Preparation and in vitro Evaluation of Ketoprofen Solid Dispersion System

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Abstract

For poorly soluble drugs, such as ketoprofen, the rate of oral absorption is often controlled by the dissolution rate in the G.I.T. Therefore the solubility and dissolution behavior of a drug is key determinants of its oral bioavailability. Several formulations of liquisolid capsules containing two ratios of ketoprofen: Vehicles (1:1 and 1:2) were prepared. In this study the ratio of microcrystalline cellulose (carrier) to silica (coating powder) was 20:1 for all formulations and then changed to 10:1. The dissolution behavior of ketoprofen from liquisolid capsules and conventional capsule formulation was investigated at two different pHs (1.2 and 6.8). The x-ray diffraction (XRD)of solid dispersion of ketoprofen in ratio of 1:1 was characterized to ascertain if there were any physicochemical interactions between the drug and carrier that could affect dissolution.The results showed that liquisolid capsules demonstrated considerably higher dissolution rate than those of conventionally made capsules. This could be attributed to increased wetting properties and surface of drug available for dissolution. XRD showed a change in crystal structure toward an amorphous form of ketoprofen.

Key words: ketoprofen, solid dispersion, bioavailability.

الخلاصة

قليل الذوبان مثل الكيتوبروفين ,يكون معدل الامتصاص الفموي ينظم بواسطة معدل الذوبان في المعدة والامعاء الدقيقة .لذلك يكون الذوبان وسلوك التذويب الى الدواء هو المفتاح الذي يحدد التوافر الحيوي الفموي.الدواءعدة صيغ من كبسولات الصلبة السائلة محتوية على نسبة من كيتوبروفين ,سواغ قد حضرت .في هذه الدراسة نسبة مايكروكرستلاين سليلوز (محمل) الى السيلكا (مسحوق مغلف) كان بنسبة 1:20 الى كل الصيغ ومن ثم غير الى 1:10.السلوك التذويبي للكيتوبروفين من كبسولة صلبة سائلة ومن الكبسولة الاعتيادية تم التحري عنه في اسس هيدروجينية مختلفة (1.2 و6.8م) .الاشعة السينية المتشتتة الى الصلب المتبعثر للكيتوبروفين بنسبة 1:1 قد وضعت للتأكد اذا كان هناك تداخل فيزياوي كيمياوي بين الدواء والمحمل والذي قد يؤثر على التذويب.وقد أظهرت النتائج بأن معدل التحرر من الكبسولات المحضرة بطريقة الصلب المتبعثر أعلى من تحرر الدواء من الكبسولات التقليدية بفرق معنوي وذلك لزيادة خواص الترطيب لسطح الدواء المعرض للاذابة ,بالاضافة الى تحول الشكل البلوري المنتظم للدواء الى الشكل العشوائي كما ظهر في نتائج تشتت الاشعة السينية .

Introduction

The enhancement of the bioavailability of poorly water-soluble drugs is one of the greatest challenges of drug development and several pharmaceutical technologies have been investigated to this end[1].Numerous efforts have been used to improve drug dissolution rate, these include, (a) reducing particle size to increase surface area,(b) solubilization in surfactant systems, (c) formation of water-soluble complexes, (d) use of pro-drug and drug derivation such as electrolyte salt forms that usually have higher dissolution rate, and (e) manipulation of solid state of drug substance to improve drug dissolution i.e. by decreasing crystallinity of drug substance through formation of solid solution[2,3].The most promising method for promoting dissolution is the formation of liquisolid system [4-7]. The concept of liquisolid compacts, as defined by Spires et al[5], can be used to formulate liquid medication such as oily liquid drugs and solution or suspensions of water-insoluble solid drugs in non-volatile vehicles, into acceptably flowing powders[8,9].

Using this new formulation technique, a liquid medication may be converted into a dry looking, non-adherent, free flowing powder by a simple blending with selected powder excipients referred to as the carrier and coating materials. Various grades of cellulose, starch, lactose, etc, may be used as the carrier, whereas very fine particle size silica powder may be used as the coating material (10-12). Various types of non volatile, hydrophilic liquids were used which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution (13).

The anti-rheumatic agent, ketoprofen exhibits poor solubility(14),numerous attempts have been done to improve the dissolution rate of this drug to obtain more rapid and complete absorption oral dosage form (15-17).In this study, ketoprofen, was formulated into liquisolid powders consisting of microcrystalline cellulose, silica, and propylglycol filled in capsules. The effect of changing in the ratio of drug: vehicle on the dissolution rate of ketoprofen from capsule was measured using number 2 USP dissolution test apparatus at pH 1.2 and 6.8 and compared to those conventionally prepared capsules (containing drug alone in hard gelatin capsule). The effect of coating material at different coating: carrier ratios and effect of change in vehicle type was also investigated.

