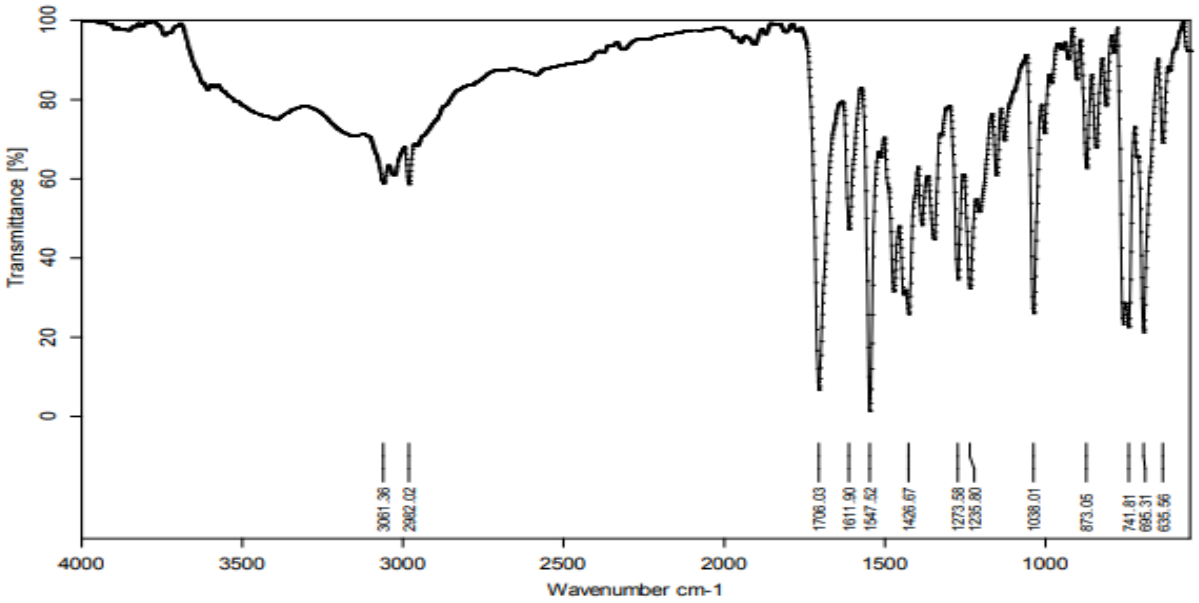

Fig. 1: Nevirapine FTIR spectrum

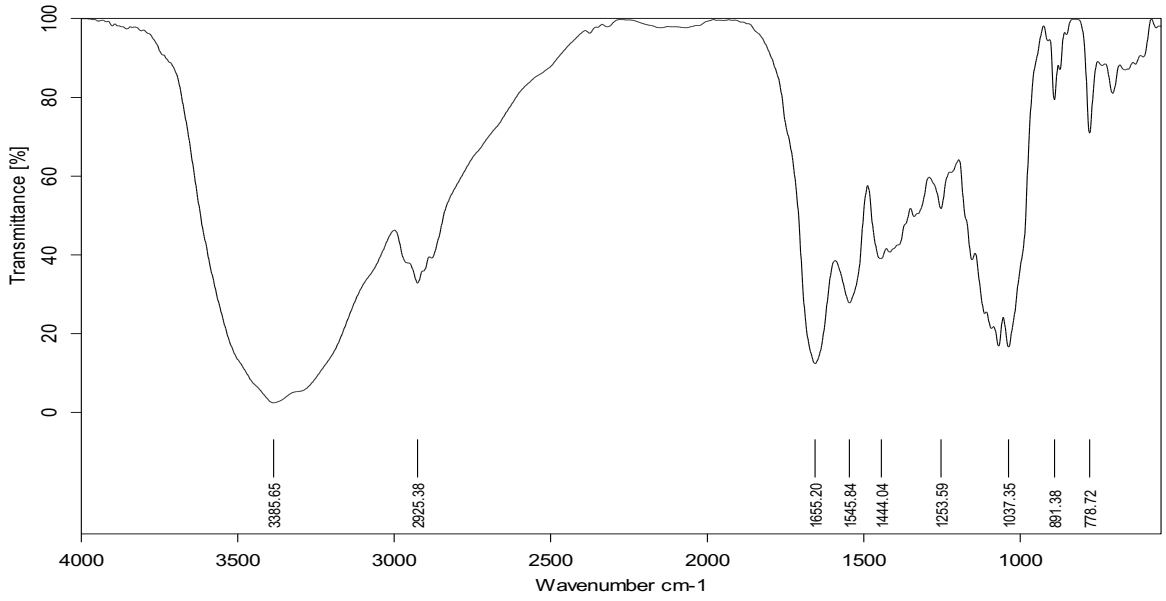

Fig. 2: Skimmed milk powder FTIR spectrum

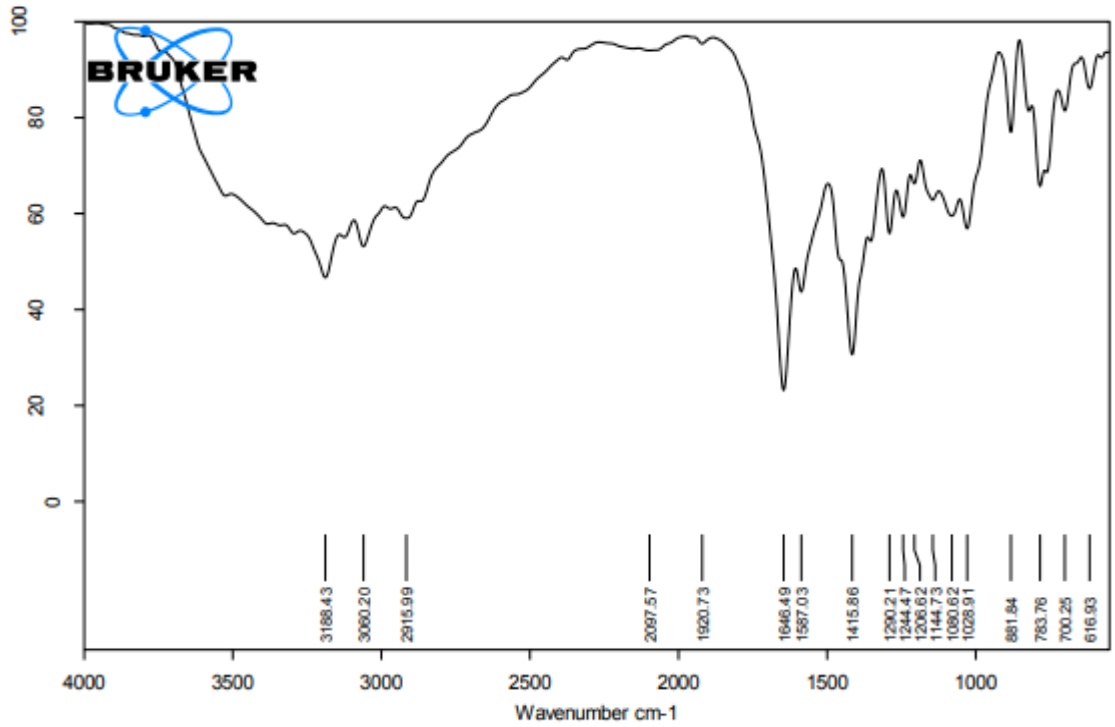

Fig. 3: F4 formulation FTIR spectrum

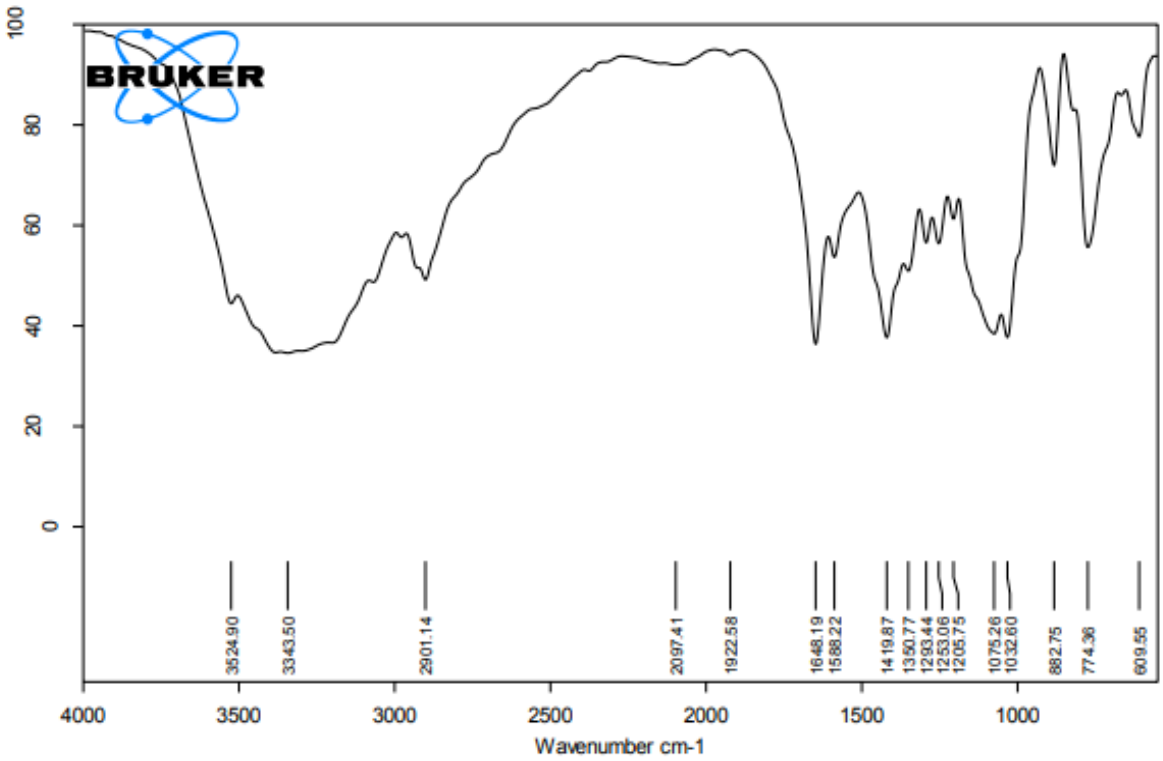

Fig. 4: F12 formulation FTIR spectrum

***In vitro* dissolution:**

From dissolution data, it was confirmed that SD showed greater dissolution rate when compared to nevirapine. This might be due to conversion of drug from amorphous form to crystalline, size reduction of particles, increased wettability and prevention of aggregation by SMP. PM increased dissolution to lesser extent but SD formulated by SE method and MW method improved it to a greater extent. [14-15]

Dissolution of nevirapine was 16.2 % at 45 minutes, while its SD showed it upto 87.66%. Nevirapine: SMP in 1:7 ratio prepared by SE showed maximum dissolution.

