



SOLUBILITY IMPROVEMENT OF CLOPIDOGREL BISULFATE PREPARED WITH VARIOUS POLYETHYLEN GLYCOL DENSITY AND DIFFERENT KIND OF HYDROXY PROPYL CELLULOSE BY SOLVENT EVAPORATION METHOD

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Abstract: Various strategies have been used for improve drug solubility of poorly water soluble drugs. The aim of this study was to increase solubility dan dissolution rate of Clopidogrel Bisulfate (CLPB) by solid dispersion with various density of Polyethylenglycol (PEG) and some Hydroxypropyl Cellulose (HPC) as matrix. As carriers, PEG used in three variation such as PEG 4000, PEG 6000 and mixed both (1:1), meanwhile for HPC used in different kind of specifications such as HPC–SL, HPC–SSL, LHPC–11, LHPC–21. Active ingredient and each of matrices prepared by solvent evaporation method. Despite of solubility and dissolution test, Powder X-Ray Diffraction (PXRD) and Fourier Transform Infrared Spectroscopy (FTIR) used for evaluate interaction between drug and all of carriers. Outcome of this study shown that all of matrices can improve solubility. From the solubility test found that mixed PEG (1 : 1) as the highest solubility than each of PEGs used. Whereas from all of kind of HPC found that only HPC-SL which gave the highest solubility. At only the most solubility improvement from different kind of those matrix was evaluate for dissolution test. The dissolution result exhibited that mixed PEG (1:1) was reach the highest concentration at the same time (60 minutes) from the test. From FTIR spectrums and PXRD diffractograms shown that all of matrices changed drug nature. The most distinguish nature of drug displayed by HPC-SL diffractogram where all of drug crystallinity alters to amorphous characteristic suit to HPC-SL patterns.

Keywords : Clopidogrel bisulfate, Polyethylen glycol, Hydroxypropyl cellulose, Solid dispersions, Solubility, Dissolution rate.

Introduction

Clopidogrel Bisulfate (CLPB) that one of choice for reduces platelet aggregation is

extensively used for prevention of myo-cardial infarction and disability (stroke, heart failure) in patients. CLPB is a thienopyridine class inhibitor of P2Y₁₂ ADP platelet receptors, which is important for in activation of platelets and eventual cross-linking by the fibrin protein (Collet *et al.*, 2009, Shailendra *et al.*, 2011, Mounika *et al.*, 2012).

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CLPB is chemically methyl (+)-(S)- α -(o-chlorophenyl)-6,7-di-hydrothieno(3,2-c) pyridin-5(4H)- acetate hydrogen sulfate as shown in Figure 1, solubility is slightly soluble in neutral pH of water and ethyleter, soluble

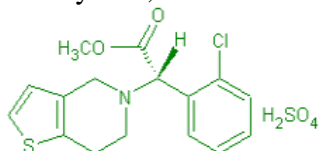


Figure 1. Structure of clopidogrel bisulfate in acidic pH of water and methanol. With this solubility parameter make drug absorbed quickly in gastric and reach in maximum blood plasma after 45 minutes (Louis *et al.*, 2013).

This characteristics make the drug get in Biopharmaceutical Class 2, which has low solubility, but high permeability. Several techniques can be used for enhance the drug solubility and the dissolution of the drugs. One of practically method in simple and low cost effort is solid dispersion. At solid dispersion technique drugs incorporated in an inert hydrophilic carrier or matrix in a solid state (Shailendra *et al.*, 2011).

The aim of this investigation used variation of Polyethylenglycol (PEG) density and several kinds of Hydroxypropyl Celulose (HPC) as carriers. The present study was to formulate CLPB with PEG 4000, PEG 6000 and mix both (1 : 1) and also with HPC-SL, HPC-SSL, LHPC-11, LHPC-21. Those quali-fication parameters such as solubility and in vitro dissolution study was statistically com-pared between PEG and HPC formulation. Powder X-Ray Diffractometer (PXRD) and Fourier Transform Infra Red Spectroscopy (FTIR) was carried out to clarify the interaction between those materials (drug and excipient carriers).

Material and Methods

Materials

Clopidogrel Bisulfate was obtained from Dr. Reddys (India) supplied from PT. Kimia Farma Tbk. PEG 4000 and 6000 was acquired from Pan Asia Chemical supplied from PT. Brataco Chemical. HPC-SL and HPC-SSL was obtained from Nippon-Soda (Japan), whereas LHPC-11and LHPC-21was procu-red from Shin-Etsu (Japan). Those all kinds of HPC was supplied by PT. Lawsim Zecha. All other

chemicals and solvents used were of suitable analytical grade.