Experimental

Materials

Ketoprofen was provided by Menarini Interntionl, Italy,Microcrystalline cellulose (MCC) from Whatman international Ltd,Sodium starch glycolate from SDI (Samara Drug Industries),nm-sized silica from Sigm-aldrich.Propylene glycole (PG) from Searle company (England),Polyethylene glycol (PEG400) from BDH chemical Ltd,England, Tween 80 from Merck schuchard,Germany,Hard gelatin capsules from ACPC Jordan.

Equipment

U.V spectrophotometer carry uv,varian, Australia, Sartorios balance werke GMDH ,type 2842, Germany, USP dissolution apparatus coply scientific, England, Ultrasonic shaker coply scientific, England, PH-meter Hanna instrument,pH221, Italy, Filter paper HatzeldEder,Germany.

Expermental

Capsules dosage form each containing 50mg of ketoprofen was prepared in 10 formulas as shown in table (1). Ketoprofen was dispersed in the vehicle (PG, PEG and Tween80) to prepare the liquid medication in a ratio of 1:1and 1:2 (drug: vehicle) then binary mixtures of MCC-silica with ratios of (20:1) and (10:1) were added to the mixture containing the drug and vehicle under continuous mixing in a mortar. Sodium starch glycolate as a disintegrant was mixed with one formulation for a period of 10 minutes; the final mixture of formula was filled in a hard gelatin capsules, conventional capsule containing drug alone was also formulated.

Spectrophotometric analysis

Scanning to obtain wave length of maximum absorption was done between 200-400nm in artificial gastric and intestinal fluids, which recorded λ_{max} of 259nm. Spectrophotometric analysis of ketoprofen sample in aqueous solutions was performed at 259 nm.Standard curve was prepared by serially diluting a stock solution of the drug in artificial gastric fluid (pH 1.2) and artificial intestinal fluid (pH6.8). Analysis was carried out on triplicate samples.

Dissolution Studies

The USP basket method was used for all the in vitro dissolution studies. Simulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) without enzyme were used as dissolution media. The rate of stirring was 50 $\pm$ 2 rpm. The amount of ketoprofen was 50 mg in all formulations; the dosage forms were placed in 900 ml of simulated gastric or intestinal fluid and maintained at 37 $\pm$ 0.1°C.

At appropriate intervals (5, 10, 20, 30, 40, 50, 60 and 70 min), 5 ml of the samples were taken and filtered through filter paper. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume.The samples were then analyzed at 259 nm by UV spectrophotometer. The mean of at least three determinations was used.

X-ray diffraction (XRD)

X-ray diffraction patterns were recorded on an x-ray powder diffraction system (PANalytical Spectris Pvt.Ltd, Singapore using Ni-filtered, CuKa radiation, a voltage of 40 KV, and a current of 25mA). The scanning rate employed was $1°min^{-1}$ over the angle 2q range of 0-50°. The XRD patterns of ketoprofen raw material and solid dispersion (1:1) were recorded.

Results and discussion

Effect of vehicle type on the release of ketoprofen at different pH

The release of ketoprofen from formulas F1, F2, and F3, which are formulated using PG, Tween80 and PEG as a vehicle respectively is shown in figure 1. It appears that there is a significant difference ($p<0.05$) in the release of ketoprofen from formula F1-F3 relative to the drug alone. These results indicated that changing the vehicle type in the preparation of solid dispersion tends to increase drug release and changes the amount released due to differences in the crystalline nature and hence energies of the solid dispersion obtained [18]. and may be due to differences in the solubility of the drug in these vehicles .This observation was similar to those reported by others for non-steroidal anti-inflammatory drugs (NSAI) [7].Finally improvement in the release of ketoprofen from solid dispersion could be due to several factors, such as lack of crystallinity i.e amorphization, increasd wetting, dispersibility and particle size reduction [18-20].

Effect of vehicle ratio on the release of ketoprofen at different pH

The release of ketoprofen from formulas F1, F2 and F3 (1:1 drug to vehicle) and F5, F6 and F7 (1:2 drug to vehicle) at different pH is shown in figure 2. It appears that there is a non significant difference ($P>0.05$) in the release of drug from 1:1 drug to vehicle than 1:2 drug to vehicle.These results indicated that the increase in the load factor (the ratio of the amount of liquid medication over the quantity of carrier material in the system) did not result in additional improvement in the release of the drug than 1:1 ratio, but when compared with the release of the drug alone, there is a significant increase ($p> 0.05$) since 65%, 60% and 64% released from solid dispersion prepared with PG, Tween 80 and PEG compared with 53% from capsule containing drug alone after 70 minutes at pH 1.2 . Although in both pH values there is a decrease in the release of the drug, the greater decrease shown at pH 1.2

Effect of change the ratio carrier: coating on the release of ketoprofen at different pH

