Research Article *ISSN: 2277-8713*
Karan Patel, IJPRBS, 2013; Volume 2(2): 243-261 *IJPRBS*

ISSN: 2277-8713
IJPRBS
A Path for horizing your innovative work
INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

SOLUBILITY ENHANCEMENT OF PHENYTOIN BY SOLID DISPERSION AND IT'S COMPARISON WITH INCLUSION COMPLEXATION

PATEL KARAN M, PATEL KINJAL K, PATEL HITESH M, SONI SARTHAK J, PATEL PINKAL R,PATEL DHARA B

IJPRBS-QR CODE

PAPER-QR CODE

Department of Pharmaceutical Sciences, HNGU, Patan

Accepted Date:

17/04/2013

Publish Date:

27/04/2013

Keywords

Phenytoin,
Solid dispersion,
Inclusion complex,
HP-β-CD,
Poloxamer - 407

Corresponding Author

Mr. Karan M. Patel

Abstract

The purpose of this study was to enhance the solubility and dissolution rate of Phenytoin by making solid dispersion with poloxamer-407 and inclusion complexation with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD). It belongs to Class II of Biopharmaceutical Classification System (BCS) which is characterized by high membrane permeability, slow dissolution rate due to low aqueous solubility. For the Solid Dispersion this present report describes the saturation solubility study, drug content analysis, Ratio optimization, preparation of the solid dispersion by melting fusion method. The solid dispersion is compressed into a fast disintegrating tablet. The dissolution rate of the complex was determined In vitro and was compared with that of pure drug. The dissolution data shows 1: 3 weight ratio was optimized ratio. The In-vitro dissolution study of optimized ratio shows 89.85 % corrected cumulative drug release (% CCDR) in 2Hrs and 20mins, whereas with pure drug the value 39.3 % CCDR in water. The Dissolution rate of the dispersion was 2.2 times as much as that of the pure drug. For the inclusion complexation this present report describes the study of the phase solubility diagram, preparation of the inclusion complex by the kneading method, physical evaluation, and determination of the In-vitro dissolution profile in water as well as in 0.1 N HCl. The dissolution rate of the complex was determined In vitro and was compared with that of pure drug. The In-vitro dissolution of optimized ratio shows 91.5 % CCDR in 2Hrs and 20mins, whereas with pure drug the value 39.3 % CCDR in water. The Dissolution rate of the complex was 2.05 times as much as that of the pure drug. After analyzing In-vitro dissolution profile of both the technique it can be concluded that inclusion complex making with HP-β-CD enhance the dissolution rate as well as the solubility more than solid dispersion.

1. INTRODUCTION:

1.1 Bioavailability of poorly water-soluble drugs

The bioavailability is a measurement of the extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action[1]. The bioavailability is mainly controlled by the delivery of the drug as determined by its pharmaceutical formulation, its solubility, and its permeability through the gut wall. In addition, the bioavailability decreases through decomposition of the drug in the gastrointestinal tract, by formation of non-absorbable complexes, by metabolization, or by premature elimination[2].

1.2 Ways of solubility enhancement

In general, there are both chemical and physical ways to improve the solubility of a drug[3]. The formations of soluble salts, like ibuprofen-lysinate instead of ibuprofen, or prodrugs, for instance sulfamoyl sulfonate prodrugs, are chemical tools, which are often found in pharmaceutical formulations[4]. Physical methods to improve the dissolution rate can be derived from the equation by Noyes and Whitney.[5]:

$$\frac{dc}{dt} = \frac{A * D * (Cs - Ct)}{V * h}$$

Nano-particles can be produced by high pressure homogenization, wet ball milling or precipitation and can be incorporated into tablets for oral delivery. Cyclodextrins (CD) formulations are quite common complexation which aids to enhance solubility[6]. Cyclodextrins are molecules with a great variety resulting in about 100 different CD derivatives commercially available[8]. According to the BCS, four different types of drug absorption regimes are distinguished. They are explained in table.

1.3 Solid Dispersion

1.3.1 Definition

The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix in solid state, prepared by melting (fusion), solvent evaporation or melting solvent method.[13] The dispersion of drug in solid diluents by traditional mechanical mixing is not included in this category. Solid dispersion is 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.

