

FABRICATION AND CHARACTERIZATION OF EZETIMIBE SOLID DISPERSION FOR SOLUBILITY ENHANCEMENT

ABSTRACT

The objective of the present study was to formulate solid dispersions (SD) of Ezetimibe to improve the solubility and dissolution rate to facilitate faster onset of action. Ezetimibe is a poorly water soluble BCS class II drug and used as a hypolipidemic agent. It has poor bioavailability (35-65%) due to its low dissolution profile in gastro intestinal tract. In the present study, eight solid dispersion formulations of Ezetimibe with polymers PEG-4000 and PEG-6000 were prepared by solvent evaporation and fusion methods. Solid dispersion formulations were characterized by content uniformity, flow properties and in vitro dissolution studies. Present study concluded that the Ezetimibe solid dispersion formulations are a suitable approach to improve the solubility and dissolution rate of ezetimibe than pure form of drug.

Keywords: PEG-4000, PEG-6000, solid dispersion, Ezetimibe,.

INTRODUCTION

Solubility is an important aspect for oral dosage forms, to deliver required drug concentration in systemic circulation to produce desired pharmacological response¹. On an average more than 90 % of available drugs have poor solubility, poor permeability, or both². For this reason there is always a need to use high doses of poor soluble drugs to achieve minimum effective concentration of drug in systemic circulation³.

There are so many approaches to enhance the solubility of such poorly water-soluble drugs like particle-size reduction, salt formation, solubilization, and complexation with β cyclodextrins. All these methods suffer from one or the other drawbacks⁴. Among various approaches, the solid-dispersion technique is the most successful in improving the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical and advantageous⁵. A solid dispersion can be defined as "dispersion of one or more active ingredients in an inert carrier matrix in solid-state". Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug⁶.

The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles by various methods⁷. It enhances solubility by reducing particle aggregation, eliminating crystalinity, increasing wettability, dispersibility and altering the surface properties of drug particles⁸. When solid-dispersion is exposed to aqueous media the carrier dissolves and drug releases as fine colloidal particles, the resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs⁹. Ezetimibe is a BCS class II drug. Ezetimibe is a poorly water soluble drug and act as a hypolipidemic agent¹⁰. Ezetimibe decreases plasma cholesterol levels by inhibiting the cholesterol absorption in the intestine. It has 35-65% of bioavailability due to its low dissolution profile in gastro intestinal tract¹¹. Ezetimibe binds to a carrier of cholesterol absorption, the Niemann Pick C1-Like 1 (NPC1L1) protein on the gastrointestinal tract epithelial cells and in hepatocytes thus decreasing the LDL in the body and prevent various life threatening diseases. In the present investigation an attempt has been made to increase the dissolution profile of Ezetimibe by solid dispersion¹².

The aim of the present study was to prepare solid dispersions in order to achieve increased dissolution rates. Therefore, in the present study, solid dispersions of Ezetimibe were prepared by solvent evaporation technique and fusion method. Acetone was selected as a solvent as drug has highest solubility in this solvent. Acetone is categorized under class II solvents, less toxic than other chlorinated solvents can be easily evaporated and recovered because of its low boiling point.

MATERIALS AND METHOD

Ezetimibe was gift sample from Afrab-chem ltd, Nigeria. PEG 4000 and PEG 6000 were obtained from Dana Drugs ltd, Lagos, Nigeria and all other reagents used were of analytical grade.

Preparation of solid dispersions:

1. Solvent Evaporation method¹³

Required amount of Ezetimibe was dissolved in 10 ml of acetone. Accurately weighed carriers PEG 4000, PEG 6000 corresponding to different drug: carrier ratio by weight was dispersed in drug solution. The solvent was allowed to evaporate on water bath under occasional stirring at temperature of 40-42°C in a protected environmental condition containing an exhaust system. The dried mass was pulverized and was passed through a mesh sieve of number of 100. The powder was subsequently dried at 40°C for 3 hours in a tray drier.

2. Fusion method¹⁴

In fusion method the binary solid dispersions were made using PEG-4000, PEG-6000 as carriers with varying drug: carrier ratios by the fusion method. Solid dispersion of Ezetimibe and carriers were obtained by melting carrier in a porcelain dish at 80–85° and to this Ezetimibe added with thoroughmixing for 1-2 minutes followed by quick cooling. The dried mass was then crushed and passes through sieve no.40 to get uniform sized particles.