The release of ketoprofen from formulas F8, F9 and F10 which are formulated using (10:1) carrier to coating with F1, F2 and F3 which are formulated using (20:1) carrier to coating was decreased from 81, 74 and 79 to 79, 70 and 75% after 10 minutes of dissolution at pH 6.8, as shown in figure 3. It appears that there is non significant ($p>0.05$) difference in the release of the drug at pH 1.2 and 6.8. The main decrease in the release of the drug from formulas with 10:1 carrier to coating ratio is due to smaller amount of carrier powder and larger quantities of fine drug loaded silica particles, and the ratios of the amounts of their liquid medication per powder substrate are relatively higher, during the dissolution process, the primary particles produced after the disintegration of the liquisolid capsule with low ratios are overloaded with liquid medication. In such cases, even though the drug diffusion through the primary particles may be rapid, it might lead to overwhelming (solubility-wise) of the stagnant (adjacent to the primary particles) dissolution layers with drug, resulting in local precipitation of drug during the initial stages of the dissolution process, thereby presenting decreased dissolution rates [21].

Effect of disintegrant on the release of ketoprofen at different pH

The release of ketoprofen from F4 is faster and higher than that from formula F1 due to the presence of sodium starch glycolate as a disintegrant as shown in figure 4.

It appears that there is insignificant difference ($p>0.05$), so there is only improvement in the dissolution which is attributed to great ability of SSG to absorb higher amount of water when exposed to an aqueous enviroment and this accelerate dissolution [22,23], and this improvement is higher at pH 6.8 than at lower pH.

X-ray diffraction

In diffractograms, the peak position (angle of diffraction) is indicative of a crystal structure and the peak height is a measure of sample crystallinity the diffractogram of pure of ketoprofen exhibit a series of intense peaks which are indicative of ketoprofen crystallinity. The diffractogram of ketoprofen solid dispersion prepared (1:1 ratio) still show diffraction peaks corresponding to the pure ketoprofen indicating the presence of crystallinity with a

marked decrease in their intensity and sharpness compared with original [24]. This suggests that part of drug structure may have been converted to the amorphous state, and this probably explains why the dissolution of the drug was increased by solid dispersion technique.

Conclusion

The liquisolid capsules can be promising alternative for the formulation of water insoluble drug; and higher dissolution rate displayed by liquisolid capsule may also enhance oral bioavailability due to increased wetting properties and solubility of drug in the liquid vehicle.

References

[1] Karavas E, Georgarakis E , Sigalas MP, Avgoustakis K , Bikiaris D . Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug–polymer interactions. Eur. Jou. of Pharm. and Biopharm. 2007, 66 ,p . 334–347.

[2] Gupta MK, Bonger RH, Goldman D, Tseng Y. Mechanism for further enhancement in drug dissolution from solid dispersion granules upon storage. Pherm. Dev. and Tech. 2002.vol 5, issue 1, p 103-112.

[3] Patel R, Masnoon, Dr.Natvarlal M, Patel M. Formulation strategies for improving drug solubility using solid dispersions. Pharmaceutical review articles.2009. vol.7. issue6.

[4] Javadzadeh Y .etal Liquisolid technique as a tool for enhancement of poorly water-soluble drugs and evaluation of their physicochemical properties. Acta Phar. 2007, 57, p.99-109.

[5] Spireas S and Sadu S, Enhancement of prednisolone dissolution properties using liquisolid compacts. Int.Jou.Pharm.1998, vol.166, p.177-188.

[6] Spireas S, Sadu S.and Grover R. In vitro release evaluation of hydrocortisone liquisolid tablet J.Pharm.Sci.1998, ovl.87, p.867-872.

[7] Javadzadeh Y, Reza M, Barzegar-Jalali M, Nokhodch A .The effect of type and concentration of vehicles on the dissolution rate of poorly soluble drug (indomethacin) from liquisolid compact.J. Pharm. sci. 2005, 8(1):18-25,2005

[8] El-Moneim D, El-Kkamal AH. Dissolution enhancement of glibenclamide using liquisolid tablets technology .Acta.Pharm. 2001, 51: 173-181.

[9] Javadzadeh Y, Siahi-Shadbad MR, Barzegar-Jalali M and Nokhodchi A. Enhancement of dissolution rate of piroxicam using liquisolid compacts .Sci.Direct.II Farmaco.April 2005, vol.60, issue 4, p.361-36.5.

[10] Spireas S, Wang T and Grover R. Effect of powder substrate on the dissolution properties of methchlrothiazide liquisolid compacts .Drug Dev.Ind.Pharm. 1999,vol.25,p. 163-168.

[11] Takeuchi H, Nagira S, Yamamoto H, Kawashima Y .Solid dispersion particles of tolbutamide prepared with fine silica particles by the spray – drying method .Powder tech .2004, vol.141, Issue3,p187-195.