1.4 Methods of preparation

Methods which generally used for the preparation of solid dispersion are

1. Melting (fusion) method.

2. Solvent evaporation

3. Melting solvent method

4. Kneading method

5. Lyophilization

6. Spray drying

7. Hot melt extrusion

8. Electrostatic spinning method

9. Supercritical fluid technology (SCF)

1.5 Definition of Inclusion complexation

Cyclodextrins (CDs), with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes.

1.6 Hydroxy Propyl β CycloDextrines (HP-β-CDs)

Degree of substitution (DS) plays an important role in balancing the CD water solubility and its complexing ability. It was reported that increasing the degree of substitution up to an optimum level improves the CD aqueous solubility, but beyond that, the steric hindrances of the host molecule impair CD complexing (efficiency) capacity. HP-β-CD derivatives with a low degree of substitution showed the best complexing properties with low surface activities. Binding of guests to these CD derivatives was very similar to β-CD at low degrees of substitution, but, as the substitution increased, the steric hindrances weakened the binding and the effect was dependent upon the particular guest.

2. MATERIALS AND METHODS

2.1 MATERIALS

Phenytoin was obtained from Lincoln pharmaceutical (Ahmedabad ,India).Cross carmelose Sodium , MCC , Aspartame , Mannitol were obtained from ACS

chemicals(Ahmedabad ,India). HP-β-CD was obtained from Oxford Laboratory (Mumbai, India). Poloxamer-407 was obtained Ajit enterprise (Ahmedabad, India). All other ingredients used were of laboratory reagents and used as much without further testing.

2.2 METHODS

2.2.1 Preparation of physical mixtures

Physical mixture of phenytoin with poloxamer – 407 containing six different weight ratios (1:0.5, 1:1, 1:2, 1:3, and 1:4) were prepared separately. Phenytoin and poloxamer – 407 were accurately weighed, pulverized and then mixed thoroughly by light titration for 5 min in a glass mortar until homogenous mixture was obtained.

Similarly physical mixture of Phenytoin with Hydroxy Propyl Beta Cyclodextrine (HP-β-CD)containing three different weight ratio (1:0.5, 1:1, 1:2) were prepared.

2.2.2 Preparation of solid dispersion by Melting Fusion Method

Phenytoin solid dispersions, consisting of various proportions of poloxamer- 407 were prepared as described below. In order to determine the solid solubility of phenytoin in Poloxamer-407, the following solid dispersions (Phenytoin proportion stated first) were prepared in various ratio 1 : 0.5; 1 : 1; 1 : 2 ; 1 :3 ; 1 : 4. . For those different weights like 300 mg, 600 mg, 1.2 gm, 1.8 gm, 2.4 gm of poloxamer-407 were taken with 20 mg of drug to prepare different ratio. Poloxamer-407 in above different weight were taken and heated while stirring in a water bath maintained at 70°C. The solid dispersions were prepared by the melt (fusion) method as follows. To each fused ratio, an appropriate weight of Phenytoin powder was added to produce the required proportion. The mixture was then stirred for 1 hr at increasing temperature until all the phenytoin had dissolved and was uniformly dispersed in the matrix. The fused mixture was allowed to cool slowly to room temperature with stirring. The solid dispersions were then dried for ≈24 hrs in desiccators at room temperature. The solidified melts were then sieved (20 meshes, ≈850 µm) and stored in amber-colored glass bottles at room temperature.

2.2.3 Preparation of inclusion complex by Kneading Method

Solid inclusion complex of Phenytoin and HP-β-CD were prepared in molar ratio by following kneading method. Solid inclusion complex of phenytoin and HP-β-CD were prepared in different molar ratio of 1:0.5, 1: 1, 1: 2. For that different weights like 70.30 mg, 140.6 mg, , 281.20 mg of HP-β-CD were taken with 25 mg of drug to prepare different ratio. HP-β-CD was mixed in a glass mortar along with water to obtain a homogeneous paste. The drug was slowly added to the paste and the mixture triturated for 1 hr. During the process the water content of the paste was empirically adjusted to maintain the consistency of the paste. The paste was dried at 45 ^{0}C for 48 hrs, pulverized and passed through sieve No.100.

3. EVALUTION OF COMPLEX:

The acceptable range of compressibility and bulk density are given in Table 14. All the formulations show lower % compressibility, with a maximum of 7.55% compressibility. Since powders having % compressibility less than 20-21 has good flowability. Acceptable range of Compressibility is 5.00%–15.00% Formulations SD1 to SD5 and CD1 to CD3 showed the Compressibility in the acceptable range, The solid dispersion and inclusion complex can be said to have good flow ability .Results are tabulated in Table.