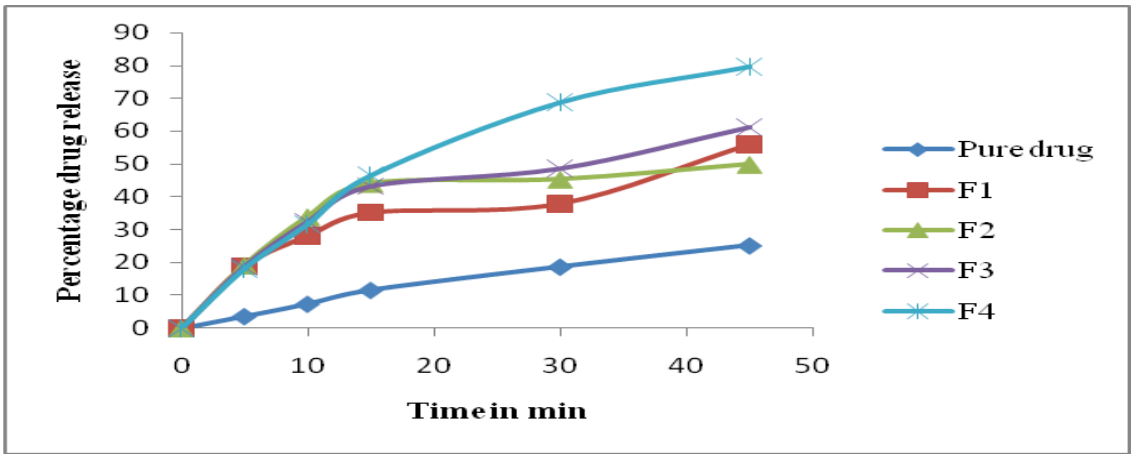

Fig. 5: Dissolution data of F1- F4 formulations

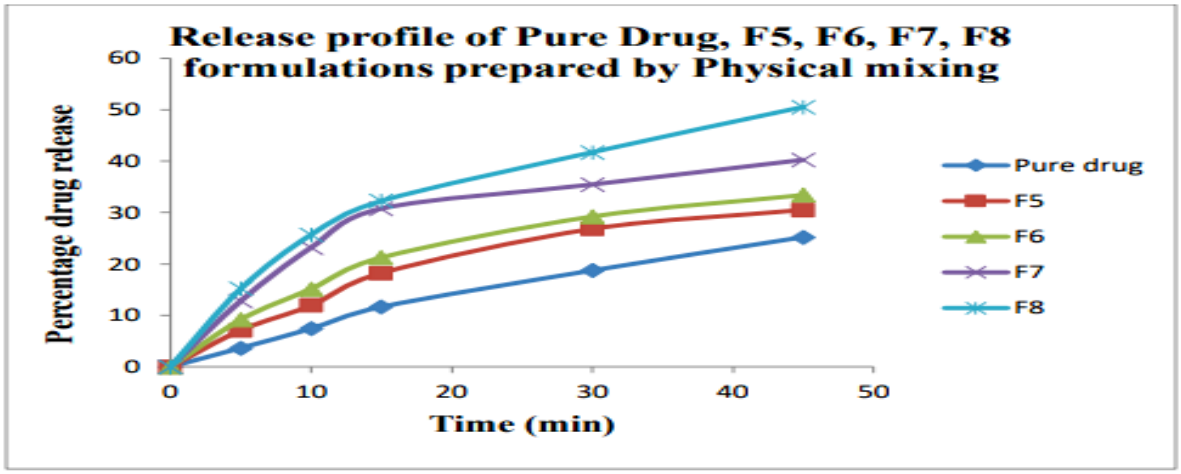

Fig. 6: Dissolution data of F5- F8 formulations

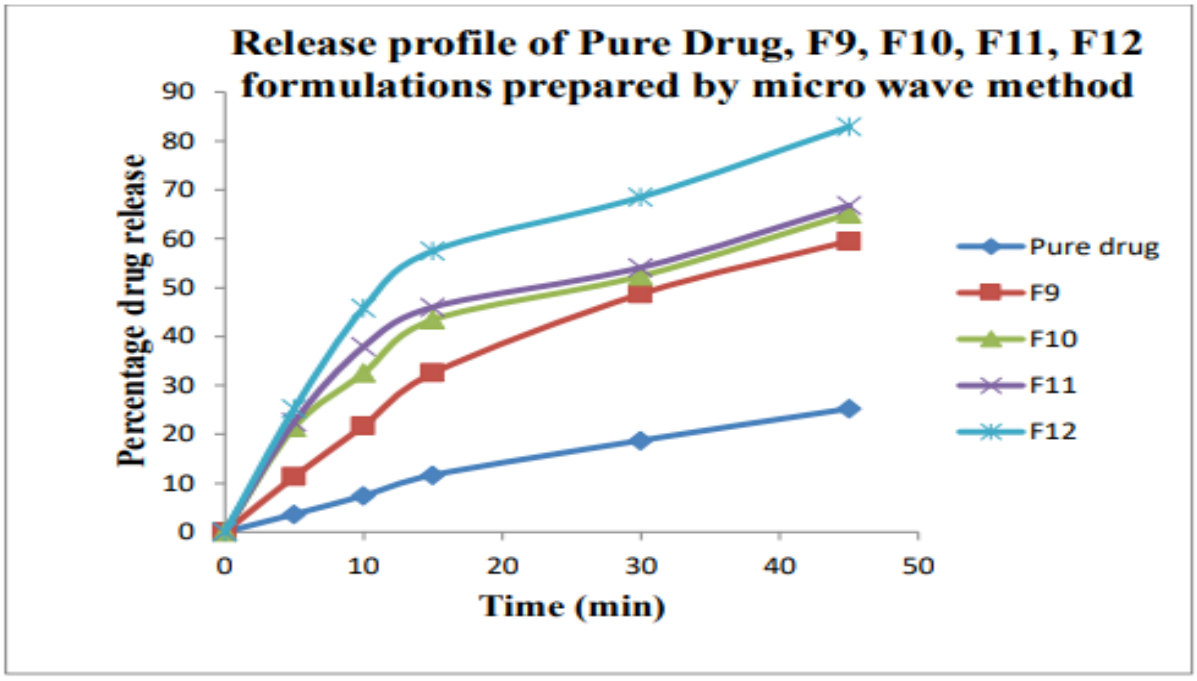

Fig. 7: Dissolution data of F9- F12 formulations

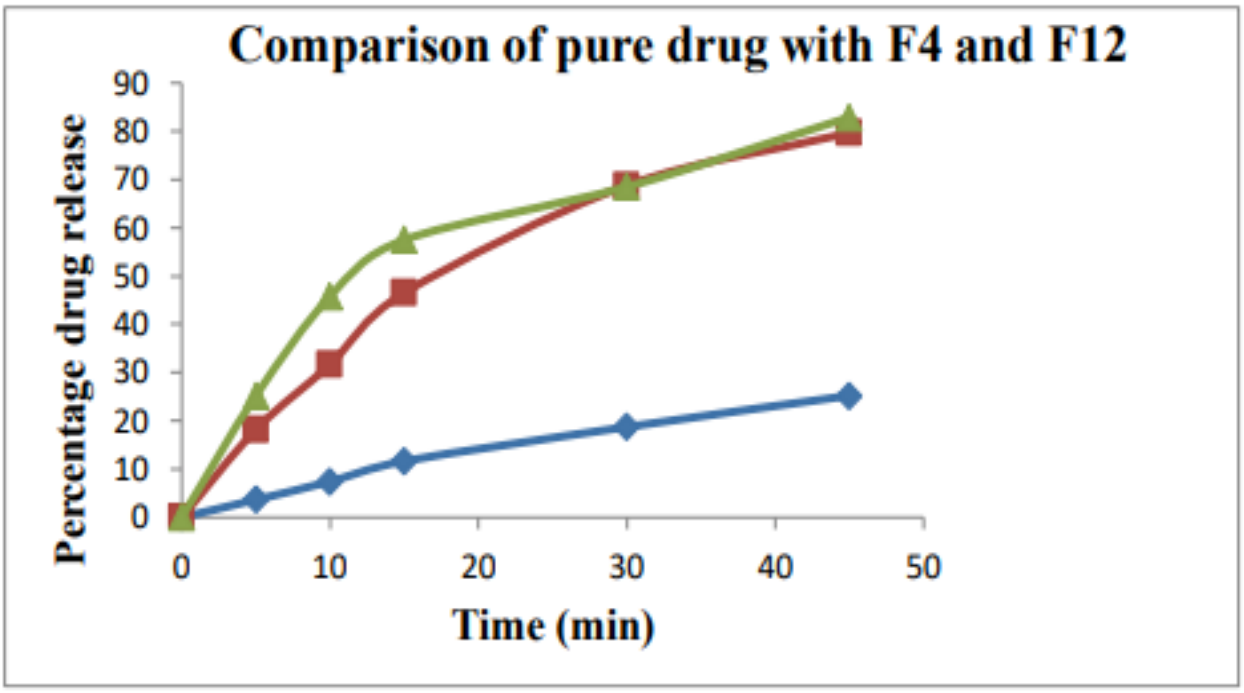

Fig. 8: Comparison of dissolution data between pure drug, F4 and F12 formulations

CONCLUSIONS

Formulation F4 (nevirapine: SMP in 1:7 ratio) showed highest release of drug among all the formulations. FTIR data indicated absence of interactions between nevirapine and SMP. Hence SD of nevirapine prepared with SMP by SE, MW and PM method could be used for enhanced dissolution.

REFERENCES

1. Teofilo V, Bruno S, Paulo C. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovery Today 2007; 12:23-24.
2. Bo T, Gang Ch, Jian CG, Cai HX. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discovery Today 2008; 13: 606-612.
3. Luhadiya A, Agrawal S, Jain P, Dubey PK. A Review on Solid Dispersion. International Journal of Advanced Researsh in Pharmaceutical and Bio Sciences. 2012; 1(2):281-291.
