➢ISBN : 978-979-18458-4-7➢

ENHANCEMENT OF PIROXICAM INTRINSIC DISSOLUTION RATE WITH SOLID DISPERSION SYSTEM USING BETA CYCLODEXTRIN

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Abstract

Objective: *This research was aimed to increase the intrinsic dissolution rate (IDR) of piroxicam with solid dispersion system of piroxicam-betacyclodextrin (SDSPB). This system can overcome the dissolution problem of piroxicam.*

Method: Determination of piroxicam IDR was performed using intrinsic dissolution tester in 100 rpm speed of stir. Free CO2 water was used as solvent. Piroxicam concentration in was measured using spectrophometer. The piroxicam IDR of SDSPB which was prepared using solvent method with freeze drying was compared with control (piroxicam alone). Then the interaction of piroxicam with betacyclodextrin was analyzed using IR spectra.

Result:*The IDR of SDSPB and piroxicam pellet are 1.2247 and 0.244 mgcm^{-2}minute^{-1} respectively. This enhancement was predicted due to inclusion complex and electrostatic interaction of piroxicam and betacyclodextrin.*

Conclusion: *The SDSPB can enhance six times fold of piroxicam IDR ($p \leq 0,05$). The researches purposed to formulate SDSPB tablet and to test its bioavailability are needed to confirms this IDR enhancement.*

Keywords : *piroxicam, cyclodextrin, solid dispersion, inclusion complex*

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INTRODUCTION

Absorption process in gastrointestinal is simplified in two steps. Firstly, the dissolution in gastrointestinal medium and secondly, permeation trough gastrointestinal membrane to reach blood in capilar of venaporta hepatica (Shargel et al, 2005). The poor water solubility drugs have dissolution problem since the gastrointestinal medium consist of water dominantly. Thus to overcome this problem many pharmaceutical technology including micronization, formation of complexes (Perrut, 2003) and solid dispersions (Ruan et al, 2005; Chiou and Riegelman, 1971) are developed. The solid dispersion system are being the focused of recent studies (Serajudin, 1999; Sethia and Squilante, 2003) and several successful products have been commercialized in pharmaceutical market.

In solid dispersion system, the very fine drug particle is dispersed in solid water soluble carrier, i.e. PVP (polyvinyl pirolidone), PEG (polyetilen glykol), urea, and cyclodextrin (Chiou and Riegelman, 1971). This system can be prepared by melting (fusion) method or solvent evaporation method (Habib, 2001), or combination (Chiou and Riegelman, 1971, Dabbagh and Taghipour, 2007). In fusion method, the physical mixture of drug and carrier is heated in high temperature (about 150^{o}C, depend on their melting point) to reach liquid state, and then it is cooled quickly to get solid dispersion. Because of this high temperature, many drugs degrade (Chiou and Rigelman, 1971). In solvent method the physical mixture of drug and carrier was dilute in evaporable semipolar solvent, since the drug is water insoluble and the carrier is water soluble, and the solvent must be evaporated in low temperature (Chiou and Riegelman, 1971). Some solvent are selected i.e. acetone (Al-Obaidi et al, 2009), ethanol, and water (Al-Hamidi et al, 2010).

Some approaches are used to concluded the advantage of solid dispersion system, i.e. solubility determination (Punitha et al, 2009), IDR determination (Al-Hamidi et al, 2010), bioavailability (Tianti et al, 2005), etc. In IDR determination, the dissolution rate of pellet solid dispersion is measured in constant surface area, and IDR is defined as rate of dissolution divided by surface area. If the IDR is more than 1 mg/cm^2/minute, this drug has no problem on dissolution in gastrointestinal medium. Generally this drug has more than 1% water solubility (Shargel and Yu, 1985).

Piroxicam (figure 1) is an NSAIDs which has poor solubility (23 mg/L). It is a weak acid with pKa 6,3 (Anonym, 2012). From its water solubility, it is predicted that piroxicam has problem on dissolution in gastrointestinal medium. This research was aimed to overcome this problem via solid dispersion system using betacyclodextrin, and to prove this advantage by measured its IDR.