Table 1: Composition of solid dispersion formulations of Ezetimibe

Formulation code	Carrier	Drug: Carrier	Method	Acetone
SD1	PEG 4000	1:1	Fusion method	q.s.
SD2	PEG 4000	1:3	Fusion method	q.s.
SD3	PEG 6000	1:1	Fusion method	q.s.
SD4	PEG 6000	1:3	Fusion method	q.s.
SD5	PEG 4000	1:1	Solvent evaporation method	q.s.
SD6	PEG 4000	1:2	Solvent evaporation method	q.s.
SD7	PEG 6000	1:1	Solvent evaporation method	q.s.
SD8	PEG 6000	1:2	Solvent evaporation method	q.s.

Solubility studies¹⁵

The solubility studies of different Ezetimibe and solid dispersion formulations of Ezetimibe were conducted in distilled water and phosphate buffer of 1.2, 6.8 and 7.4 pH. An excess amount of Ezetimibe solid dispersion was weighed and transferred into conical flasks which contain 10 ml of media. The content in conical flask were sonicated for 2 hrs at room temperature, there after the samples were placed on a shaker, agitated at room temperature for 48 hrs. After it, the suspensions were filtered through a Whatman filter paper. The filtrate was suitably diluted and analyzed spectrophotometrically at a wavelength of 232 nm using a double beam UV-Visible spectrophotometer.

Table 2: Solubility study of Ezetimibe and solid dispersion formulations of Ezetimibe

	Solubility (µg/ ml)			
	Distilled Water	1.2 pH buffer	6.8 pH buffer	7.4 pH buffer
Pure drug	2.37 ± 0.14	3.37 ± 0.14	4.42 ± 0.09	5.31 ± 0.06
SD1	22.43 ± 0.25	23.48 ± 0.13	24.57 ± 0.26	25.95 ± 0.14
SD2	24.59 ± 0.09	26.81 ± 0.26	29.44 ± 0.07	31.59 ± 0.26
SD3	23.47 ± 0.07	26.64 ± 0.07	28.58 ± 0.42	29.74 ± 0.25
SD4	33.56 ± 0.11	37.83 ± 0.04	36.46 ± 0.18	39.85 ± 0.16
SD5	26.87 ± 0.26	28.55 ± 0.08	32.74 ± 0.33	29.73 ± 0.09
SD6	37.48 ± 0.31	39.51 ± 0.15	40.57 ± 0.41	41.66 ± 0.07
SD7	29.41 ± 0.16	33.74 ± 0.32	35.83 ± 0.09	36.85 ± 0.14
SD8	30.46 ± 0.08	36.78 ± 0.42	37.58 ± 0.25	38.72 ± 0.25

CHARACTERIZATION OF SOLID DISPERSIONS

Percent yield¹⁶

Percent yield was determined by following formula

$$\text{Yield} = \frac{a}{(b+c)} \times 100$$

where, a is the weight of solid dispersion sifted through a 60 number mesh sieve, b is the weight of Ezetimibe taken for solid dispersion preparation, and c is the weight of polymer taken for solid dispersion preparation.

Angle of Repose¹⁷

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and

Angle of repose is determined by following formula:

$$\tan \theta = \frac{h}{r}$$

Where,

θ = angle of repose, h = height of the cone, r = radius of the cone base

Bulk density¹⁸

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ ml and is given by

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume of powder}}$$

Tapped density¹⁹

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed.

Tapped density = (Mass of powder) / (Tapped volume of powder)

Carr's Index²⁰

It indicates the ease with which a material can be induced to flow and powder compressibility. It is expressed in percentage and is given by

Carr's Index = (Tapped density - Bulk density) / (Tapped density) x 100

Hausner's ratio²¹

Hausner ratio (Hr) is an indirect index of ease of powder flow. It is calculated by the following formula:

Hausner's ratio = (Tapped density) / (Bulk density)

Drug content²²

Solid dispersions (100 mg) were accurately weighed and dissolved separately in 100 ml of 20 % v/v acetic acid. The solution was suitably diluted and the absorbance was measured at 232 nm. Drug content was calculated using the regression equation.