Angle of repose

The flow property of the prepared formulations was checked by the method, angle of repose. Acceptable range of angle of repose is 8^0 75' to 15^0 44'. All the formulations showed an angle of repose within the range as shown in Table No.16. Formulations SD1 to SD5 and CD1 to CD3 showed an angle of repose in the acceptable range, which indicates a good flow property. Results are tabulated in Table.

Saturation solubility of drug was determined by solubilizing the solid dispersion in distilled water till the solvent gets saturated and the amount of drug dissolved was then analyzed spectrophotometrically. Solid dispersions of Phenytoin prepared with poloxamer-407 polymer, all showed increased drug solubility over the pure Phenytoin and physical mixture of drug and polymer. With increase in the drug to polymer ratio increase in solubility was found with poloxamer 407 drug solubility was found to

be increased up to the ratio 1:3 further increase in the polymer concentration there is no effect on solubility of drug was found. Solubility of Phenytoin in solid dispersion and physical mixture Mechanism involve an increase in solubility of drug with poloxamer 407 is micellar solubilization.

The formulation Batch SDPM4, SD4 containing 1 : 3 weight ratio showed a release of 62.58%, 89.85% for 2.20 hours in Water respectively and Batch SD4 showed 96.06% for 2.20 hours in 0.1 N HCl. This compare to above shows that Increase in drug release was observed with Increase polymer concentration. Again increase in drug release because of drug-polymer optimized ratio.

The In-vitro dissolution for Batch CD2 shows 91.5 % CCDR in 2Hrs and 20mins, whereas with pure drug the value 39.3 % CCDR in water. The Dissolution rate of the complex was 2.05 times as much as that of the pure drug. So, from the above data it was concluded that the optimized formulation for inclusion complexation was 1: 1 molar ratio of Drug and HP-β CD. All the drug get includes into the all the present molecule of HP- β-CD.

The various batches show good drug contents. The batches like SDPM4, CDPM2, SD4 and CD2. The formulation SD4 shows 99.53±0.19 drug in complex. The formulation CD2 shows 99.34±0.19 drug in complex.

Dissolution time T30, T50 and T90 values for all formulations are given in above table. The compare with all formulation Batch the dissolution T30, T50 and T90 values of the formulation Batch SD4 for Solid dispersion and CD2 for inclusion complexation were found to be optimized batch having highest % drug release in about 3 hours.

4. Comparison of Drug Release profile of Batch SD4 & CD2 In Water

5. SUMMARY

Improving the dissolution characteristics of poorly water soluble drugs is important to achieve better bioavailability and reduced side effects. The solid dispersion and Inclusion complexation techniques are important tools in this direction. Phenytoin is stabilizes the inactivated state of sodium channels, meaning that fewer of these channels are available to subsequently open, making brain cells less excitable thus used in the treatment of epilepsy. It is

practically insoluble in water thereby shows poor bioavailability when administered orally. Thus the solid dispersion and inclusion complexation techniques were employed to enhance the solubility thereby bioavailability of Phenytoin. The hydrophilic polymer had been tried to improve the solubility and dissolution of Phenytoin. Poloxamer-407 was used to make Solid dispersion and HP-β-CD was used to make inclusion complex.

6. CONCLUSION

From the present study, the following conclusion can be drawn:

- The solid dispersion made with poloxamer-407 with 1: 3 (Drug: Polymer) ratio improve more solubility of Phenytoin.
- The inclusion complex made with HP-β-CD with 1: 1 (Drug: Polymer) ratio improve more solubility of Phenytoin.
- This enhancement in drug solubility is due to fast dissolution rate of the complex.
- After comparing the dissolution profiles of optimized ratios of both the techniques it can be concluded that the inclusion complex making with HP-β-CD was improving more solubility as compare to Solid dispersion.
- Thus, HP-β-CD could be a useful additive to solid Phenytoin. Formulations having inclusion complex with HP-β-CD result in a more rapid absorption and improved bioavailability of the drug.