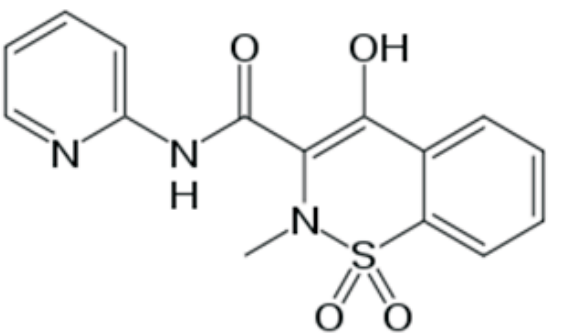

Figure 1. Piroxicam molecular structure

MATERIAL AND METHOD

Material

The piroxicam was purchased from PT Indofarma Tbk Bekasi (Dinamite Dipharma S.p.A). Betacyclodextrin (Sigma) was p.a degree. Another reagent i.e. sodium hydroxide, Ammonia, and KBr have p.a degree, produced by E Merck. Intrinsic Dissolution Tester designed by Yuwono was produced by T&A Technique and Supply, Yogyakarta. The spectrophotometer UV1601PC Shimadzu was used to determine piroxicam concentration, and the spectrophotometer FTIR8201PC Shimadzu

was used to record solid dispersion system IR spectrum.

Method

Contruction of Calibration Curve

The piroxicam solution (1,1 mg%) was scanned in 200-400 nm of wave length to get maximum absorbance wave length ($ë_{max}$). The absorbance of piroxicam solution in various concentration (0.5; 0.7; 0.9; 1.1; 1.3; and 1.7 mg%) with and without betacyclodextrin in the same concentration were measured their absorbance at $ë_{max}$. The linear regression of piroxicam absorbance as the function of concentration with and without betacyclodetrin were used to calculate the concentration of piroxicam released from their pellets in IDR test.

Preparation of Piroxicam-Betacyclodextrin Solid Dispersion

The piroxicam-Betacyclodextrin Solid Dispersion System was prepared using solvent method. Equimol Physical mixture of piroxicam and betacyclodextrin was dilute in minimum volume of ammonia solution 25%, the solution was frezzed. Then the solvent was evaporated using freeze dryer (Modulyo). Next, the KBr powder was added to the solid dispersion. This mixture was pressed on 2 tons weight for 5 minute to get KBr pellet for IR Spectrum Characterization. The same pellet without KBr was made to use in IDR test. These pellets have 1,8 cm in diameter and about 200 mg of powder was needed.

IDR Determination.

The pellet of piroxicam (or solid dispersion of piroxicam-betacyclodextrin) was set up in IDR tester. Accurate volume of free CO_2 aquadest (50,0 mL), as solvent, was maintained its temperature in 37^oC using thermostat. The pellet in IDR tester was brought in this medium, then the time was started, the IDR tester was connected to rotor, and it was rotated 100 rpm. Accurate volume of sample (3,0 mL) was taken out from medium and the equal volume of fresh medium was added to maintain the volume. The sampling time was scheduled at 2.5, 5, 10, 15, 20, 30, and 45 minutes. The concentration of piroxicam in the sample was determined using spectrophotometric method. IDR is defined as rate of dissolution per surface area. It can be calculated from the slope of curve of time of dissolution versus amount of drug dissolved per surface area (W/A).

RESULT

Calibration Curve of Piroxicam in Water

Piroxicam solution in water has $ë_{max}$ of 354,8 nm, both with and without betacyclodextrin. Figure 2 shows calibration curve of piroxicam in water. These two line are identical, and have no significant differences ($p \geq 0,05$). It can be concluded that betacyclodextrin do not change the lambda max and absorbance, so that one of these two calibration curve can be selected to calculate piroxicam concentration of sample from IDR test of solid dispersion system piroxicam-betacyclodextrin pellet or piroxicam pellet

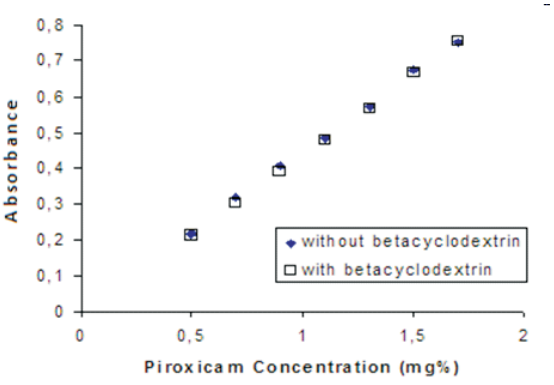

Figure 2. Calibration curve of piroxicam with betacyclodextrin (y=0.4532x – 0.01653) and without betacyclodextrin (y = 0.4446x + 6.07.10^{-4}).