Methods

Preparation of solid dispersions of CLPB by Solvent Evaporation Method

With HPC as carriers

Amounts of 750 mg of HPC (each kind of HPC-SL, HPC-SSL, LHPC-11, LHPC-21) and 500 mg of CLPB was dissolved in 38 mL of ethanol : water (7 : 3) and thoroughly mixed for 1 hour over a magnetic stirrer. The solvent was removed in crucible over the waterbath at 60°C until the solid dispersion dry. The dried mass powdered with 40 mesh sieving, then stored in dessicator over the silica gel drier until use.

With PEG as carriers

Amounts of 100 mg of CLPB and 150 mg of PEG (each of PEG 4000, PEG 6000 and mixture both (75 mg and 75 mg)) was dissolved in 5 mL of methanol and stirred for 1 hour over a magnetic stirrer. The solvent was evaporated in crucible over the waterbath at 60°C until dry. The dried mass sieved with 40 mesh and saved in dessicator over the silica gel drier until use.

Qualification of solid dispersion

Drug Content

CLPB, matrix and solid dispersion with equivalent to 10 mg CLPB were weighed precisely and each of material separately blended with suitable quantity of methanol in a 100 mL volumetric flask, add volume by distilled water until all material dissolved and reached volume borderline. Drug content was analyzed at 240 nm using UV spectrophotometer (Analytik Jena, Specord 200). Each sample was analyzed in triplicate.

Solubility studies

The drug and its solid dispersion solubility study was carried out by weighing 20 mg of drug and its solid dispersion equivalent to 20 mg of drug in a 25 mL conical flask containing 10 mL of distilled water, stirred a little then add volume until 25 mL, and shaken on a mechanical shaker for 24 hrs at room temperature. Sample was analyzed same as drug content method in 240 nm with UV spectrophotometer after suitable dilutions.

In vitro dissolution study

Amounts of drug and its solid dispersion equivalently weighed and studied using USP Dissolution Apparatus 2 (Rotating Paddle type). The dissolution was carried out for 1 hour and aliquot of 5 mL was withdrawn at adequate intervals, with pH 2.0 HCl buffer as medium and maintained at 37°C.

Characterization of Solid Dispersion

Powder X-Ray Diffraction Analysis (PXRD)

The data of powder X-Ray diffraction (Phillips, PW 1835) patterns were collected under the following conditions: voltage 35 kV; current 20mA; receiving slit 0.2 inches. Diffractograms were recorded in the continuous scan mode using a step size of 0.01° at 2θ/s with scanned range 5-50°.

Fourier infrared spectroscopy (FTIR Analysis)

KBr pellets of adequate amount of sample were prepared. The spectrum was analyzed using FTIR multiscope spectrophotometer (Shimadzu, Japan). The spectrum for each sample was recorded over the 450-4000 cm⁻¹ spectral region with a resolution of 4 cm⁻¹.

Result and Discussion

Drug Content

Content of CLPB from the prepared formulation was observed to be varying from 85.56 to 106.86 %, respectively and maximum value was reached in mixture of PEG (1 : 1) and minimum value in PEG 4000 as shown in Table 1. This means that all matrices can be as carriers of CLPB.

Table 1. Content of CLPB in different of matrix

Matrix	content (%)	Matrix	content (%)
PEG 4000	85.56±0.13	LH-11	88.06±0.03
PEG 6000	91.98±0.20	LH-21	86.84±0.01
PEG mixture	106.86±0.26	HPC-SL	102.80±0.01
		HPC-SSL	101.13±0.01

Solubility studies

The aqueous solubility of drug from all matrices was found maximum in HPC-SL (19.42 ± 0.42 µg/mL) and minimum with PEG 6000 (9.62 ± 0.09 µg/mL). It was observed as shown in Table 2. that the highest of solubility from each different matrices are PEG mixture (12.17 ± 0.205 µg/mL) and HPC-SL (19.42 ± 0.42 µg/mL). So, usually the highest solubility given a fast dissolution, for make it sure those matrix will compare each others in in vitro dissolution study.