[12] Takeuchi H, Nagira S, Yamamoto H, Kawashima Y .Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method . Int .Jou .of pharm. 2005, vol.293, Issues1-2,p.155-164.

[13] Nokhodchi A , Javadzadeh Y , Mohammed R. Barzegar-Jalali M. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J. Pharm. Sci.2005, 8(1):18-25.

[14] Wilson W. Peng Y. Augsburger L. Gneralization of a prototype intelligent hybrid system for hard gelatin capsule formulation. J. Sci. Tech.2005, 6 (3):449-457 .

[15] Ahmed.S, Nafadi MM, Fatahalla FA. Formulation of a fast –dissolving ketoprofen tablet using freeze-drying in blisters technique.Drug Dev. and Indu. Pharm. 2006, vol.32, Issue 4, p 437-442.

[16] Philip AK, Pathak K. In situ formed phase transited drug delivery system of ketoprofin for achieving osmotic controlled Level in vitro- in vivo correlation. Ind. J. Pharm Sci. 2009, 70:745-753.

[17] Nagarsenkar MS, Shenai H. Influenceof hyodroxypropyl B-cyclodextrin on solubility and dissolution profile of ketoprofen in its solid dispersions.1996, 22, No.9-10, p.987-992.

[18] Sheng JJ, Kasim NA, Chandrasckaran R, Amidon GL .Solubilization and dissolution of insoluble weak acid, ketoprofen: effect of pH combined with surfactant .Eur.J. Pharm. Sci. 2006, 29, 306-314.

[19] Verheyen S , Blaton N, Kinget R , Van den Mooter G .Mechanism of increased dissolution of diazepam temazepam from polyethylene glycol 6000 solid dispersions International Journal of Pharmaceutics .(2002) vol.249.p45_ 58.

[20] Arias MJ, Gines JM, Moyamo JR, Perez-Martinez JI, Rabasco AM .Influence of the preparation method of solid dispersions on their dissolution rate: study of triameterene-D-mannitol system .Int .Jou.of Pharm.1995, 123, p.25-31.

[21] Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine) .International Journal of Pharmaceutics. (2007) ,341,p. 26–34

[22] Chaulang G, Patel P, Hardikar S, Kelkar M, Bhosale A, Bhise S. Formulation and evaluation of solid dipersion of furosemide in sodium starch glycolate. Tropical Jour. Of Pharm.Res. 2009, 8 (1):43-51.

[23] Bolhuis GK, Zuurman K and te Werik GHP. Improvement of dissolution of poorly soluble drugs by solid deposition on a super disintegrant II. The choice of super disintegrants and effect of granulation. Eur.J .of Phar.Sci.1997, 5(2):63-69.

[24] Lee S, Nam K, Kim MS, Jun SW, Park JS, Woo JS, Hwang SJ . Preparation and characterization of solid dispersions of itraconazole by using aerosol solvent extraction system for improvement in drug solubility and bioavailability. Arch. Pharm.Res. 2005, vol.28, no.7. P.866-874.

Table 1: The prepared formulas of ketoprofen liquisolid capsules

Formula no.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ketoprofen (mg)	50	50	50	50	50	50	50	50	50	50
PG	1:1	-	-	1:1	1:2	-	-	1:1	-	-
PEG	-	1:1	-	-	-	1:2	-	-	1:1	-
Tween80	-	-	1:1	-	-	-	1:2	-	-	1:1
MCC(mg)	100	100	100	100	100	100	100	50	50	50
Silica (mg)	5	5	5	5	5	5	5	5	5	5
Sod. Starch Glycolate (mg)	-	-	-	5	-	-	-			