IDR Determination

Concentration of piroxicam release from piroxicam pellet and solid dispersion system of piroxicam-betacyclodextrin pellet are shown in figure 3. In dissolution test, "sink condition" is required, it means that the bulk concentration must be lower than 1/10 of its solubility. This condition is shown by linear curve between concentration as the function of time. From figure 3, it can be concluded that during 30 minutes of dissolution the sink condition is appear, because of its high R^2. Thus the data can be proceeded to calculate IDR.

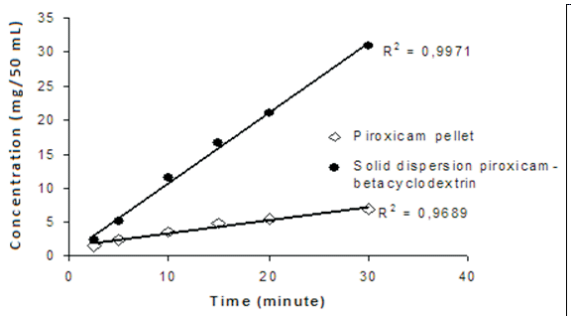

Figure 3. Identification of sink condition

The linear equation in figure 4 shows that solid dispersion system could enhance IDR six times fold from control. IDR of piroxicam from solid dispersion is 1.225 mg cm^{-2} $menit^{-1}$. Thus this system showed that piroxicam had no problem in dissolution in gastrointestinal medium.

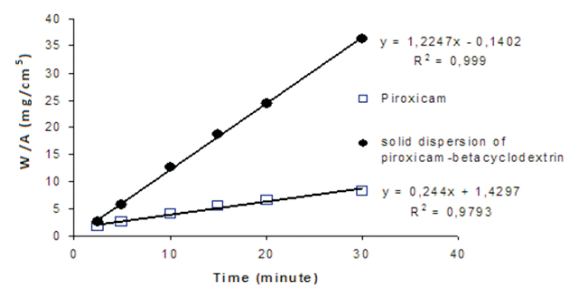

Figure 4. The amount of piroxicam dissolved per surface area. IDR of piroxicam is 0.244 $mgcm^{-2}minute^{-1}$, IDR of piroxicam from solid dispersion is 1.225 $mgcm^{-2}minute^{-1}$

Prediction of Interaction between Piroxicam and Cyclodextrin

The interaction between piroxicam and betacyclodextrin was predicted based on computer software analyzed (HiperChem) and FTIR spectra. From the molecule structure of piroxicam and betacyclodextrin, it is predicted that piroxicam can be entrapped into the hollow space of betacyclodextrin as shown in figure 5. This constructure is called inclusion complex, and since betacyclodextrin has the high water solubility, the piroxicam entrapped will be pulled to dissolve.

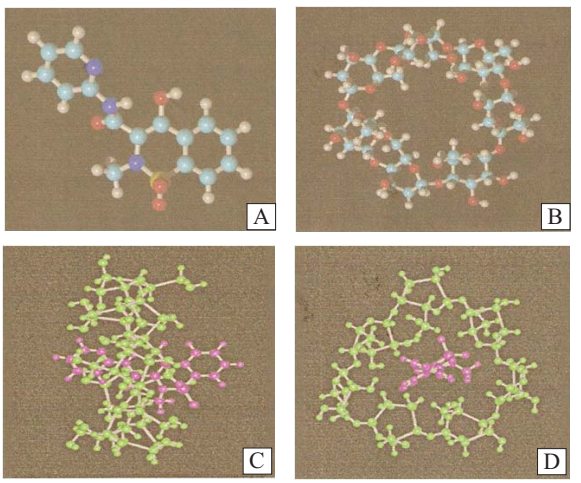

Figure 5. HiperChem prediction of interaction between piroxicam and betacyclodextrin. A: Piroxicam structure, B: Betacyclodetrin structure, C: Side view of Piroxicam (purple) entrapped in betacyclodextrin (green), D:Front view of Piroxicam (purple) entrapped in betacyclodextrin (green).