Figure 1

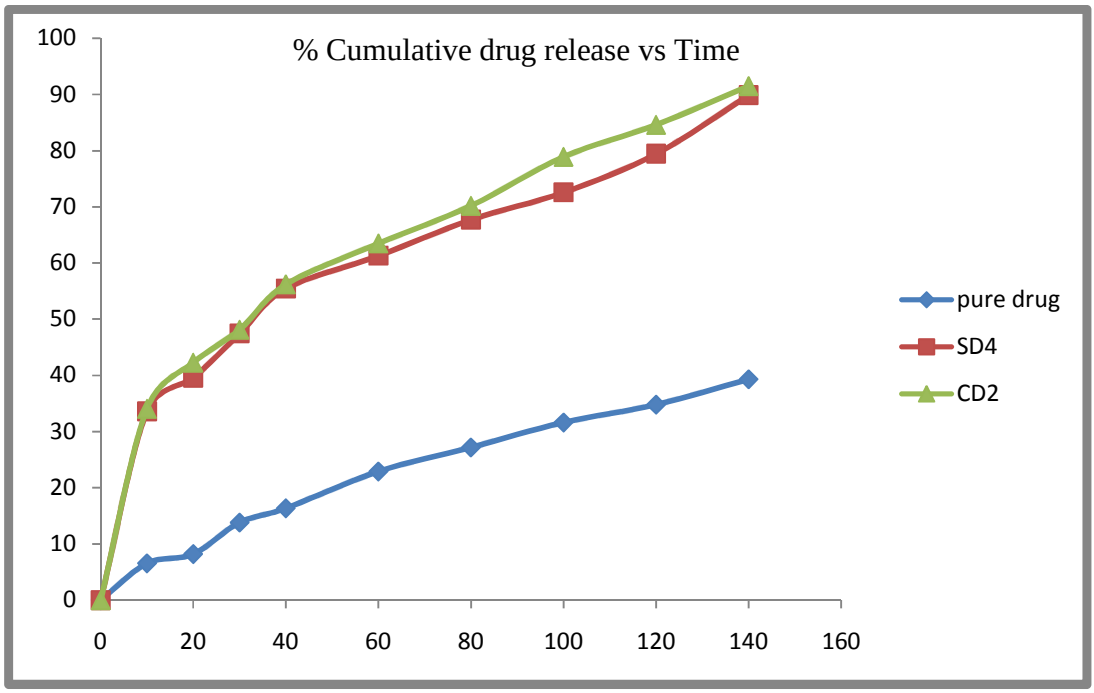

Table 1 :BCS Classification of drugs on basis of solubility and permeability

Class	Dissolution in aqueous	Permeation over
I	Fast	Fast
II	Slow	Fast
III	Fast	Slow
IV	Slow	Slow

Table 2 : Preparation of Solid Dispersion And Physical Mixtures, Inclusion complex

Methods of Preparation	Type of polymer	Drug to polymer Ratio	Batch code
Physical Mixture	Poloxamer – 407	1:0.5	SDPM1
		1:1	SDPM2
		1:2	SDPM3
		1:3	SDPM4
		1:4	SDPM5
	Hydroxyl propyl β cyclodextrin	1:0.5	CDPM1
		1:1	CDPM2
		1:2	CDPM3
Kneaded Product	Hydroxyl propyl β cyclodextrin	1:0.5	CD1
		1:1	CD2
		1:2	CD3
Melting Fusion Method	Poloxamer – 407	1:0.5	SD1
		1:1	SD2
		1:2	SD3
		1:3	SD4
		1:4	SD5

Table 3 : Data of Physical parameter study of Solid dispersion and Inclusion Complex