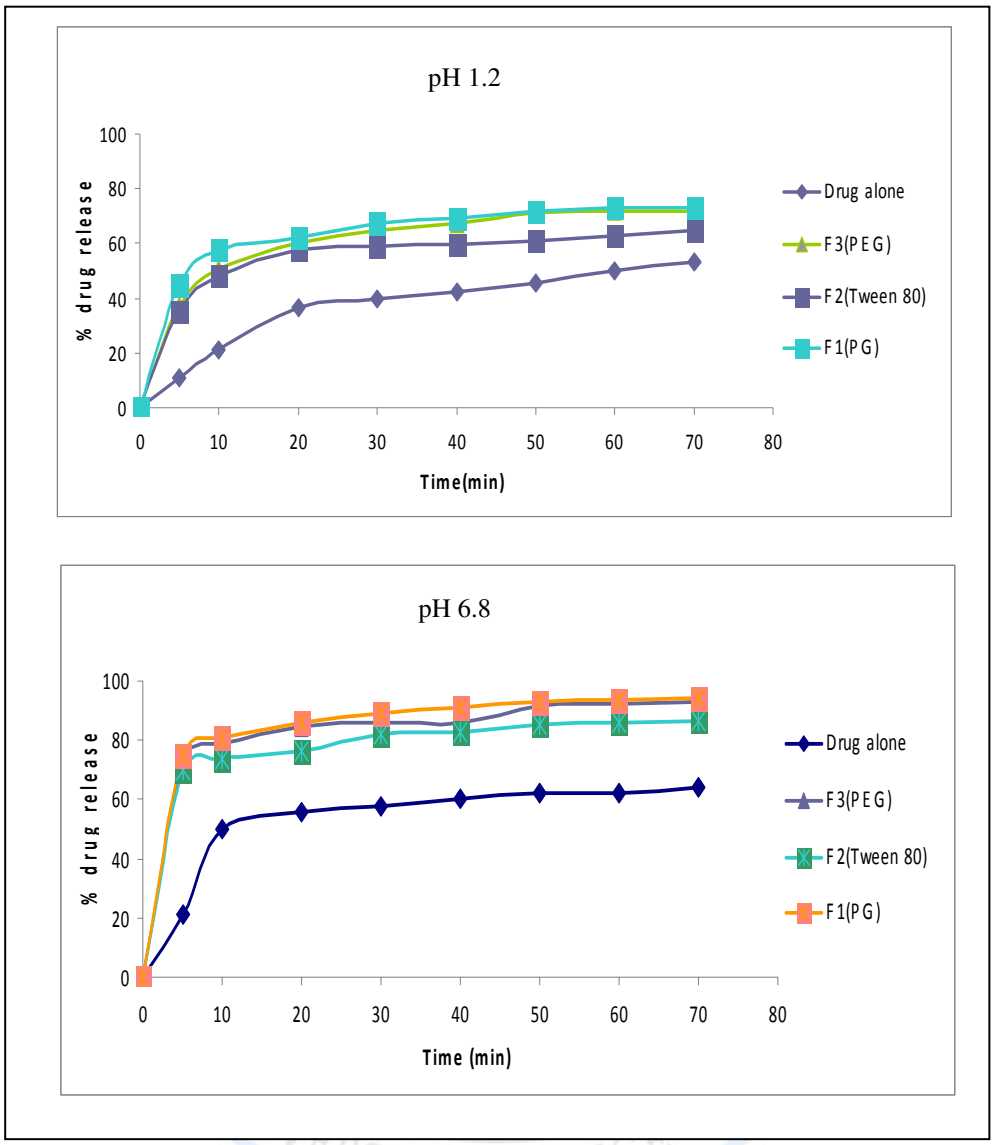


Figure (1) Effect of the vehicle type on the release of ketoprofen at different pHs (1.2, 6.8) and 37° C