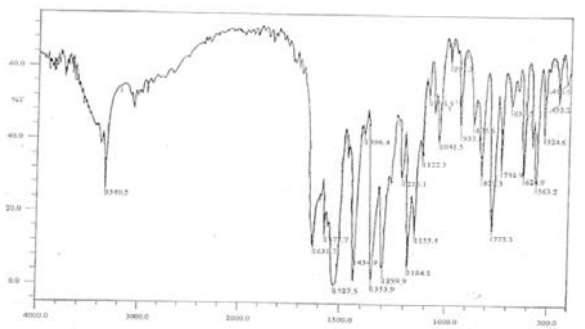

Figure 6. FTIR spectra of piroxicam in KBr pellet

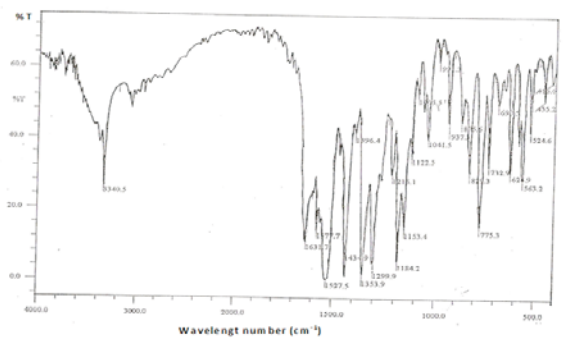

Figure 7. FTIR spectra of betacyclodextrin in pellet KBr

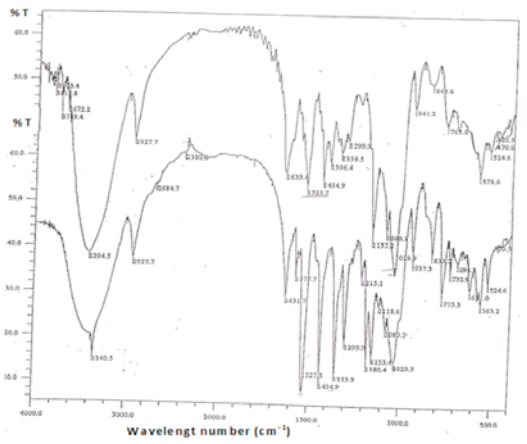

Figure 8. Super impose of FTIR spectra of piroxicam-betacyclodextrin physical mixture of and solid dispersion system of piroxicam and betacyclodextrin.

FTIR spectra of piroxicam, betacyclodextrin, physical mixture of piroxica-betacyclodextrin, and solid dispersion system of piroxicam-betacyclodextrin are shown in figure 6, 7, and 8 respectively. Solid dispersion system of piroxicam-betacyclodextrin has FTIR spectra differ with its physical mixture. In wavelength number between 1550 cm^{-1} to 1000 $cm^{-1,}$ the solid dispersion system has less intensity than its physical mixture. This is because of electrostatic interaction between piroxicam and betacyclodextrin. The disappearing of S=O (1184.2) and NH amine (1577.7) in solid dispersion system indicated that electrostatic bound was formed between those functional group. The electron delocalization in piroxicam formed positive and negative pole as shown in figure 9. The dispute of electronegativity between H and O in betacyclodextrin formed positive partial and negative partial as shown in figure 9. The positive pole of piroxicam can interact with the negative partial of betacyclodextrin, while the negative pole of piroxicam can interact with positive partial of betacyclodextrin.