BATCH	B.D	T.D	H.R	%Compressibility	Angle of repose
SDPM1	0.180±0.013	0.187±0.013	1.04± 0.06	3.63± 0.484	11.68 ±3.037
SDPM2	0.177± 0.05	0.191 ±0.06	1.078± 0.01	7.28± 0.07	12.52± 2.84
SDPM3	0.180± 0.011	0.188 ±0.01	1.043± 0.02	4.17± 0.13	12.52± 4.059
SDPM4	0.181± 0.09	0.194± 0.09	1.060± 0.02	5.64± 0.16	13.78± 3.30
SDPM5	0.168± 0.03	0.186 ±0.04	1.107± 0.01	6.24 ±0.032	15.44± 3.152
CDPM1	0.191± 0.04	0.204 ±0.04	1.066± 0.01	6.24 ±0.012	13.53± 4.24
CDPM2	0.195 ±0.03	0.206± 0.03	1.053± 0.01	5.08 ±0.056	11.44± 3.974
CDPM3	0.193± 0.03	0.208 ±0.03	1.08	7.55± 0.036	13.58± 5.17
SD1	0.063±0.03	0.066±0.06	1.057±0.06	5.37±0.56	14.24±1.83
SD2	0.062±0.03	0.063±0.08	1.023±0.02	2.32±0.27	12.13±2.83
SD3	0.066±0.04	0.069±0.02	1.045±0.03	4.29±0.24	12.43±3.76
SD4	0.059±0.08	0.060±0.01	1.015±0.03	1.29±0.27	9.09±2.04
SD5	0.062±0.02	0.065±0.01	1.05	4.87±0.095	11.05±2.48
CD1	0.143±0.04	0.154±0.04	1.077	7.17±0.025	11.56±1.54
CD2	0.128±0.03	0.136±0.05	1.041±0.02	6.257±2.0	9.55±1.92
CD3	0.133±0.02	0.140±0.02	1.047±0.06	4.49±0.53	8.75±1.94

Values in parenthesis are standard deviation (±SD), n=3

Table 4: Saturation Solubility of Phenytoin in solid dispersion

Sr. No.	Sample	Solubility of phenytoin (mg/ml)	
		Solubility in water	Solubility in 0.1 N HCL
1	Pure Drug	0.79 ±0.03	0.87± 0.05
2	SDPM1	0.88± 0.03	0.93 ±0.04
3	SDPM2	1.06± 0.06	1.21 ±0.05
4	SDPM3	1.28± 0.08	1.55 ±0.07
5	SDPM4	1.63± 0.13	1.93± 0.05
6	SDPM5	1.40± 0.07	1.72 ±0.04
7	SD1	1.44± 0.02	1.84± 0.03
8	SD2	1.65± 0.04	2.11± 0.05
9	SD3	1.99 ±0.04	2.31 ±0.06
10	SD4	2.75 ±0.12	2.61± 0.08
11	SD5	2.44 ±0.19	2.22± 0.05

Table 5: Data of % cumulative Drug Release For Batches CD1 – CD3 In 0.1 N HCL

TIME(min)	%Cumulative Drug Release			
	Pure drug	CD1	CD2	CD3
0	0	0	0	0
10	9.16 ±0.36	25.2±0.9	40.38±0.46	32.10±1.01
20	12.34± 0.56	32.82±1.23	49.29±0.45	38.4±1.11
30	16.12 ±0.41	44.28±0.77	56.88±0.77	53.01±0.65
40	20.29 ±0.41	52.32±0.46	67.32±0.77	60.9±1.11
60	24.03± 0.46	63.51±1.08	74.52±1.67	69.4±0.92
80	29.12± 0.46	70.32±0.77	80.71±.07	76.59±0.77
100	34.00 ±1.12	77.01±0.92	88.11±1.04	82.11±0.45
120	40.25 ±0.37	81.12±1.13	94.2±0.52	88.08±0.46
140	47.16± 0.41	85.59±1.04	98.1±0.9	90.9±0.9

Table 6 Data of % cumulative Drug Release for Batches SD1 – SD5 in 0.1 N HCl

TIME(min)	%Cumulative Drug Release					
	Pure drug	SD1	SD2	SD3	SD4	SD5
0	0	0	0	0	0	0
10	9.16 ±0.36	28.07± 0.80	28.98± 0.22	31.18± 0.31	37.96± 0.41	34.52± 1.20
20	12.34± 0.56	37.04± 0.33	39.20± 0.26	41.96± 0.46	44.23± 0.16	43.52± 1.29
30	16.12 ±0.41	45.03± 0.41	47.26± 0.25	49.18 ±0.21	52.05± 0.21	51.37± 0.2
40	20.29 ±0.41	53.33± 0.57	55.13± 0.42	58.01± 0.26	60.64± 0.42	59.73± 0.91
60	24.03± 0.46	60.61± 0.32	62.22± 0.36	65.29± 0.36	68.53± 0.15	67.45± 0.53
80	29.12± 0.46	67.34± 0.37	69.20± 0.31	72.30± 0.57	75.17 ±0.21	73.03± 0.35
100	34.00 ±1.12	73.34± 0.32	75.14± 0.30	78.04± 0.15	81.30 ±0.36	79.87± 0.66
120	40.25 ±0.37	79.43± 0.52	81.03± 0.36	83.83± 0.37	90.03± 0.23	85.04± 0.73
140	47.16± 0.41	82.14± 0.51	86.02± 0.42	90.45± 0.32	96.06± 1.04	93.03± 1.04