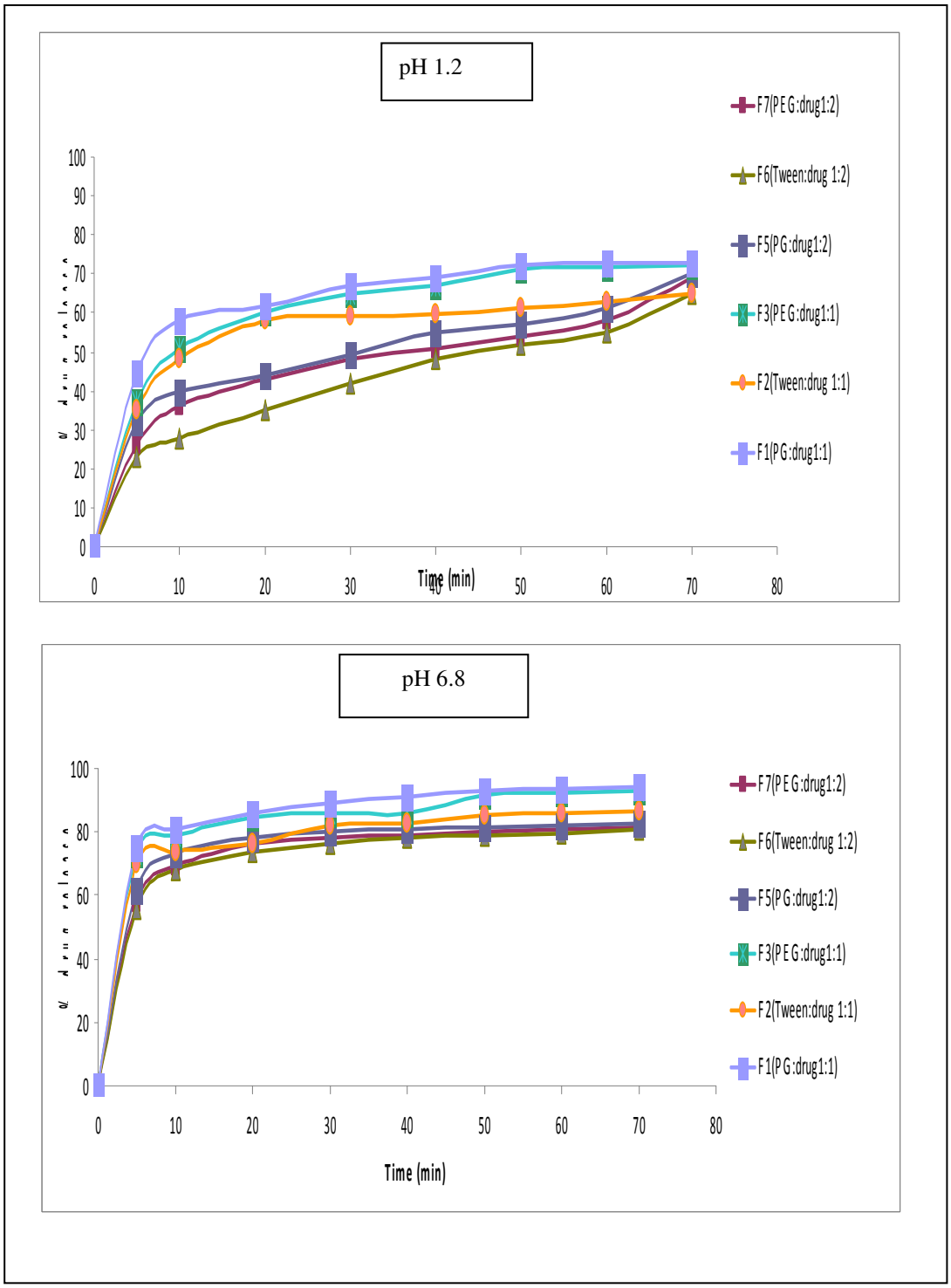
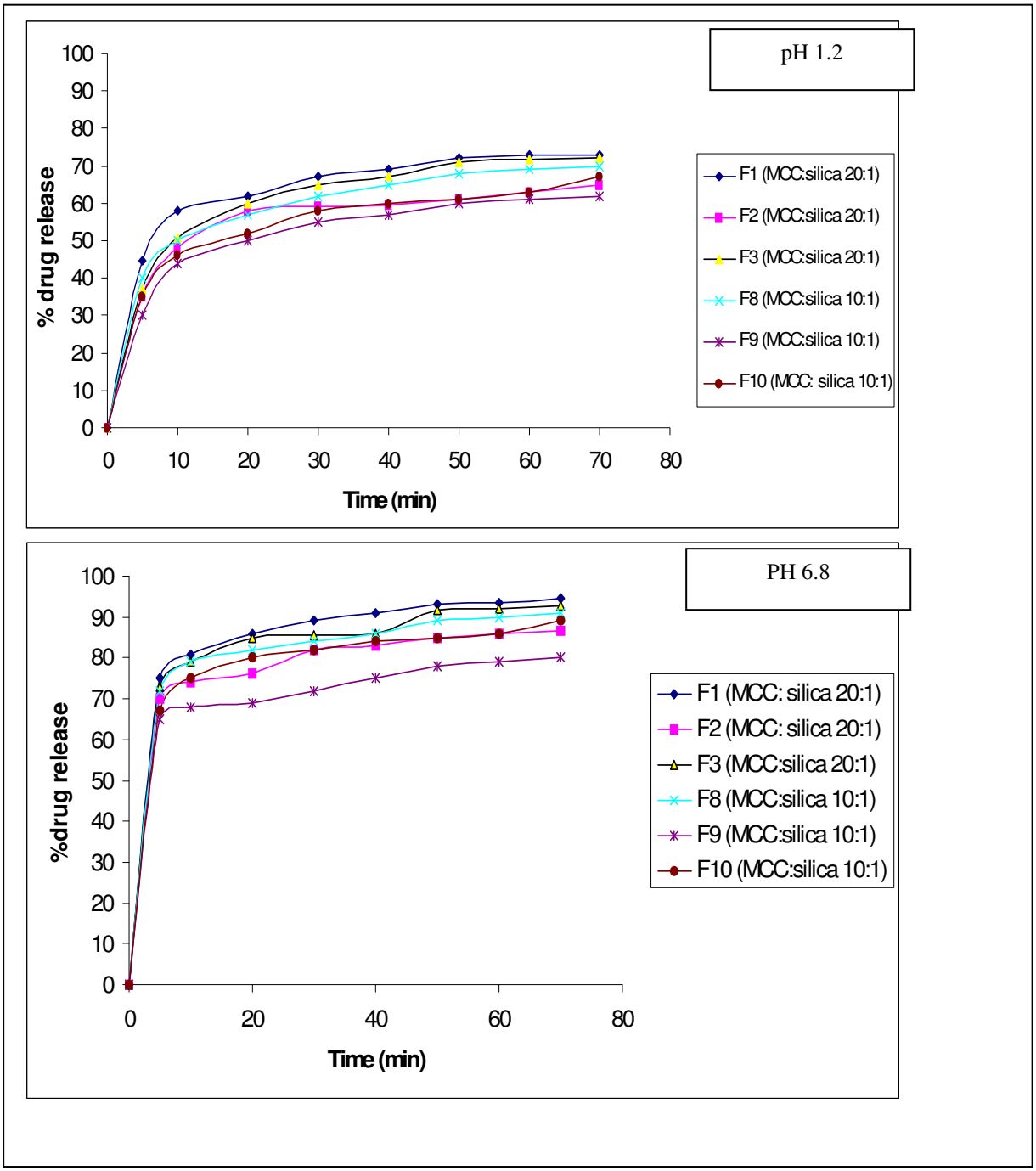