In vitro dissolution studies²³

Ezetimibe a pure drug and solid dispersions were subjected to dissolution test using in-vitro dissolution rate apparatus-I of USP XXIV (Basket method). This test was performed using 1000 ml of dissolution medium (0.1N HCL) at 37 ± 2 °C. Accurately weighed samples (plain drug and surface solid dispersions) of drug were filled in '00' size hard gelatin capsule by hand filling method and placed in basket of dissolution apparatus which was rotated at 50 rpm. A 5 ml aliquot of dissolution medium was withdrawn and replaced with equal volume of fresh dissolution medium at appropriate time intervals and analyzed spectrophotometrically by measuring absorbance at 232 nm.

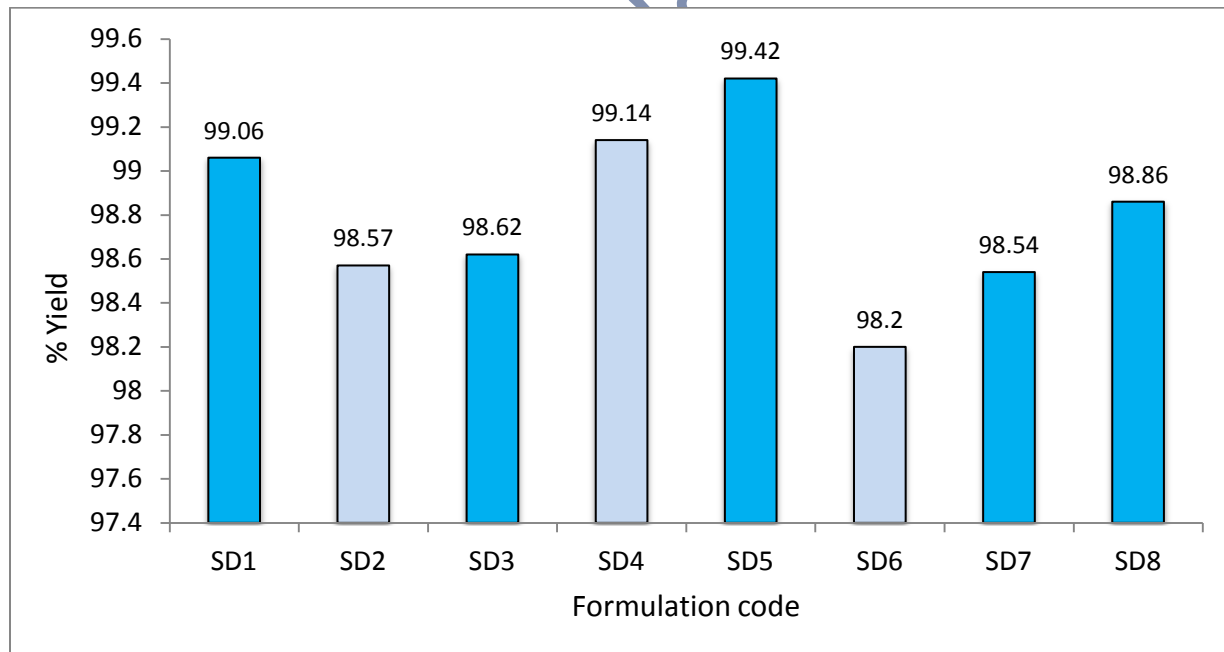


Figure 1: % Yield of solid dispersion formulations of Ezetimibe

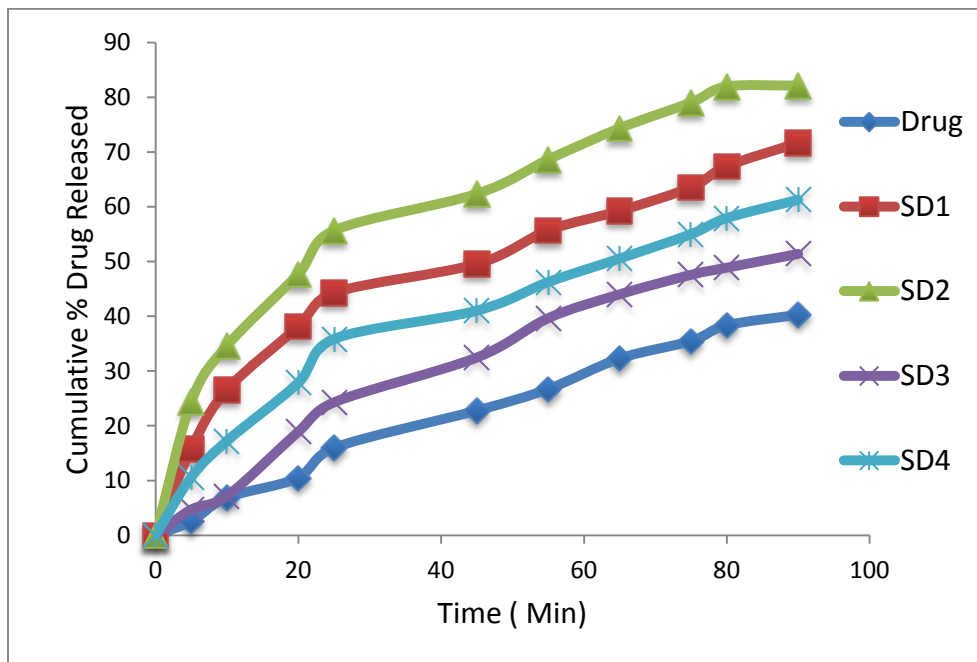


Figure 2: Dissolution profile of Ezetimibe solid dispersion formulations of batch SD1-SD4