Table 7 Drug Content Estimation of Various Batches

Sr. No.	Batch code	Drug content (%) (Mean±S.D.)
1	SDPM1	95.4± 0.19
2	SDPM2	95.52 ±0.474
3	SDPM3	96.53 ±0.185
4	SDPM4	98.84± 0.473
5	SDPM5	97.34± 0.662
6	CDPM1	96.78 ±0.286
7	CDPM2	99.35 ±0.375
8	CDPM3	98.53 ±0.473
9	SD1	95.27± 0.394
10	SD2	96.27± 0.289
11	SD3	98.65± 0.285
12	SD4	99.53± 0.19
13	SD5	97.96 ±0.39
14	CD1	97.34± 0.280
15	CD2	99.34 ±0.19
16	CD3	98.15± 0.474

Table 8: T30,T50,T90, Values For Various Batches of Solid dispersion and InclusionComplex

Batch	Media	T_{30}(min)	T_{50}(min)	T_{80}(min)
SD1	Water	54.35	90.58	163.04
	0.1 N HCl	51.13	85.22	153.40
SD2	Water	51.49	85.82	154.47
	0.1 N HCl	48.83	81.38	146.48
SD3	Water	48.70	81.16	146.09
	0.1 N HCl	46.43	77.39	139.30
SD4	Water	46.74	77.91	140.23
	0.1 N HCl	43.72	72.87	131.17
SD5	Water	48.19	80.32	144.58
	0.1 N HCl	45.15	75.24	135.44
CD1	Water	57.61	96.02	172.84
	0.1 N HCl	49.07	81.79	147.21
CD2	Water	45.90	76.50	137.70
	0.1 N HCl	42.81	71.36	128.44
CD3	Water	54.90	91.50	164.71
	0.1 N HCl	46.20	77.01	138.61

Table 9: Data of % cumulative Drug Release For Batches SD4 and CD2 In Water

Time in minutes	% Cumulative Drug Release		
	Pure Drug	SD4	CD2
0	0	0	0
10	6.54± 0.23	33.57±1.09	34.05 ±0.27
20	8.20± 0.72	39.57±0.69	42.27 ±0.23
30	13.8± 3.23	47.43±0.65	48.15 ±0.50
40	16.35± 0.73	55.44±0.65	56.19 ±0.43
60	22.89± 1.22	61.29±0.69	63.48 ±0.55
80	27.18 ±0.95	67.71±0.86	70.2 ±0.9
100	31.62± 0.93	72.57±0.64	78.9 ±1.87
120	34.77± 1.26	79.44 ±0.69	84.6 ±1.8
140	39.3± 0.81	89.85±3.51	91.5 ±0.52

7. REFERENCES

1. Kerns EH. High throughput physicochemical profiling for drug discovery. J Pharm Sci 2001, 90, 1838-1858.

2. Meylan WM & Howard PH. Atom/fragment contribution method for estimating octanol-water partition coefficient. J Pharm Sci 1995, 84, 83-92.

3. Shah VP, Konecny JJ, Everett RL, McCullough B, Noorizadeh AC & Selly JP. In vitro dissolution profile of water-insoluble drug dosage forms in the presence of surfactants. Pharm Res 1989,6, 612-618.

4. Amidon GL, Lennernäs H, Shah VP & Crison JR. A Theoretical basis for a biopharmaceutic drug classification - the correlation of in-vitro drug product dissolution and in-vivo bioavailability. Pharm Res 1995,12, 413-420.

5. Noyes AA & Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc 1897, 19 , 930-934.

6. Pouton CW. Formulation of self-emulsifying drug delivery systems. Adv Drug Del Rev 1997 , 25, 47- 58.

7. Chiou WL & Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci 1971, 60, 1281-1302.

8. Amidon GL, Lennernäs H, Shah VP & Crison JR. A Theoretical basis for a biopharmaceutic drug classification - the correlation of in-vitro drug product dissolution and in-vivo bioavailability. Pharm Res 1995, 12, 413-420.