DISCUSION

This study shows that the solid dispersion system of piroxicam-betacyclodextrin could enhances the IDR of piroxicam. Since piroxicam has dissolution as absorption rate limiting step, the increasing of IDR could overcome the

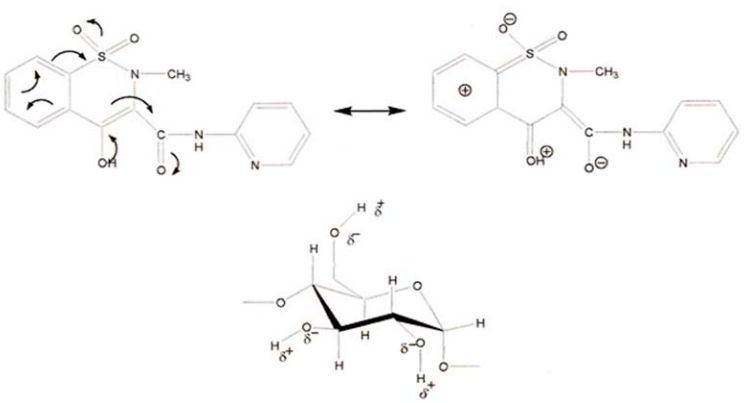

Figure 9. Up: Electron delocalization of piroxicam, down: partial polarization of betacyclodextrin monomer

problem of piroxicam absorbtion. It was predicted that the interaction between piroxicam-betacyclodextrin in solid dispersion system will involve the inclusion and electrostatic complex.

Our result is consistent with the previous study about overcoming the piroxicam dissolution problem. Verma et al (2003) could overcome the dissolution problem of piroxicam by forming the nicotinamide-piroxicam solid dispersion using fusion method. Another studies are listed in table I.

CONCLUSION

Solid dispersion system of piroxicam-betacyclodextrin enhances the IDR of piroxicam. It is predicted that the interaction between piroxicam and betacyclodextrin in solid dispersion system involve inclusion complex and electrostatic complex. The researches purposed to formulate SDSPB tablet and to test its bioavailability are needed to confirms this IDR enhancement.

Table I. Some effort to overcome piroxicam dissolution problem

Carrier/complexing agent	Method of solid dispersion development	References
polyvinylpyrrolidone (PVP) K-17 PF, PVP K-90	Solvent method	Tantishaiyakul et al, 1999
PEG4000, urea	fusion and solvent methods	Pan et al, 2000
polyethylene glycol 400, polyvinyl pyrolidone K-30	Solvent method	Patel et al, 2003
microcrystalline cellulose, potato starch	Solvent method	Charumanee et al, 2004
myrj 52, Eudragit® E100, mannitol	Solvent method, precipitation method	Valizadeh et al, 2007
Polyvinylpyrrolidone	Antisolvent precipitation, spray drying techniques	Wu et al, 2008

Betacyclodextrin as a carrier for solid dispersion system has succeeded to enhance the dissolution of many drugs (Table 2). The hollow structure is responsible on this ability via inclusion complex.

ACKNOWLEDGMENT

The author would like to thank to Dr. Tedjo Yuwono who has found time to discus about this research.

Table II. Usage of betacyclodextrin to enhance dissolution of poor solubility drugs

Drugs	Method of solid dispersion development	references
Ketorolac	Solvent method	Nagarsenker et al, 2000
Ketoconazole	Solvent method	Balata et al, 2010
Domperidone	Solvent method	Swami, et al, 2010
Fenbendazole	Solvent method	Nagesh et al, 2011
Ibuprofen	Solvent method	Kumar et al, 2012

REFERENCES

Al-Hamidi H, Edwards AA, Mohammad MA, Nokhodchi A, 2010, To Enhance Dissolution Rate Of Poorly Water-Soluble Drugs: Glucosamine Hydrochloride As A Potential Carrier In Solid Dispersion Formulations, Colloids Surf B Biointerface,76(1):170-178

Al-Obaidi H, Brocchini S, and Buckton G, 2009, Anomalous Properties Of Spray Dried Solid

Dispersions, *J.Pharm. Sci.,* 98(12):4724-4737

Anonym, 2012, http://www.drugbank.ca/drugs/DB00554, accessed in May 2012

Balata G, Mahdi M, Bakera RA, 2010, Improvement of solubility and dissolution properties of ketoconazole by solid dispersions and inclusion complexes, AJPS, 5 (1) :1-12.