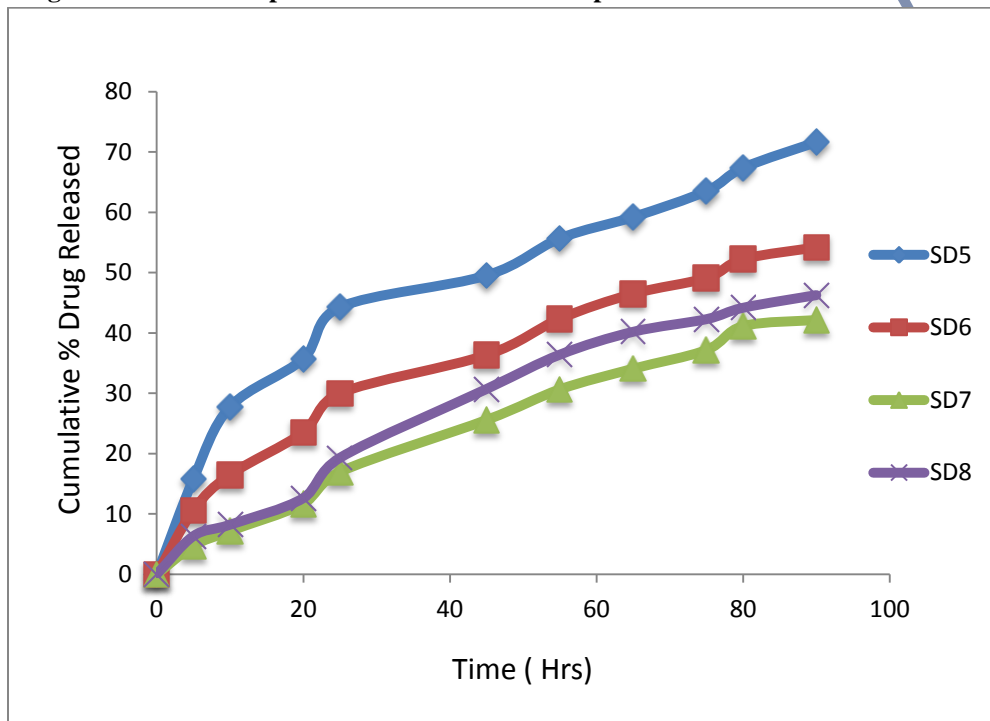


Figure 3: Dissolution profile of Ezetimibe solid dispersion formulations of batch SD5-SD8

RESULTS AND DISCUSSION

The equilibrium solubility data are presented in table 2. The solubility of Ezetimibe powder in distilled water at $37 \pm 0.5^\circ\text{C}$ was $2.37 \pm 0.14 \mu\text{g/ml}$, whereas solubility of the solid dispersion formulations were in the range of $322.43\text{-}37.48 \mu\text{g/ml}$. In other aqueous media i.e. in phosphate buffer of pH 1.2, 6.8 and 7.4, there was increased solubility of solid dispersion formulations in comparison to pure drug. It was found that as the pH of the media increased, there was increase in solubility drug and solid dispersion formulations. These findings suggest that solid dispersions had much more enhanced equilibrium solubility as compared with pure drug powder and physical mixtures.