9. Kim, C.K., Park, J.S. Solubility enhancers for oral drug delivery: can chemical structure manipulation be avoided? Am. J. Drug Del. ,2004, 2, 113-130.

10. Serajuddin, A.T.M,. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci.1999, 88,1058-1066.

11. Okonogi, S., Oguchi, T., Yonemochi, E., Puttipipatkhachorn, S., Yamamoto, K. Improved dissolution of Ofloxacin via solid dispersion. Int. J. of Pharma. 1997, 156, 175-180.

12. Chen, Y., Zhang, G.Z., Neilly, J., Marsh, K., Mawhinney, D., Sanzgiri, Y.D. Enhancing the bioavailability of ABT-963 using solid dispersion containing Pluronic F-68. Int. J. Pharm. 2004,286, 69- 80.

13. Chiou, W.L., Riegelman, S. Pharmaceutical application of solid dispersion. J. of Pharma. Sci. 1971, 60(9), 1281-1302.

14. Goldberg, A.H., Gibaldi, M., Kanig, J.L. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II.

Experimental evaluation of eutectic mixture: urea-acetaminophen system. J. Pharm. Sci.,1966, 55, 482-487.

15. Okonogi, S., Oguchi, T., Yonemochi, E., Puttipipatkhachorn, S., Yamamoto, K. Improved dissolution of Ofloxacin via solid dispersion. Int. J. of Pharma.1997,156, 175-180.

16. Craig, D.Q.M. The mechanism of drug release from solid dispersion in water soluble polymers. Int. J. of Pharm. 2002, 231, 131-144.

17. Findlay, "the phase Rule" 9th ed. Dower New York N. Y. 1951, 477.

18. Sekiguchi, K., Obi, N. Studies on absorption of eutectic mixture-I A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharma Bull. 1961, 9, 866-872.

19. Martin, A.N., Swarbrick, J., Cammarata, A. Physical pharmacy 2nd ed. Lea & Fabiger, Philadelphia, 1961, 313.

20. Hancock, B.C., Parks, M. What is the true solubility advantage for amorphous pharmaceuticals? Pharm. Res. 2000, 17, 397-404.

21. Chiou, W.L., Riegelman, S. Pharmaceutical application of solid dispersion. J. of Pharma. Sci. 1971,60(9), 1281-1302.

22. Tsinontides, S.C., Rajniak, P., Hunke, W.A., Placek, J., Reynolds, S.D.. Freeze drying-principles and practice for successful scale-up to manufacturing. Int. J. Pharm. 2004, 280. 1, 1-16.

23. Bandry, M.B., Fathy, M.. Enhancement of the dissolution and permeation rates of meloxicam by formation of its freeze-dried solid dispersions in polyvinylpyrrolidone K-30. Drug Dev. Ind. Pharm. 2006, 32 (2), 141-150.

24. Chronakisa, I.S., Triantafyllou, A.O. Solid state characteristics and redispersible properties of powders formed by spray-drying and freeze-drying cereal dispersions of varying (1 3, 1 4)-ß glucan content. J. of cereal sci. 2005, 40, 183-193.

25. Rankell, A.S., Lieberman, H.A., Schiffmann, R.F., Drying. In: L. Lachman , H.A., Lieberman and J.L.Kanig eds. The theory and practice of industrial pharmacy. 3rd edition, Varghese Publishing house, Bombay, 1987, pp no 61.

26. Weuts, I., Kempen, D., Verreck, G., Decorte, A., Heymans, K., Peeters, J., Brewster, M., Mooter, G. Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG 6000 prepared by spray drying. Eur. J. Pharm. Biopharm.2005, 59, 119-126.

27. Chauhan, B., Shimpi, S., Paradkar, A.. Preparation and evaluation of glibenclamidepolyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. Eur. J. Pharm. Sci. 2005,26, 219-230.

28. Breitenbach, J.. Melt extrusion: from process to drug delivery technology. Eur. J. Pharm. Biopharm.2002, 54,107-117.

29. Chokshi, R., Hossein, Z.. Hot –Melt Extrusion Technique: A Review. Iran. J. Pharm. Res.2004, 3, 3-16.

30. Perissutti, B., Newton, J.M., Podezeck, F., Rubessa, F.. Preparation of extruded Carbamazepine and PEG 4000 as a potential rapid release dosage form. Eur. J. Pharm. Biopharm.2002, 53,125-132.