Table 2. Solubility of CLPB in different of matrix

Matrix	solubility (µg/mL)	Matrix	solubility (µg/mL)
PEG 4000	10.76±0.22	LH-11	14.81±0.69
PEG 6000	9.62±0.09	LH-21	14.88±0.205
PEG mixture	12.17±0.205	HPC-SL	19.42±0.42
CLPB	9.25±0.13	HPC-SSL	15.76±0.05

In vitro dissolution study

In this dissolution study was compared between two different polymers which given the highest solubility. From the dissolution profile (Figure 2.) was found that PEG mixture showed faster dissolution as compared with HPC-SL formulation. The HPC-SL at the first water contact seem to detained the drug from release. It might from cellulose ability to adsorb amount of water for swelling themselves first then released drug after that. The PEG showed no barrier to release the drug. It seem to be vanish when contact with water.

Powder X-Ray Diffraction

The diffractogram patterns from PXRD mean of crystallinity nature of the drug and solid dispersion. Their crystalline state was described in high peak intensity. It was observed that crystallinity of CLPB in PEG.

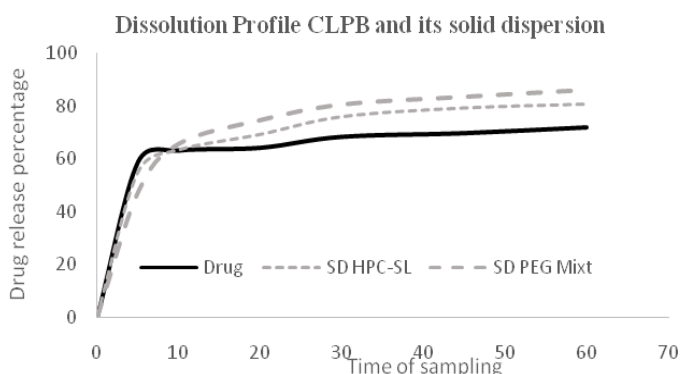


Figure 2. In vitro dissolution profile of Clopidogrel Bisulfate and its solid dispersion

mixture stayed but the peak heights intensity of patterns lower than the pure drug. It means that the crystallinity of drug decrease in PEG matrix. Different patterns with HPC-SL as carrier which all the intensity of the pure drug was lost. The diffractogram patterns of drug altered to HPC-SL patterns get into more amorphous.

FTIR Analysis

IR spectrum of CLPB compared with its solid dispersion in HPC-SL and PEG mixture showed no additional peak at all solid dispersion spectrum. It means all matrices not given off any chemical interaction.

It was observed that spectrum around 2950–3500 cm^{-1} became strong intensity in all formulation then pure drug. It was indicated that

between drug and all matrices has strong physical interaction caused by hydrogen bonding.

Conclusion

The enhancement of solubility of Clopidogrel Bisulfate with HPC and PEG as carriers in solvent evaporation method has been investigated. The investigation resulted that solubility and dissolution rate of the drug can be improved extensively.

The solid state properties of those solid dispersion and drug were characterized by PXRD and FTIR studies showed the strong physical interaction between them without any chemical interaction.