Charumanee S, Okonoki S, and Sirithunyalug J, 2004, Improvement of the Dissolution Rate of Piroxicam by Surface Solid Dispersion, *CMU. Journal,*. 3(2):77-85

Chiou WL, Riegelman S, 1971, Pharmaceutical Applications Of Solid Dispersion Systems. *J Pharm Sci.*, 60:1281–1302

Dabbagh MA and Taghipour B, 2007, Investigation Of Solid Dispersion Technique In Improvement Of Physicochemical Characteristics Of Ibuprofen Powder, *Iranian J. Pharm. Sci., 3*:69-76.

Habib MJ, 2001, Pharmaceutical Solid Dispersion Technology, Ed III, Technomic Publishing, Lancaster

Kumar MA, Lakhsmi PK, Giriprasad PS, 2012, Development and Evaluation of Solid Dispersion Formulated Ibuprofen Tablets Using Cyclodextrin Carier, *IJPRD*, 3(11):93-101

Nagesh C, Vijay K, Venkatesh JS, Shankaraiah mm, Amnt k, 2011, Improving The Solubility Of Antihelmintic Drug By Solid Dispersion And Inclusion Complex, *IRJP*, 2(8): 100-104

Pan RN, Chen JH, Chen RR, 2000, Enhancement of Dissolution and Bioavailability of Piroxicam in Solid Dispersion Systems, Drug. Dev. Ind. Pharm., 26(9):989-994.

Patel DM, Shah RR, Jogani PD, 2003, Studies To Enhance Dissolution Of Piroxicam, *IJPS,* 65(3):264-267

Perrut M, 2003, Supercritical Fluids Applications In The Pharmaceutical Industry, *Stp Pharma Sci*, 13:83–91

Punitha S, Karthikeyan D, Devi P, and Vedha-Hari BN, 2009, Enhancement of Solubility and Dissolution of Celecoxib by Solid Dispersion Technique, *JPST*, 1(2):63-68

Ruan LP, Yu BY, Fu GM, Zhu DN, 2005, Improving The Solubility Of Ampelopsin By Solid Dispersions And Inclusion Complexes. *J.Pharmceut Biomed*., 38:457– 464

Serajuddin ATM, 1999, Solid Dispersion Of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, And Recent Breakthroughs, *J Pharm Sci.,* 88:1058–1066.

Sethia S, Squillante E, 2003, Solid Dispersions: Revival With Greater Possibilities And Applications In Oral Drug Delivery. *Crit Rev Ther Drug*, 20, 2003, 215– 247

Shargel, L., Pong, S.W., and Yu. A.B.C., 2005, *Applied Biopharmaceutics and Pharmacokinetics,* Ed V, 411-450, The McGraw-Hill, Singapore.

Swami G, Koshy MK, Pandey M, Saraf S, 2010, Preparation And Characterization Of Domperidone- Â-Cyclodextrin Complexes Prepared By Kneading Method, Int J Pharm Pharm Sci, 1:68-74.

Tantishaiyaku V, Kaewnopparat N, Ingkatawornwong S, 1999, Properties Of

Soliddispersions Of Piroxicam In Polyvinylpyrrolidone, Int J Pham, 181(2):143–151

Tianti E, Binarjo A, and Yuwono T, 2005, Ketersediaan Hayati Dispersi Padat FurosemidDengan Polietilenglikol 4000 (PEG 4000) Pada Kelinci Jantan, *MFI*, 16(2), 1124 – 129,

Valizadeh H, Zakeri-Milani P, Barzegar-Jalali M, Mohammadi G, Bahreini MAD, Adibkia K, and Nokhodchi A, 2007, Preparation and Characterization of Solid Dispersions of Piroxicam with Hydrophilic Carriers, Drug Dev Ind Pharm., 33(1):45-56.

Verma MM, Kumar MT, Balasubramaniam J, Pandit JK. 2003, Dissolution, Bioavailability And Ulcerogenic Studies On Piroxicam-Nicotinamide Solid Dispersion Formulations. Boll Chim Farm,142(3):119-124.

Wu K, Li J, Wang W, Winstead DA, 2009, Formation and Characterization of Solid Dispersions of Piroxicam and Polyvinylpyrrolidone Using Spray Drying and Precipitation with Compressed Antisolvent, *J Pharm Sci,* 98(7) 2422–2431