4. Ahmed A, Sandra K, Karsten M. A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: Characterization, dissolution, in vitro digestion and incorporation into solid pellets. Eur. J. Pharm. Sci. 2008; 35:457–464.
5. Kapadiya N, Singhvi I, Mehta K, Karwani G, Dhrubo JS. Hydrotropy: A promising tool for solubility enhancement: A review. International Journal of Drug Development and Research 2011; 3(2):26-33.
6. Payem Z, Ping IL. Solid molecular dispersions of poorly water soluble drugs in poly (2-hydroxy ethyl methacrylate) hydrogels. Eur. J. Pharm. Biopharm 2007; 65:320-328.
7. Teresa MM, Victoria MM, Gloria ES. Characterization and solubility study of solid dispersions of flunarizine and polyvinylpyrrolidone. IL Farmaco 2002; 57:723-727.
8. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. 2002*;* 231(2):131-144.
9. Rajashree H, Vilasrao K. Preformulation Study of the Inclusion Complex Irbesartan-β-Cyclodextrin. AAPS PharmSciTech 2009; 10(1):276-281.

10. Santhosh P, Anand KM, Hanumantha RK, Anand D, Shiva P, Aparna C. Development, evaluation and characterization of solid dispersion for solubility and dissolution enhancement of irbesartan. International Journal of Research in Pharmacy and Chemistry 2012; 2(2):418-427.
11. Ashwini K, Ram KC, Chaitanya Ch. Enhancement of solubility and dissolution rate of irbesartan by solid dispersion technique. Asian Journal of Pharmaceutical and Clinical Research 2011; 4(2):36-40.
12. Raju S, Pravin B, Vivekanand Ch, Sanjay B, Laxmikant Z. Preparation and characterization of microwave assisted candesartan cilexetil solid dispersions. Research & Reviews: Journal of Pharmaceutical Science 2013; 9-19.
13. Anjan KM, Narasimha MP, Radha RE, Pallavi SS, Ruchita KP. An updated review on technical advances to enhance dissolution rate of hydrophobic drugs. Int. Res. J. Pharm. 2012; 3 (10): 1-7.
14. Ahire BR, Rane BR, Bakliwal SR, Pawar SP. Solubility enhancement of poorly water-soluble drug by solid dispersion techniques. International Journal of PharmTech Research 2010; 2(3):2007-2015.
15. Prasada VR, Nagabhushanam MV, Prabhakar Ch. Hydrophilic polymers and superdisintegrants for dissolution enhancement of celecoxib 2011; 2 (2 - 3):257-263.