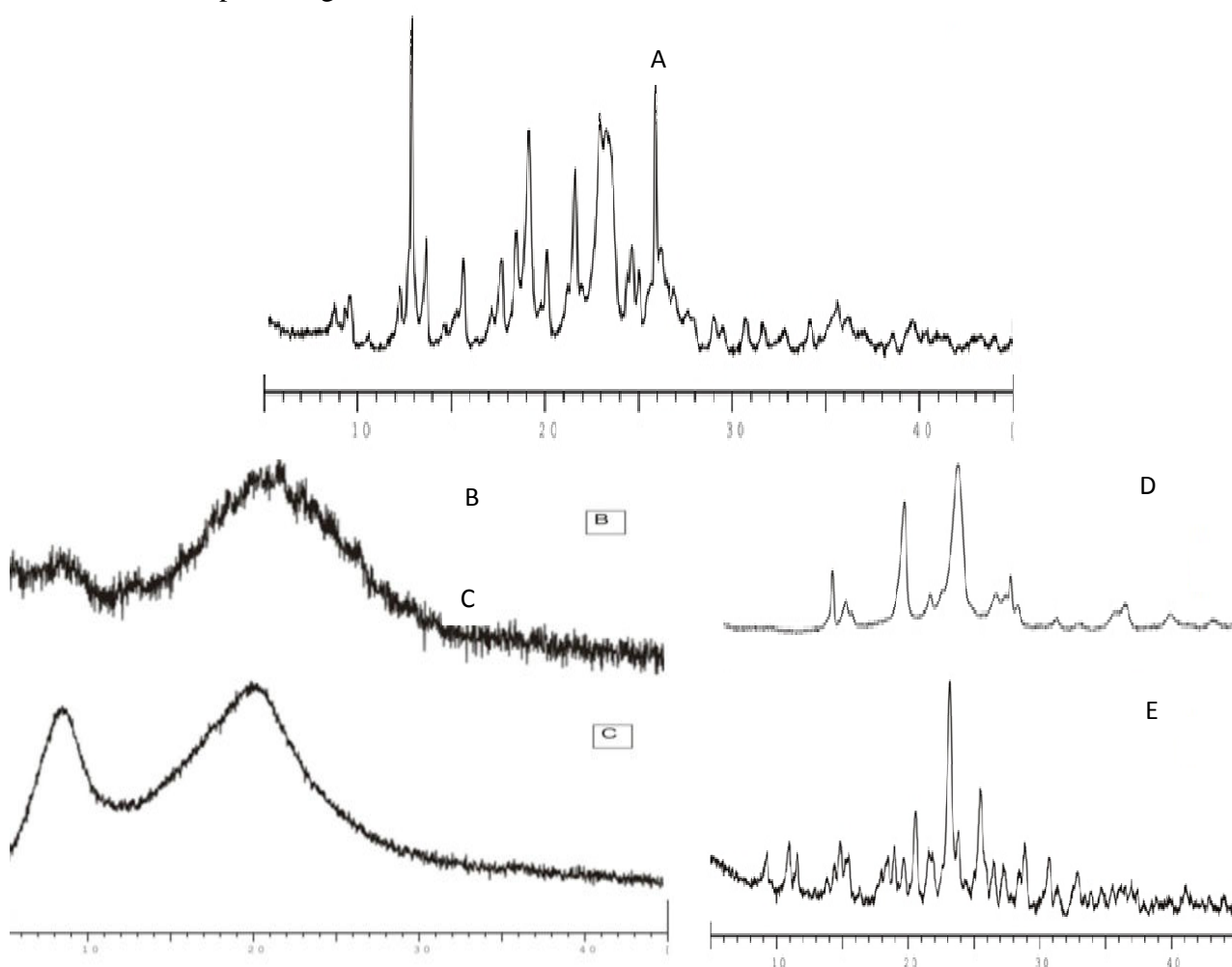


Figure 3. X-ray diffractograms of (A) CLPB, (B) HPC-SL, (C) solid dispersion HPC-SL (D) mixed PEG (1 : 1), (E) solid dispersion of mixed PEG (1 : 1)