Table 3: Different evaluation parameters of solid dispersion formulations of Ezetimibe

Formulation code	% Yield	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose (θ)	% Drug content
SD1	99.06	0.92	0.95	3.15	1.032	22 ^o 7'	99.05
SD2	98.20	0.89	0.93	4.30	1.044	21 ^o 6'	98.15
SD3	98.62	0.85	0.89	4.49	1.047	23 ^o 9'	99.37
SD4	99.14	0.83	0.88	5.68	1.060	20 ^o 4'	98.85
SD5	99.42	0.91	0.93	2.15	1.021	20 ^o 5'	99.07
SD6	99.42	0.90	0.94	4.25	1.044	25 ^o 8'	99.66
SD7	98.54	0.86	0.91	5.49	1.058	21 ^o 9'	99.15
SD8	98.86	0.87	0.92	5.43	1.057	26 ^o 1'	99.18

Calculated percent yield of eight solid dispersion formulations of Ezetimibe lies in range of 98.20 to 99.42 % w/w. Out of all the formulation of batch SD6 have shown highest yield (99.42 %) whereas formulation of batch SD2 have shown minimum yield 98.20%.

Solid dispersion formulations of Ezetimibe were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio (table 3). Angle of repose was less than 35° and Carr's index values were less than 21 and Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

The drug content in all Ezetimibe solid dispersion formulations containing PEG 4000 as well as PEG 6000 is above than 98.15 % as shown in Table 3. The drug content was found to be minimum (98.15 %) for SD7 whereas SD6 have shown maximum (99.66 %) drug content. PEG 6000 containing formulations showed better results than PEG 4000 formulations because of its high molecular weight which are responsible for the formation of fine microcrystal and absence of drug clusters.

Dissolution data of Ezetimibe solid dispersion formulations are reported in Fig.2 and Fig.3. From the result, it can be seen that all the prepared solid dispersion showed an enhancement in the dissolution rate of the drug compared to plain drug. Solid dispersions prepared by using PEG 4000 showed enhanced dissolution when compared to other PEG 6000.

The rank order of dissolution rate improvement for various carriers are; PEGS 4000>PEG 6000.

CONCLUSION

Eight formulations were prepared by the solvent evaporation method and fusion method. All prepared solid dispersion formulations showed significantly higher drug dissolution in comparison with pure drug. In the solid dispersion there are many mechanisms responsible for exhibiting faster release like the decrease in particle size, partly to the wettability and to some extent to increase in the solubility of the drug due to the solubilising effect of carrier used or to the increase in surface area of the drug in the product. From the obtained results it can be concluded that solid dispersions improved the dissolution rate of poorly soluble drug Ezetimibe.

The results of the Ezetimibe solid dispersion was indeed promising although more evaluation are needed before it can be finally recommended for capsule or tablet dosage form of Ezetimibe.

REFERENCES

- Okhodchi, A, Javazadeh Y, Reza M, Barzega JM. The effect of type and concentration of vehicles on the dissolution rates of a poorly water improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm.* 2000; 50(1):47–60.
- Otsuka M, Onoe M, Matsuda Y. Hygroscopic stability and dissolution properties of spray-dried solid dispersions of furosemide with eudragit. *J Pharm Sci.* 2006; 82(1): 32–38.
- Martinez-Oharriz MC, Rodrig-Espinosa C, Martin C, Goni MM, Trosllarduya MC, Sanchez, M. Solid dispersions of diflunisal-PVP: Polymorphic and amorphous states of the drug. *Drug. Dev. Ind. Pharm.* 2002; 28(6): 717-725.
- Serajuddin, A. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs, *J. Pharm. Sci.* 1999; 88(10):1058–1066.
- Cassidy OE, Rouchotas C. Comparison of surface modification and solid dispersion techniques for drug dissolution. *Int J Pharm.* 2000; 195(2):1–6.
- Sekiguchi K, Obi N. Studies on absorption of eutectic mixture II. absorption of fused conglomerates of chloramphenicol and urea in rabbits. *Chem Pharm Bull (Tokyo).* 1964; 12: 134-144.
- Leon Lachman, Herbert A, Liberman and Joseph L Karnig. The theory and practice of industrial pharmacy. 3rd ed. Lea and Febigen, Philadelphia. 1986; 301-302.