Figure (2) Effect of change in vehicle ratio on the release of ketoprofen at different pHs(1.2,6.8) and 37°C


pH 1.2
% drug release
Time (min)
F1 (MCC:silica 20:1)
F2 (MCC:silica 20:1)
F3 (MCC:silica 20:1)
F8 (MCC:silica 10:1)
F9 (MCC:silica 10:1)
F10 (MCC: silica 10:1)
PH 6.8
%drug release
Time (min)
F1 (MCC: silica 20:1)
F2 (MCC: silica 20:1)
F3 (MCC:silica 20:1)
F8 (MCC:silica 10:1)
F9 (MCC:silica 10:1)
F10 (MCC:silica 10:1)

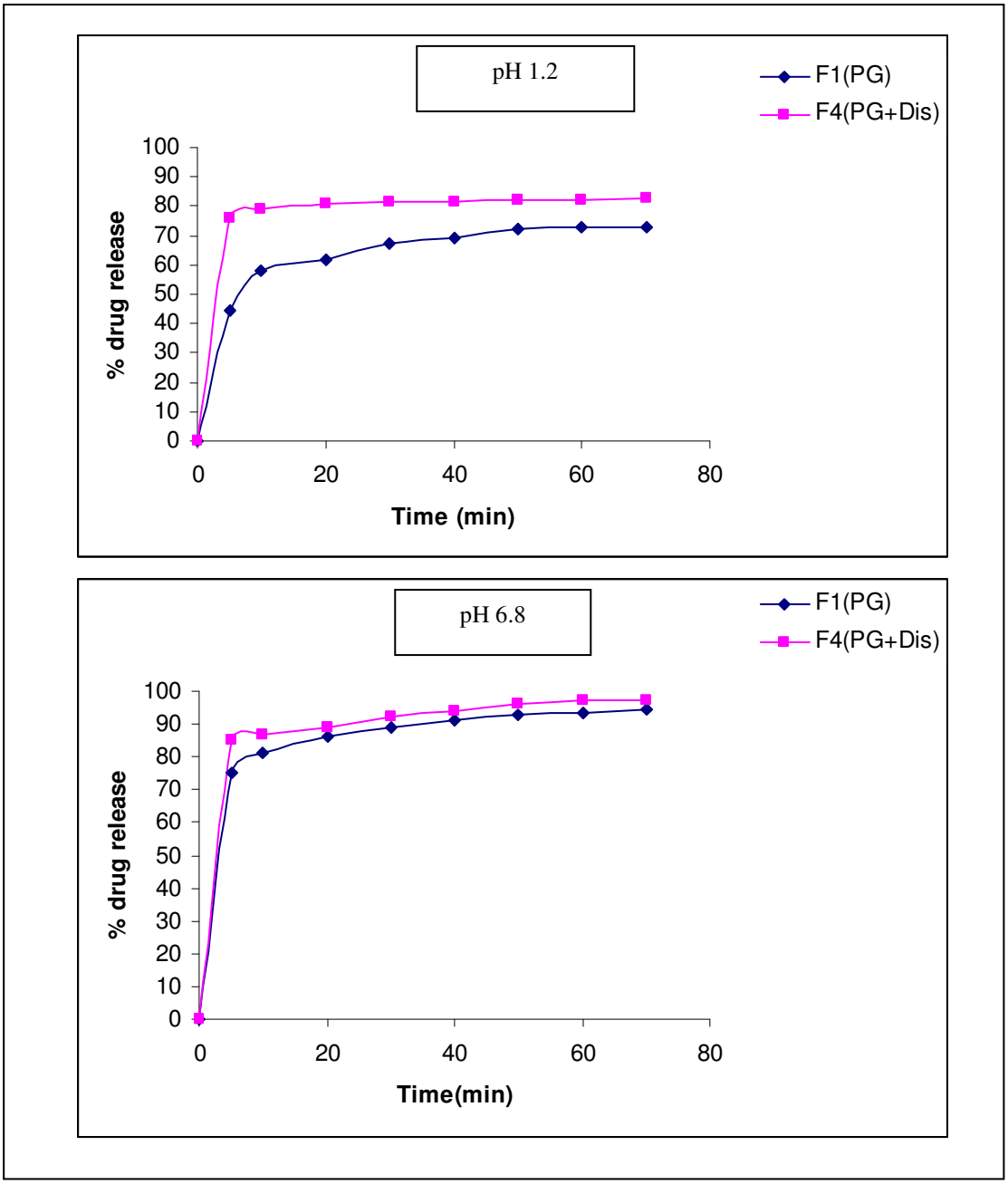


Figure (4) effect of disintegrant on the release of ketoprofen at different pHs (1.2, 6.8) and 37° C

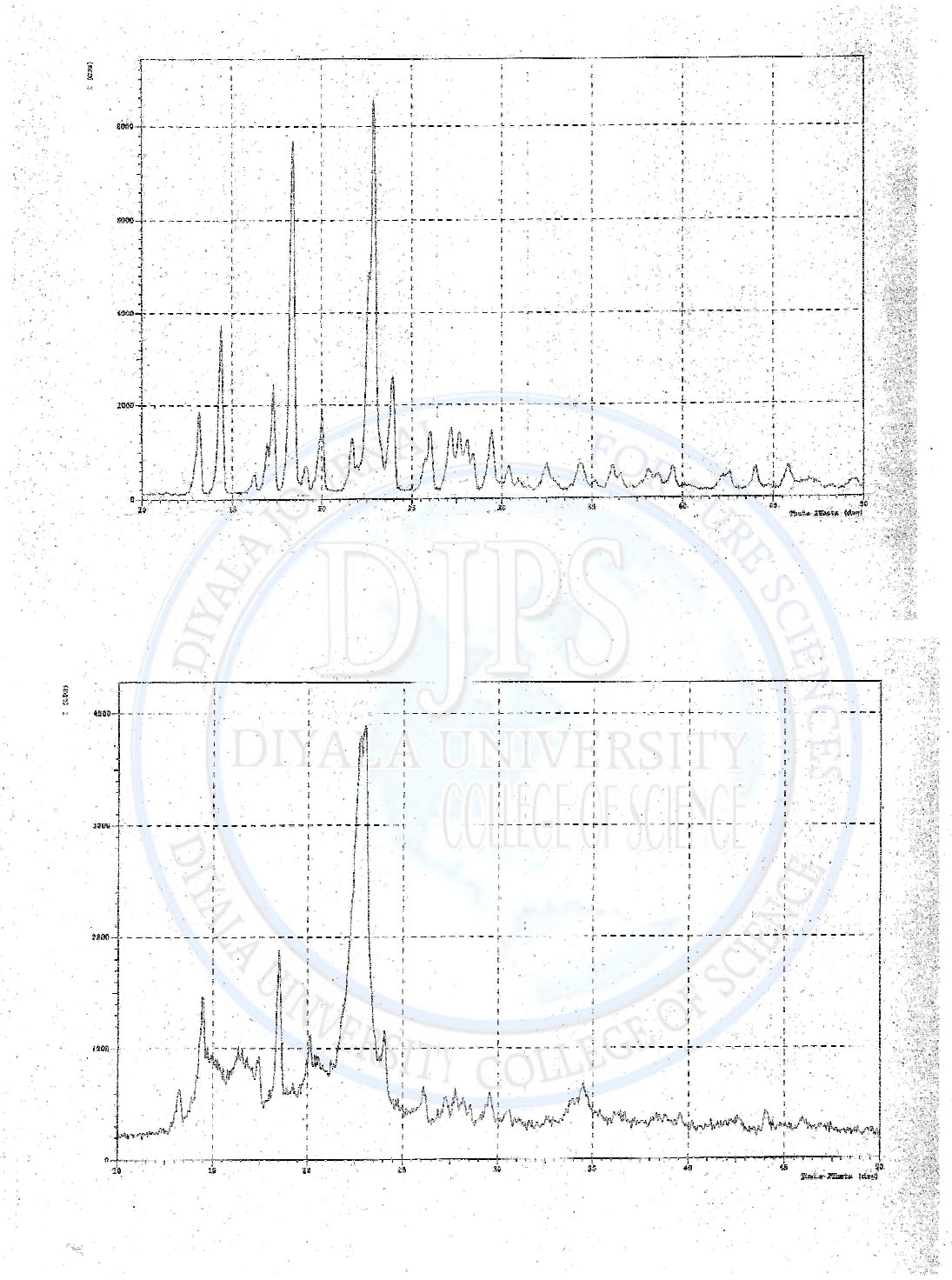


Figure (5) X– ray Diffraction pattern of pure ketoprofen and ketoprofen solid dispersion