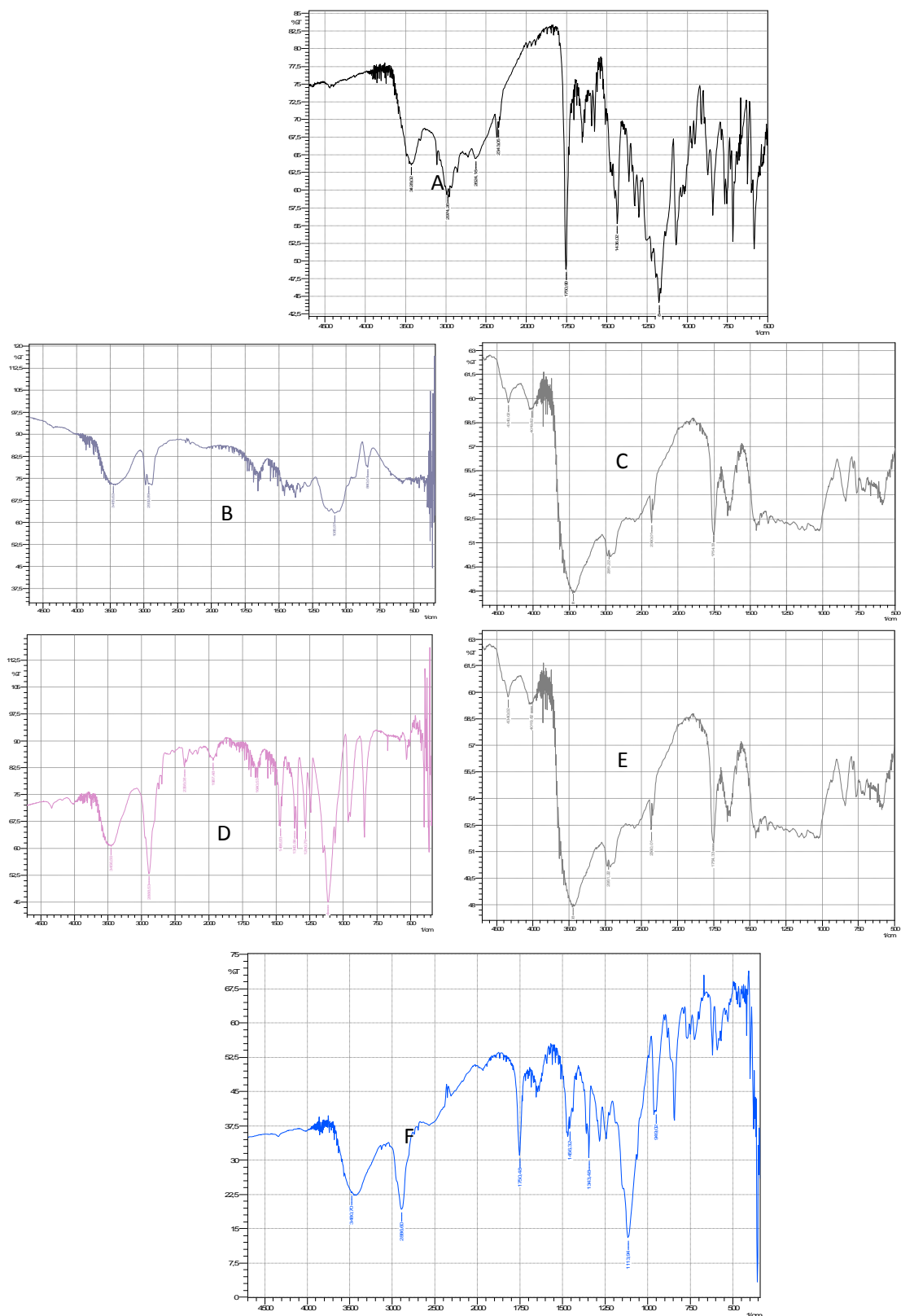


Figure 4. Spectrum IR of (A) CLPB, (B) HPC-SL, (C) SD of HPC-SL, (D) PEG 4000, (E) PEG 6000, (F) SD of mixed PEG (1:1)

References:-

- Bharti, Gupta N., Pooja, S., Neeraj, B., Kulwinder, S., 2013. To Enhance The Solubility Of Poorly Water Soluble Drugs By Using Solid Dispersion: A Review, *Int. Res J Pharm. App Sci.*, 3(2):27-32.
- Collet, J; Hulot, JS; Pena, A; Villard, E; Esteve, JB; Silvain, J; Payot, L; Brugier, D et al. 2009. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *The Lancet* **373**(9660): 309–17. doi:10.1016/S0140-6736(08)61845-0. PMID 19108880.
- Defang, O., N. Shufang, L. Wei, G. Hong, L. Hui, and P. Weisan. 2005. In Vitro dan In Vivo Evaluation of Two Extended Release Preparations of Combination Metformin and Glipizide. *Drug Development and Industrial Pharmacy*. 31: 677-685.
- Dermiş, S., Aydoğan, E., 2009. Rapid And Accurate Determination of Clopidogrel in Tablets by Using Spectrophotometric and Chromatographic Techniques, *Commun. Fac. Sci. Univ. Ank. Series B* V.55 (1) pp. 1-16.
- Kastrati, A., Schömig, A., , Schömig, E. 2004. Are we making efficient use of clopidogrel, *European Heart Journal* 25: 454–456.
- Louis, Place, dan R. Renauld. 2013. *Product Monograph: Plavix*. Canada: Sanofi-Aventis Canada Inc. 55-56.
- Patel, Vandana, Kukadiya, H., Mashru, R., Surti, N., Mandal, S. 2010. Development of Microemulsion for Solubility Enhancement of Clopidogrel, *Iranian Journal of Pharmaceutical Research*, 9 (4): 327-334.
- Shalendra K. Singh, Som, S., Shankhwar, U., 2011. Formulation and Optimization of Solid Dispersion of Clopidogrel with PEG 6000, *Journal of Applied Pharmaceutical Science*, 01 (08); 2011: 217-22.