8. Barakat NS, Elanazi FK, Almurshedi AS. The influence of various amphiphilic excipients on the physicochemical properties of carbamazepine-loaded microparticles. *J Microencapsulation*. 2009; 26(3): 251-262.
9. Papageorgiou GZ, Bikiaris D, Karavas E, Politis S, Docoslis A, Park Y, Stergiou A, Georgarakis E. Effect of physical state and particle size distribution on dissolution enhancement of nimodipine/ PEG solid dispersions prepared by melt mixing and solvent evaporation. *AAPS Journal*. 2006; 8(4): E623-E631.
10. Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, Pharmacokinetics and drug interactions. *Clin. Pharmacokinet*. 2005; 44 (5): 467-494
11. Martindale. The complete drug reference, 32nd ed., London: the pharmaceutical press. 1999; 1473.
12. Garcia Calvo M, Lisnock J, Bull HG, Hawes BE, Burnett DA, Braun MP, The target of ezetimibe is niemann-pick c1-like 1 (npc111). *Proc Natl Acad Sci USA*. 2005, 102: 8132.
13. Huang J, Wigent RJ, Schwartz JB. Nifedipine Molecular Dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blends for controlled drug delivery: Effect of matrix composition. *Drug dev. ind. pharm*. 2006, 32, 1185-1197.
14. Azarmi S, Roa W, Lobenberg R. Current perspectives in dissolution testing of conventional and novel dosage forms. *Int J Pharmaceutics*. 2007; 328(1): 12-21.
15. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. *Eur J Pharm Sci*. 2001; 13: 123-133.
16. Balasubramaniam J, Rajesh Y, Bindu K, Hemalatha T, Swetha M, Vinay UR: Enhanced dissolution and bioavailability of raloxifene hydrochloride by cogrinding with different superdisintegrants. *Chem Pharm Bull*. 2010; 58: 293-300.
17. Chaulang G, Patel P, Hardikar S, Kelkar M, Bhosale A, Bhise B: Formulation and Evaluation of Solid Dispersions of Furosemide in Sodium Starch Glycolate. *Trop J Pharm Res*. 2009; 8(1): 43-51.
18. Tran T-D, Tran PH-L, Choi H-G, Han H-K, Lee B-J: The roles of acidifiers in solid dispersion and physical mixtures. *Int J Pharm*. 2010; 384(1): 60-66.
19. El-Maradny HA, Mortada SA, Kamel OA, Hikal AH. Characterisation of ternary complexes of meloxicam-HP β CD and PVP or L-arginine prepared by the spray drying technique. *Acta Pharm*. 2008; 58: 455-466.
20. Ritger PL, Peppas NA, A Newa M, Bhandari KH, Kim JO. Enhancement of solubility, dissolution and bioavailability of ibuprofen in solid dispersion systems. *Chem Pharm Bull*. 2008; 56(4):569-74.
21. Rowe RC, Sheskey, PJ, Weller PJ. hydroxyl-propyl cellulose Handbook of Pharmaceutical ex-cipients, Pharmaceutical Press, *American Pharmaceutical Association*. 2003, (6), 289-291.
22. Trapani G, Franco M, Latrofa A., Tullio C., Provenzano MR, Serra M, Muggironi M, Biggio G, Liso G. Dissolution properties and anticonvulsant activity of phenytoin-polyethylene glycol 6000 and polyvinylpyrrolidone K-30 solid dispersions. *Int J Pharm*. 2001; 225; 63-73.
23. Chun-Woong Park, Preparation and in vivo evaluation of immediate-release pellet containing celecoxib solid dispersion, *J of pharm invest*. 2012; 42; 121-126.